

Acid Hydrazides, Potent Reagents for Synthesis of Oxygen-, Nitrogen-, and/or Sulfur-Containing Heterocyclic Rings

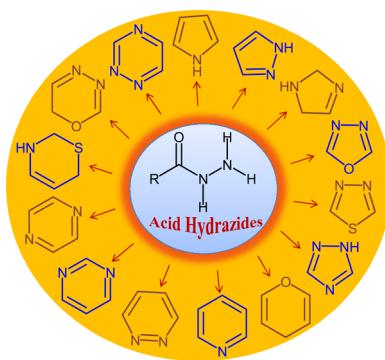
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1. INTRODUCTION

Heterocycles form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but also to the functioning of any developed human society as well. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles.

Numerous natural drugs such as quinine, papaverine, atropine, codeine, emetine, reserpine, procaine, morphine, and theophylline are heterocycles. The majority of the compounds we are familiar with as synthetic drugs such as chlorpromazine, diazepam, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril, and methotrexate are also heterocycles. Some dyes (e.g., mauveine), luminophores, (e.g., acridine orange), pesticides (e.g., diazinon) and herbicides (e.g., paraquat) are also heterocyclic in nature. Each of these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Moreover, all biological processes are expressed through chemical reactions. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism, and transfer of genetic information are all based on chemical interactions involving participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, ATP, DNA, RNA, and serotonin. Why does nature exploit heterocycles? The appropriate answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an

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inexhaustible resource of novel compounds. There are many common features in chemistry and physics between such related compounds as pyrrole and aniline or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine, and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: incorporation of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to cater the needs of biochemical systems.

Synthesis of various heterocycles has been a research objective for over a century, and a variety of well-established methods are available in the literature. Development of new approaches for their syntheses, employing efficient and atom economical routes, is currently a popular research area. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among the new synthetic transformations, uses of hydrazides are among the most attractive precursors for synthesizing heterocyclic compounds.

Moreover, hydrazides include a vast group of organic derivatives of hydrazine containing the functional active group $-\text{C}(=\text{O})\text{NH}_2$. First representatives, namely, hydrazides of formic acid and acetic acid, were produced as far back as 1895 by Kurzius.¹ Great interest in the chemistry of hydrazides and its derivatives is explained by diversity and at times by originality of their properties. Hydrazides find wide applications as drugs, chemical preservers for plants, for manufacturing polymers, glues, etc., in industry, and for many other purposes.² This class of compounds and their derivatives such as hydrazone have been described as useful synthons of various heterocyclic rings of different ring sizes with one or several heteroatoms that exhibit interesting applications as pharmaceuticals,^{3,4} herbicides,⁵ antibacterial agents,⁶ and dyes.^{7,8} The synthetic strategy, in general, for various heterocyclic moieties from hydrazide precursors, has been made by cyclization or cycloaddition with numerous reagents. Hydrazide analogues⁹ also possess other biological activities like anticonvulsant,¹⁰ antidepressant,¹¹ anti-inflammatory,¹² antimalarial,¹³ antimycobacterial,¹⁴ anticancer,¹⁵ and antimicrobial^{16–19} activities.

Hydrazides are rather reactive substances; they are bidentate as ligands. Depending on medium acidity, these reagents form complexes in either amide (type I) or imide (type II) forms²⁰ (Figure 1).

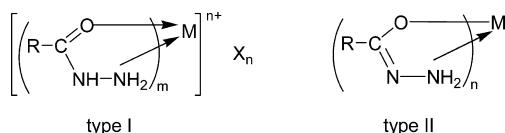


Figure 1. Hydrazides as ligands.

Isonicotinic acid hydrazide, commercially known as (INH, isoniazid) (Figure 2), has been one of the most effective agents in tuberculosis therapy since 1952, when its action against *Mycobacterium tuberculosis* was first discovered.²¹ It appears that INH, like numerous other compounds, has physiological potency in the inhibition of root growth development of levels substantially lower than those that elicit any morphological responses in the tops of established plants.²² It is perhaps from the ranks of such compounds that materials suitable for pre-emergence weed control should be sought. Thus, isonicotinic acid hydrazide has been used in medical practice for more than

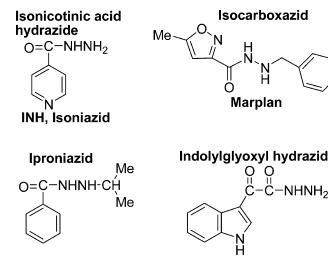


Figure 2. Representative drugs incorporating hydrazide scaffold.

half a century under the name of *isoniazid*, and it has not lost its value to the present day.^{23,24} Further, on this basis, it has given rise to *phthivazid*, *saluzid*, and *metazid*,²⁵ and there continues to be discovered modified analogs such as *flurenizid*²⁶ with improved pharmacological properties. It is now widely used together with rifampicin and streptomycin for chemotherapy of tuberculosis.

Isocarboxazide, also known as Marplan (Figure 2), is a powerful monoamine oxidase (MAO) inhibitor.²⁷ As phenelzine, isocarboxazide is used for depressions which do not respond to other drugs. Iproniazid (Figure 2) is an antidepressant used as psychostimulators.²⁸

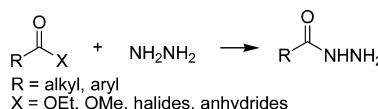
The simple indolylglyoxylyl hydrazide (Figure 2) is mentioned by Heinzelman and Szmuszkoovicz²⁹ as a fairly potent 5-hydroxytryptophan decarboxylase inhibitor ($I_{50} 10^{-4}$ M).

The scope of the present review is to provide practical guidance for synthetic chemists. Bearing in mind that the major interest in heterocycles is the synthesis of biologically active compounds, we arranged the material systematically according to the size and shape of the heterocyclic ring, i.e., five- and six-membered heterocyclic rings containing one, two, or three of the same or different heteroatoms (O, N, or S, respectively) from various acid hydrazides. This systematic arrangement may be useful to any chemist searching for bioisosteres of a heterocyclic scaffold, or a heterocyclic substituent will find a whole range of useful structures.

2. SYNTHESIS OF ACID HYDRAZIDES

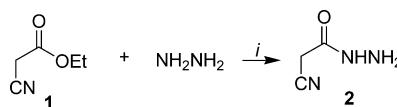
Usually acid hydrazides are formed by combining hydrazine with various acyl derivatives which include esters, cyclic anhydrides, and acyl halides. A general scheme for formation of acid hydrazides is depicted in (Scheme 1).

Scheme 1



Cyanoacetic acid hydrazide **2** was obtained in 93% yield by careful addition of hydrazine hydrate to ethyl cyanoacetate **1** in ethanol with stirring at 0 °C (Scheme 2).³⁰

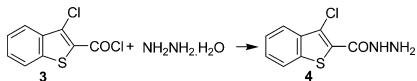
Scheme 2^a



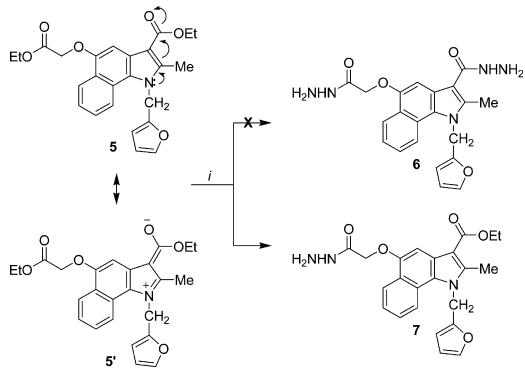
^a(i) 0 °C, EtOH.

Treatment of 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **3** with hydrazine hydrate afforded the corresponding acid hydrazide **4** in 73% yield (Scheme 3).^{31,32}

Scheme 3



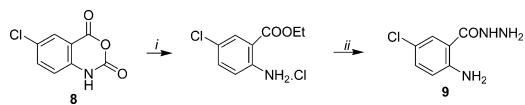
Reaction of benz(*g*)indole dicarboxylate **5** with hydrazine hydrate in refluxing ethanol and a catalytic amount of pyridine chemoselectively produced only 63% of benz(*g*)indole monocarbohydrazide **7** instead of the expected dicarbohydrazide **6** wherein the C₃-carboethoxy group remained unchanged toward nucleophile hydrazine hydrate (Scheme 4).³³ The resistance of

Scheme 4^a

^a(i) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, Py.

the C₃-carboethoxy group of **5** toward nucleophilic attack of the hydrazine hydrate might be attributed to the canonical form **5'** of these compounds, where the C₃-carboethoxy group has less double-bond character.^{34–36}

The cyclic anhydride **8** on hydrolysis with ethanolic hydrochloric acid and subsequent reaction with hydrazine hydrate yielded 92% of 5-chloroanthranilic acid hydrazide **9** (Scheme 5).³⁷

Scheme 5^a

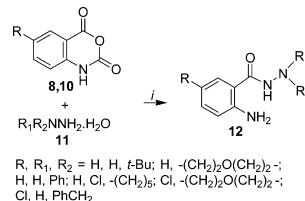
^a(i) EtOH, HCl; (ii) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH.

The hydrazides **12** were obtained from the anhydrides **10** and the hydrochlorides of disubstituted hydrazines **11** in the presence of triethylamine and pyridine in an atmosphere of nitrogen (Scheme 6).³⁸

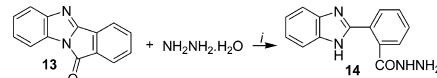
The benzo[4,5]imidazo[2,1-*a*]isoindol-11-one **13** on refluxing with hydrazine hydrate at 120 °C yielded 80% of benzimidazolylbenzoyl hydrazide **14** (Scheme 7).³⁹

3. REACTIONS OF ACID HYDRAZIDES

Due to the huge number of references, reactions of acid hydrazide with various reagents are classified separately in one category and the enormous number of records was arranged in order of increasing number of heteroatoms in different type of

Scheme 6^a

^a(i) TEA, Py, N_2 , 2-chloroacetyl chloride, refluxing, 15 h.

Scheme 7^a

^a(i) Oil bath, 120 °C.

the heterocycles formed, starting with five- and six-membered rings. These systematic collections in the present review expand the ample possibilities to the synthetic methods accessed by the chemistry for synthesis of heterocyclic compounds and may possibly be useful to pick the route for further research.

3.1. Synthesis of Five-Membered Rings with One Heteroatom

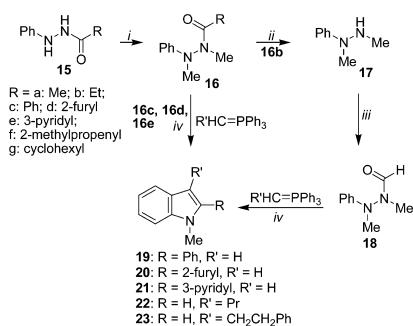
3.1.1. Pyrrole and Their Fused Derivatives. Pyrrole is an important ubiquitous heterocyclic moiety throughout the plant as well as animal kingdom because of its involvement as a subunit of haem, the chlorophyll, vitamin B₁₂, and some bile pigments. Pyrroles have been found to exhibit a wide spectrum of biological activities.^{40–42} In addition, 2,5-dimethylpyrrole derivatives have shown interesting antiulcer⁴³ and hypotensive⁴² activities.

Also, the indole ring system is a crucial structure in drug discovery and has become an essential component in many pharmacologically active compounds. The extensive number of synthetic routes to and applications of indoles emphasizes the great interest in this area. The most commonly used method for preparation of indoles remains the Fischer indole synthesis discovered in 1883.^{44,45} In spite of extensive studies, important efforts are still focused on providing synthetic routes under mild conditions and with good regiocontrol on the outcome of the reaction.^{46,47}

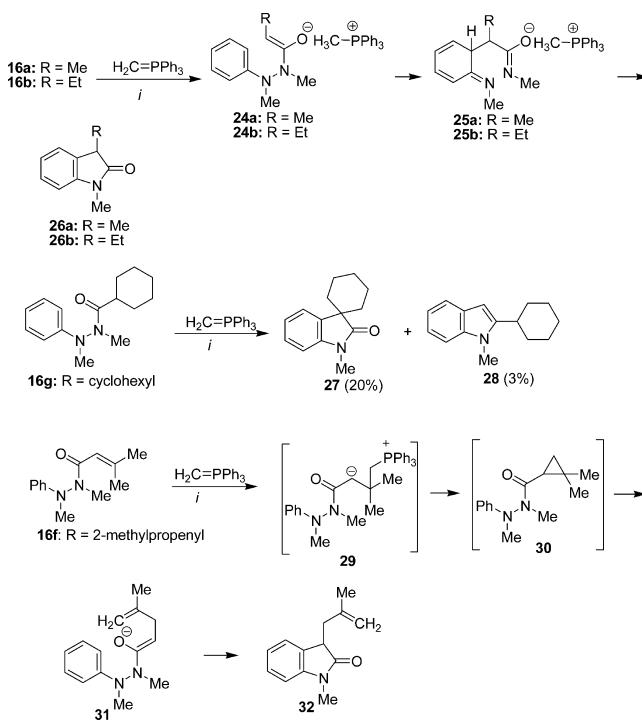
Murphy et al.⁴⁸ explored the synthesis of indoles from their recently reported alkylidenated Weinreb amides^{49,50} in non-classical Wittig reactions.^{51,52} Success in that study led the authors to investigate the reactivity of Wittig reagents with acyl hydrazides **16** (Scheme 8).⁴⁸

Reaction of phosphorus ylides with the hydrazide **16c–e** and **18** afforded the respective indole derivatives **19–23** in 41–78% yields (Scheme 8).

The authors extended the reactions to *N*-acetylhydrazide **16a** and *N*-propionyl hydrazide **16b** where the unexpected indolin-2-one **26a** and **26b** were isolated in 76% and 92% yields, respectively (Scheme 9). In these cases, the phosphorane deprotonates **16a**/**16b** to form the enolate of the hydrazide **24a**/**24b** which underwent a Brunner indolin-2-one synthesis,^{53,54} in high yield, to afford **25a**/**25b** before condensation to the final products. The reactivity of cyclohexyl hydrazide **16g** mirrored that of the acetyl case **16a** and produced 20% of spiroindolin-2-one **27** as well as a low yield of indole **28** (3%) (Scheme 9). They also proposed that conjugate addition of the phosphorane to the α,β -unsaturated hydrazide **16f** afforded **29** followed by expulsion of triphenylphosphine. The resulting

Scheme 8^a

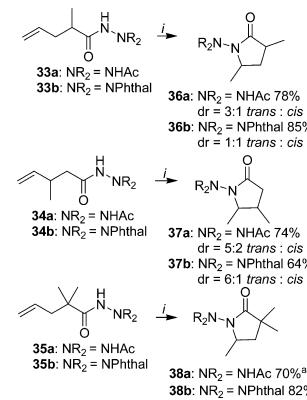
^a(i) NaH, MeI; (ii) 10N HCl, 40 °C, 72 h; (iii) *t*-BuCO·O·CHO; (iv) toluene, Δ.

Scheme 9^a

cyclopropane 30 then underwent either base-induced deprotonation of one of the gem-dimethyl groups in tandem with ring opening of the cyclopropane to form the enolate 31 or thermal prototropic formation of the enol that is equivalent to 31, followed by deprotonation. The enolate 31 then underwent a Brunner reaction to the indolin-2-one product 32 in 24% yield.

Michael and co-workers⁵⁵ reported a dicationic platinum (bpy)Pt(II) catalyzed intramolecular hydrohydrazination of olefins 33–35 that proceeded through N–H activation of an alkenyl hydrazide followed by olefin insertion into a Pt–N bond. Reaction optimization revealed Pt(bpy)Cl₂ (10 mol %) and AgOTf (20 mol %) in DMF-*d*₇ to be an effective catalyst system for conversion of substituted hydrazides to five-membered *N*-amino lactams (*N*-amino = *N*-acetamido at 120 °C, *N*-phthalimido(NPhthal) at 80 °C, OTf = trifluoromethanesulfonate) 36–38. In the case of 33 and 34 diastereomers were observed. In both cases, the trans isomer was found to be favored,

with ratios varying from 1:1 to 3:1 for 36 and from 5:2 to 6:1 for 37 depending upon the choice of *–NR*₂ (Scheme 10).

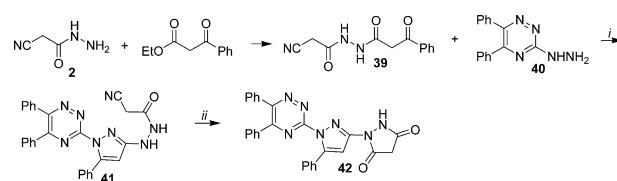
Scheme 10^a

^a(i) Pt(bpy)Cl₂ (10 mol %), AgOTf (20 mol %), DMF, T = 80 °C when NR₂ = NPhthal, 120 °C when NR₂ = NHAc. Yields given are isolated yields after 1 day unless otherwise noted. (a) 2 days.

3.2. Synthesis of Five-Membered Rings with Two Heteroatoms

3.2.1. Pyrazoles and Their Fused Derivatives. The term pyrazole was given by Ludwig Knorr in 1883. Pyrazole^{56–58} was first described by Buchner in 1889, who discovered it during decomposition of pyrazole 3,4,5-tricarboxylic acid. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons. Interest in pyrazoles stemmed from their application in drugs and dyes, as antioxidants in fuels, as anesthetics, and in agricultural fields. In medicine, derivatives of pyrazoles are used for their antiinflammatory,⁵⁹ antipyretic, analgesic, muscle relaxing,⁶⁰ antiarrhythmic, tranquilizing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic,⁶¹ and antibacterial⁶² activities. The following are a few drugs: antipyrine, used as an analgesic and febrifuge; tartrazine, most commonly used as a yellow dye for food; phenylbutazone (butazolidin), an antiinflammatory drug used in treatment of arthritis. Therefore, it became of interest to synthesize new pyrazole derivatives of possible biological activities.

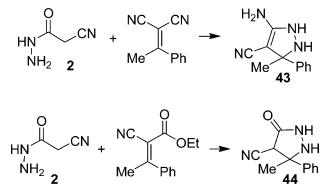
It was reported that treatment of hydrazide 2 with ethyl benzoylacetate yielded *N*'-(2-cyanoacetyl)-3-oxo-3-phenylpropanehydrazide 39, which underwent cyclocondensation with 3-hydrazino-5,6-diphenyl-1,2,4-triazine 40 in absolute ethanol to produce compound 41, which on reaction with dilute hydrochloric acid gave 55% of 1-(1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-phenyl-1*H*-pyrazol-3-yl)pyrazolidine-3,5-dione 42 (Scheme 11).⁶³

Scheme 11^a

^a(i) EtOH, reflux, 140–150 °C, 4 h; (ii) dilute HCl, reflux, 5 h.

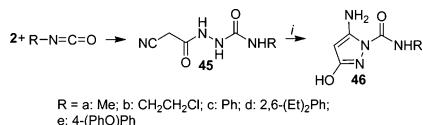
A series of pyrazole derivatives using cyanoacetic acid hydrazide was synthesized by a number of research groups (Schemes 12–19). Elnagdi and cow-workers⁶⁴ reported the

Scheme 12



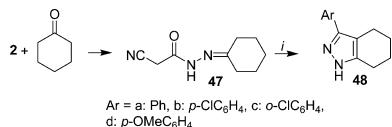
reaction of 2-(1-phenylethylidene)malononitrile and ethyl 2-cyano-3-phenylbut-2-enoate with hydrazide 2 to furnish pyrazoline 43 and pyrazolidinone derivative 44, respectively, with 75% yield (Scheme 12).

Reaction of hydrazide 2 with alkylisocyanate yielded alkylcarbamoyl derivative 45, which upon treatment with 2 N sodium hydroxide furnished the cyclized pyrazole derivative 46 in 48–92% yields (Scheme 13).⁶⁵

Scheme 13^a

^a(i) 2 N NaOH.

Condensation of hydrazone derivative 47 obtained from hydrazide 2 and cyclohexanone with aromatic aldehyde in ethanolic triethylamine gave the 3-aryl-4,5,6,7-tetrahydro-1*H*-indazoles 48 in 75–78% yield (Scheme 14).⁶⁶

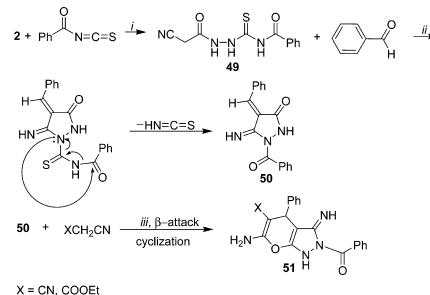
Scheme 14^a

^a(i) ArCHO, EtOH/TEA.

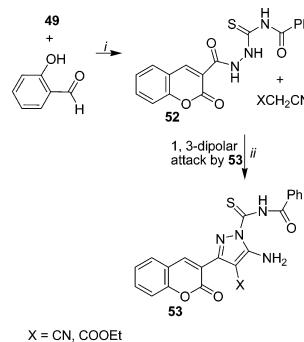
Pyrazole derivative 50 was produced in 75% yields on condensation of hydrazide 49 with benzaldehyde via 1,5-dipolar cyclization of the initially formed adduct followed by rearrangement via elimination of HN=C=S (Scheme 15).⁶⁷ Shams et al.⁶⁷ further subjected pyrazole 50 to a reaction with methylene carbonitrile reagents (XCH₂CN; X = CN and CO₂Et) affording the respective pyranopyrazole derivatives 51 in 86% (X = CN) and 65% (X = COOEt) yield via β -attack on the benzylidene moiety followed by cyclization through the pyrazole oxo function (Scheme 15).

Shams et al.⁶⁷ also treated hydrazide 49 with salicylaldehyde to produce the coumarin derivative 52, which on subsequent reaction with methylene carbonitrile reagents (XCH₂CN; X = CN and CO₂Et) formed the respective pyrazole derivatives 53 in 80% (X = CN) and 72% (X = COOEt) yield via a 1,3-dipolar attack of the hydrazinocarbonyl moiety of 52 on the methylene carbonitrile dipole (Scheme 16).

Treatment of hydrazide 2 as ambident nucleophile with phenyl 7-fluoro-4-chromone-3-sulfonate 54 in the presence of sodium

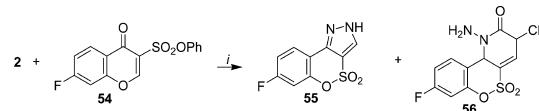
Scheme 15^a

^a(i) dioxane, rt, shaking; (ii) DMF, excess piperidine, reflux, 5 h; (iii) EtOH and DMF (5:1), TEA, reflux, 5 h.

Scheme 16^a

^a(i) EtOH, catalytic amount of piperidine, reflux, 1 h; (ii) EtOH and DMF (2:1), TEA, reflux, 5 h.

acetate and glacial acetic acid afforded a mixture of 7-fluoro-2*H*-[1,2]benzoxathiino[4,3-*c*] pyrazole 4,4-dioxide 55 and 1-amino-8-fluoro-2-oxo-1,2,3,10*b*-tetrahydro[1,2]benzoxathiino[4,3-*b*]pyridine-3-carbonitrile 5,5-dioxide 56, which are separated by means of rotational chromatography (Scheme 17).⁶⁸

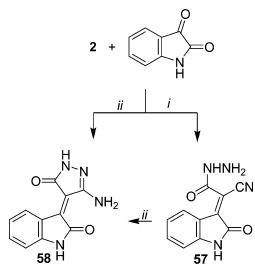
Scheme 17^a

^a(i) AcONa/AcOH, reflux at 100 °C.

Condensation of hydrazide 2 with isatin was reported at room temperature and furnished the isolated intermediate (2*E*)-2-cyano-2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetohydrazide 57, which was cyclized on heating to give (2*E*)-3-(3-amino-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)-1,3-dihydro-2*H*-indol-2-one 58. Compound 58 was also directly obtained on refluxing hydrazide 2 with isatin in ethanol containing a catalytic amount of triethylamine (Scheme 18).⁶⁹

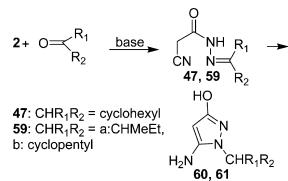
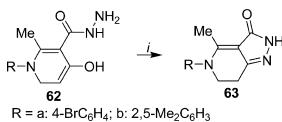
4-Amino-3-hydroxypyrazole derivatives 60 and 61 (80–86% yields) were prepared from reaction of the hydrazide 2 with ketones in the presence of a basic catalyst via cyclization of hydrazone derivatives 47 and 59 (Scheme 19).⁷⁰

Hydrazide 62 furnished the intramolecular cyclized pyrazolo derivative 63 in 82% (R = 4-BrC₆H₄) and 70% (R = 2,5-Me₂C₆H₃) yields upon refluxing in glacial acetic acid (Scheme 20).⁷¹

Scheme 18^a

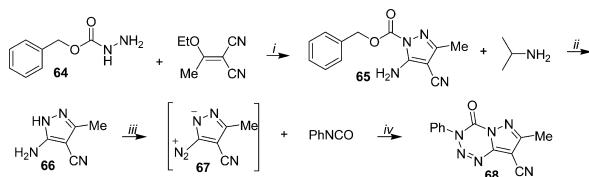
^a(i) EtOH/TEA, rt; (ii) EtOH/TEA, boiling.

Scheme 19

Scheme 20^a

^a(i) AcOH, reflux, 1.5 h.

Lam et al.⁷² reported the synthesis of 5-aminopyrazole 66 and applied it for preparation of pyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-4(3*H*)-ones 68. In this strategy, hydrazide 64 was reacted with (1-ethoxyethylidene)malononitrile at room temperature to provide benzyl 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate 65. The authors attempted to obtain compound 68 by diazotizing 65 followed by reaction with an amine⁷³ but resulted instead in formation of 66 (Scheme 21). Further

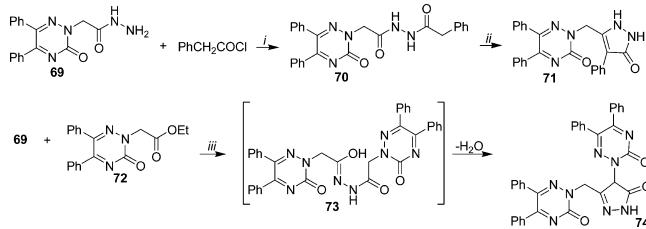
Scheme 21^a

^a(i) EtOH, rt; (ii) MeOH, rt; (iii) HCl, NaNO₂, H₂O, 0–5 °C; (iv) CH₂Cl₂/H₂O, pH 7–8, 0 °C, rt.

investigation confirmed that the diazotization of 65 did not proceed readily, and the carbobenzoyloxy group on N₁ of compound 65 was readily removed during the reaction with isopropylamine to provide 66 in 90% yield. Subsequent diazotization of 66 with 4 M HCl and sodium nitrite in water at 0–5 °C gave nonisolable 67 and was treated overnight with phenylisocyanate, which provided 7-methyl-4-oxo-3-phenyl-3,4-dihydropyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-8-carbonitrile 68 in 72% yield (Scheme 21). The authors also developed a SPS of 5-aminopyrazole 66.

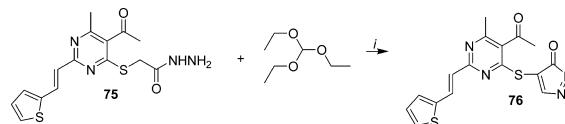
The pyrazole 71 was obtained in 75% yield by treatment of acetic acid hydrazide 69 with phenylacetyl chloride followed by cyclization of the resulting intermediate 70 in basic medium. On

the other hand, fusion of hydrazide 69 and ethyl carboxylate 72 at 200 °C gave 85% of pyrazole 74 without isolation of intermediate 73 (Scheme 22).⁷⁴

Scheme 22^a

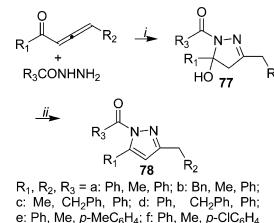
^a(i) DMF, reflux, 1 h; (ii) NaOEt/EtOH, reflux, 4 h; (iii) fused under reflux, 200 °C, 2 h.

2-(5-Acetyl-6-methyl-2-[*E*-2-(2-thienyl)vinyl]pyrimidin-4-yl)thio)acetylhydrazide 75 was reacted with triethyl orthoformate in acetic acid to afford the corresponding pyrazole derivative 76 in 56% yield (Scheme 23).⁷⁵

Scheme 23^a

^a(i) AcOH, reflux, 3 h.

Catalyst-free cyclocondensation of allenic ketones with hydrazides afforded the 1-acyl-5-hydroxypyrazolines 77 with high regioselectivity, which were further converted into 1-acyl pyrazoles 78 via BF₃·Et₂O-catalyzed dehydration in good to excellent yields: R₁, R₂, R₃ = 82% for (a) Ph, Me, Ph; R₁, R₂, R₃ = 70% for (b) Bn, Me, Ph; R₁, R₂, R₃ = 78% for (c) Me, CH₂Ph, Ph; R₁, R₂, R₃ = 69% for (d) Ph, CH₂Ph, Ph; R₁, R₂, R₃ = 70% (e) Ph, Me, p-MeC₆H₄; R₁, R₂, R₃ = 66% for (f) Ph, Me, p-ClC₆H₄ (Scheme 24).⁷⁶

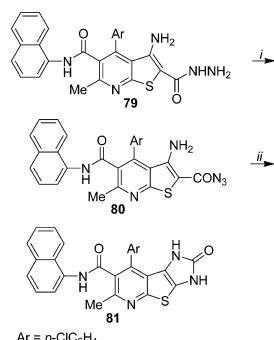
Scheme 24^a

^a(i) EtOH, 25 °C; (ii) BF₃·Et₂O (20 mol %), 25 °C, THF.

3.2.2. Imidazoles and Their Fused Derivatives. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds. For example, the amino acid histidine, the hypnotic agent etomidate,⁷⁷ the antiulcerative agent cimetidine,⁷⁸ the proton pump inhibitor omeprazole,⁷⁹ the fungicide ketoconazole,⁸⁰ and the benzodiazepine antagonist flumazenil⁸¹ are imidazole derivatives. Therefore, there is a continuous need for developing concise and practical synthetic methods for preparation of imidazole and related compounds.

Diazotization of 3-aminothieno[2,3-*b*]pyridine carbohydrazide derivative **79** gave the corresponding 3-amino-5-[(1-naphthylamino)carbonyl]thieno[2,3-*b*]pyridine-2-carbonyl azide derivative **80**, which was subjected to Curtius rearrangement^{82,83} to give 72% of *N*-1-naphthyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4',5':4,5]thieno[2,3-*b*]pyridine-7-carboxamide derivative **81** (Scheme 25).⁸⁴

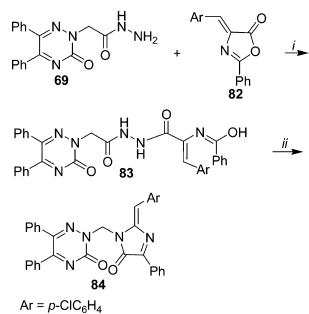
Scheme 25^a



^a(i) AcOH, NaNO₂/H₂O, stirred, 6 h; (ii) xylene, reflux 18 h.

Imidazole **84** was synthesized in 50% yield from reaction of hydrazide **69** with oxazolone **82** via cyclization of acid hydrazido derivative **83** in basic medium (Scheme 26).⁷⁴

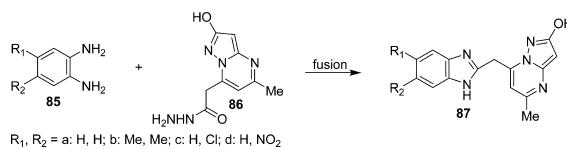
Scheme 26^a



^a(i) aq EtOH (80%), reflux, 6 h; (ii) 2N NaOH, reflux, 4 h.

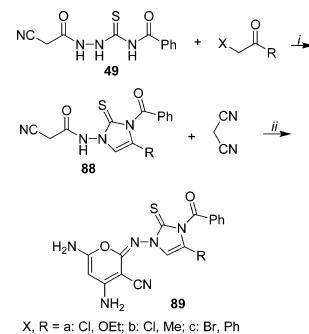
Condensation of *o*-phenylenediamines **85** with hydrazide **86** to melting reactants at 240 °C afforded 2-hydroxy-7-[benzimidazol-2-yl]methyl-5-methylpyrazolo[1,5-*a*] pyrimidines **87** in 60–80% yields (Scheme 27).⁸⁵

Scheme 27



Shams et al.⁶⁷ reported the reaction of cyanoacetic 2-[(benzoylamino)thioxomethyl] hydrazide **49** with α -halo-*tones* (XCH_2COR ; A: X = Cl, R = OEt; b: X = Cl, R = Me; c: X = Br, R = Ph) to afford the respective imidazolethione derivatives **88** (a, 75%; b, 88%; c, 70%) which on subsequent treatment with malononitrile afforded the pyran systems **89** (a, 82%; b, 82%; c, 88%) via nucleophilic attack on the carbonitrile reagent followed by 1,6-dipolar intramolecular cyclization (Scheme 28).

Scheme 28^a



^a(i) EtOH, reflux, 5 h; (ii) 1,4-dioxane, TEA, 4 h.

3.3. Synthesis of Five-Membered Rings with Three Heteroatoms

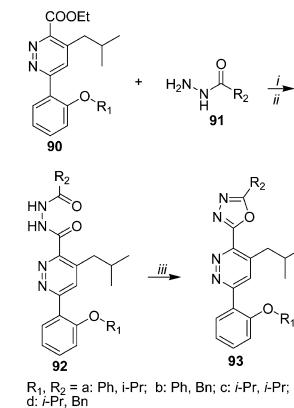
3.3.1. Oxadiazoles and Their Fused Derivatives. 1,3,4

Oxadiazoles are commonly utilized pharmacophores due to their metabolic profile and ability to engage in hydrogen bonding. In particular, marketed antihypertensive agents such as tiadazosin⁸⁶ and nesapidil⁸⁷ as well as antibiotics such as furamizole⁸⁸ contain the oxadiazole nucleus. 2-Amino-1,3,4-oxadiazoles have demonstrated biological activity as muscle relaxants⁸⁹ and antimicrobials,⁹⁰ while 2,5-diaryl-1,3,4-oxadiazoles are known to be platelet aggregation inhibitors.⁹¹ 5-Aryl-2-hydroxymethyl-1,3,4-oxadiazoles have shown diuretic, analgesic, antiinflammatory, anticonvulsive, and antiemetic properties,⁹² and 2-hydroxyphenyl-1,3,4-oxadiazoles behave as hypnotics and sedatives.⁹³ Widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry as demonstrated by these examples establishes this moiety as a member of the privileged structures class.

Rebek et al.⁹⁴ reported the hydrolysis of the ethyl ester **90** with LiOH, followed by coupling with *N*-acyl hydrazides **91** mediated by EDCI/HOBt which led to formation of intermediates **92** in good yields. Dehydration of *N,N'*-diacyl hydrazides **92** using POCl₃ yielded 45–53% of α -helix mimetic oxadiazole-pyridazine-phenyl scaffold **93** (Scheme 29).

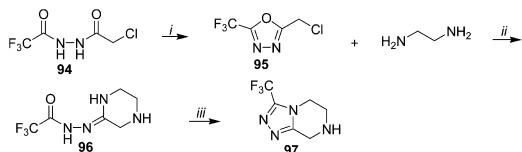
Dehydrative cyclization of hydrazide **94** in the presence of phosphorus oxychloride furnished the chloromethyloxadiazoles **95** in 79% yield. On addition of oxadiazole **95** to a solution of ethylenediamine, amidine **96** formed was found to crystallize from the reaction mixture at room temperature, which on

Scheme 29^a



^a(i) LiOH, THF/H₂O; (ii) EDCl, HOBr, DCM; (iii) POCl₃, MeCN, reflux, 12 h.

refluxing afforded 92% of [1,2,4]triazolo[4,3-*a*]piperazines **97** (Scheme 30).⁹⁵

Scheme 30^a

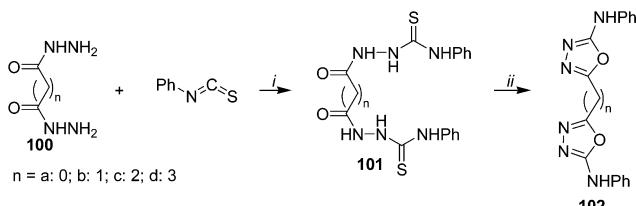
^a(i) POCl_3 , reflux, 80 °C, 17 h; (ii) MeOH , -20 °C; (iii) MeOH , reflux.

Reaction of isatoic anhydrides **98** with appropriate hydrazides in acetic acid led to formation of 1-(2-substituted amino-benzoyl)-2-arylhdyrazines, which underwent cyclization in the presence of polyphosphoric acid (PPA) to form 2,5-diaryl-substituted 1,3,4-oxadiazoles **99** in 35–42% yields (Scheme 31).⁹⁶

Scheme 31^a

^a(i) AcOH ; (ii) PPA.

Cyclodehydration of semicarbazides for synthesis of the oxadiazole moiety has been reported by various researchers (Schemes 32–38). Oxidative cyclization of oxalyl diphenylthiosemicarbazides **100** in the presence of $\text{Ph}_2\text{N-C}\equiv\text{S}$ afforded bis-2-(5-phenylamino-1,3,4-oxadiazole) **102** in 57–67% yields (Scheme 32).⁹⁷

Scheme 32^a

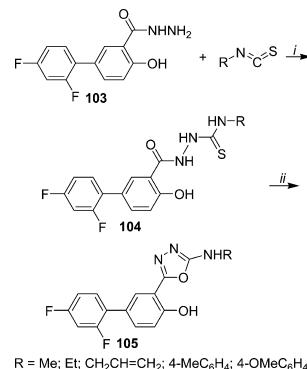
^a(i) EtOH ; (ii) EtOH , NaOH/KI , I_2 .

Thiosemicarbazides **101** in the presence of alkaline I_2/KI solution afforded bis-2-(5-phenylamino-1,3,4-oxadiazole) **102** in 57–67% yields (Scheme 32).⁹⁷

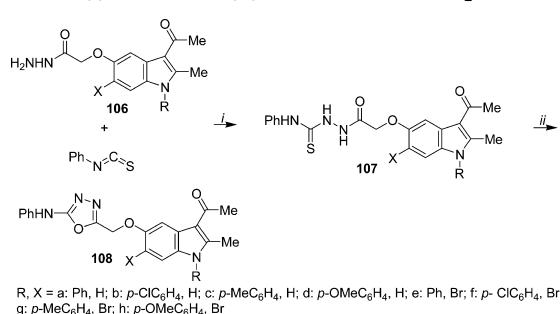
Similarly, Kucukguzel et al.⁹⁸ and Gadaginamath et al.³⁴ reported the oxidative cyclization of alkyl/arylthiosemicarbazides **104** and thiosemicarbazide **107** in alkaline iodine solution to give the 1,3,4-oxadiazole **105** in 43–75% yields (Scheme 33) and 1,3,4-oxadiazole **108** in 53–64% yields (Scheme 34), respectively. In the same way, Basavaraja et al.⁹⁹ also described the synthesis of 1,3,4-oxadiazole derivatives.

1-Cinnamoyl-4-phenyl semicarbazide **110**, synthesized by reaction of phenyl isocyanate with the cinnamic acid hydrazide **109**, was subjected to acid-catalyzed intramolecular cyclization with sulfuric acid to afford 78% of 2-cinnamoyl-5-aminophenyl 1,3,4-oxadizoles **111** (Scheme 35).¹⁰⁰

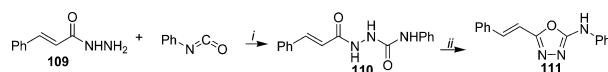
Ring closure of thiosemicarbazide **113** was carried out in the presence of $\text{Hg}(\text{OAc})_2$ in refluxing acetic acid to afford 41–50% of 1,3,4-oxadiazoles **114** (Scheme 36).¹⁰¹

Scheme 33^a

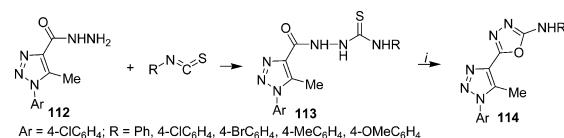
^a(i) EtOH ; (ii) EtOH , NaOH/KI , I_2 .

Scheme 34(i) EtOH, Δ ; (ii) $\text{EtOH}, \text{KOH/KI}, \text{I}_2$ 

R, X = a: Ph; b: *p*-ClC₆H₄; c: *p*-MeC₆H₄; d: *p*-OMeC₆H₄; e: Ph, Br; f: *p*-ClC₆H₄, Br; g: *p*-MeC₆H₄, Br; h: *p*-OMeC₆H₄, Br

Scheme 35^a

^a(i) CHCl_3 , reflux, 1 h; (ii) H_2SO_4 , stirring.

Scheme 36^a

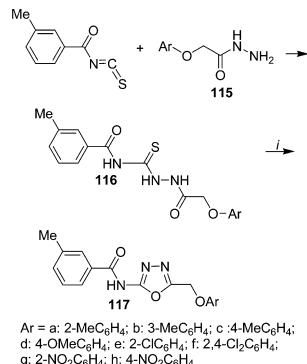
^a(i) $\text{Hg}(\text{OAc})_2$, AcOH .

Li et al.¹⁰² adapted a similar procedure for synthesis of 1,3,4-oxadiazoles **117** in 83–94% yields by treating 4-(3-methylbenzoyl)-1-(2-phenoxyacetyl)thiosemicarbazide **116** with mercuric acetate in glacial acetic acid (Scheme 37).

The thiosemicarbazides **119** obtained by nucleophilic addition reaction of 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid hydrazide **118** with phenyl isothiocyanate underwent cyclization to 1,3,4-oxadiazole **120** in low yield (31%) by boiling the former with mercuric oxide in absolute ethanol (Scheme 38).¹⁰³

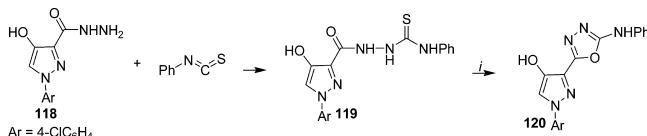
Condensation of the acid hydrazide **4** with formic acid yielded 3-chloro-2-(*N*-formyl acid hydrazide)benzo[*b*]thiophene **121**, which on further refluxing with phosphorus pentoxide in xylene afforded 53% of 2-(3-chloro-1-benzothien-2-yl)-1,3,4-oxadiazole **122** (Scheme 39).³²

Reaction of hydrazide **123** with formic acid resulted in 1-formyl-2-{7*H*-1,2,4-triazolo[1,5-*d*]tetrazol-6-ylsulfanyl} acetylhydrazine **124**, which underwent ring closure with phosphorus

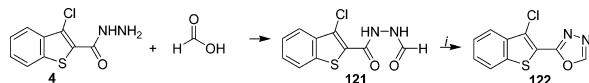
Scheme 37^a

Ar = a: 2-MeC₆H₄; b: 3-MeC₆H₄; c: 4-MeC₆H₄;
d: 4-OMeC₆H₄; e: 2-CIO₂C₆H₄; f: 2,4-Cl₂C₆H₄;
g: 2-NO₂C₆H₄; h: 4-NO₂C₆H₄

^a(i) Hg(OAc)₂/AcOH, reflux.

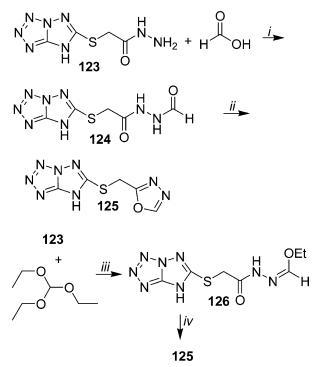
Scheme 38^a

^a(i) HgO, EtOH.

Scheme 39^a

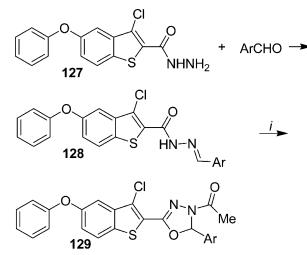
^a(i) P₂O₅, xylene, reflux.

pentoxide to yield 44% of 1,3,4-oxadiazole 125. In an alternative route, compound 125 was obtained in 56% yield by thermal cyclization of ethoxyformaldehyde hydrazone 126 generated on refluxing the mixture of 123 and triethyl orthoformate (Scheme 40).¹⁰⁴

Scheme 40^a

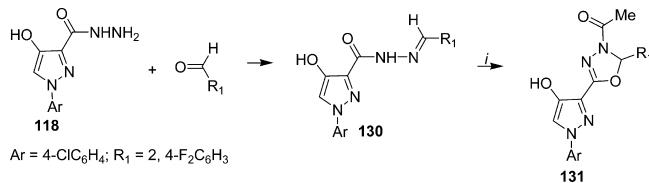
^a(i) reflux; (ii) P₂O₅, toluene; (iii) reflux; (iv) Δ.

Acetic acid anhydride was also used by a group of researchers for formation of oxadiazole derivatives (Schemes 41–43). Cyclocondensation of benzalhydrazone derivative 128 with acetic anhydride furnished acetyl oxadiazoles 129 in 49–75% yields (Scheme 41).¹⁰⁵ Similarly, the 1,3,4-oxadiazoline 131 was prepared in 70% yield exclusively by cyclization of the intermediate 130 (Scheme 42).¹⁰³

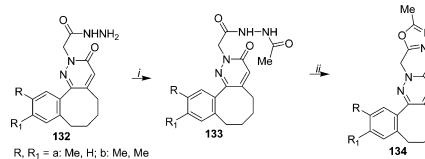
Scheme 41^a

Ar = a: Ph; b: 3-BrC₆H₄; c: 4-ClC₆H₄; d: 4-OC₆H₄; e: 4-OH-3-OMeC₆H₃; f: N-(Me)₂C₆H₄; g: 4-OMeC₆H₄; h: 3,4-(OMe)₂C₆H₃; i: 2,3,4-(OMe)₃C₆H₃; j: 2-NO₂C₆H₄; k: 3-OC₆H₅-MeC₆H₄; l: 4-SMeC₆H₄

^a(i) Ac₂O, reflux.

Scheme 42^a

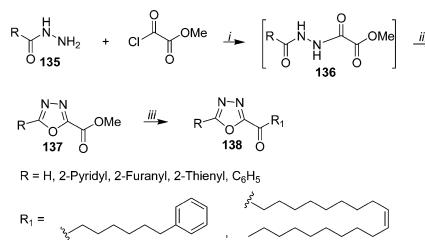
^a(i) Ac₂O, reflux.

Scheme 43^a

^a(i) Ac₂O/AcOH, reflux; (ii) POCl₃, MeCN.

Dehydrative ring closure of the N-acetyl derivative 133, obtained from refluxing hydrazide 132 in acetic acid anhydride, with phosphorus oxychloride in acetonitrile furnished the corresponding oxadiazole derivatives 134 in very low yields (25–28%) (Scheme 43).¹⁰⁶ Various 1,3,4-oxadiazoles prepared by reaction of different aryl-substituted hydrazones of respective 4-fluorobenzoic acid hydrazide and 4-pyrrol-1-yl benzoic acid hydrazide with acetic anhydride were also reported by Kocigit-Kaymakcoglu et al.¹⁰⁷ and Vagdevi et al.¹⁰⁸

The hydrazide 135 on nucleophilic displacement reaction with methyl oxalyl chloride in the presence of triethylamine produced a diacyl hydrazide intermediate 136, which underwent cyclization upon treatment with *p*-toluenesulfonyl chloride (TsCl) to yield 1,3,4-oxadiazole derivative 137 in 75–94% yields (Scheme 44).^{109,110} Subsequent addition of the requisite

Scheme 44^a

^a(i) TsCl, TEA; (ii) TsCl, TEA; (iii) R₁Li or R₁MgBr.

Table 1. Synthesis of Oxadiazoles 152–167 from Acid Hydrazides and Carbon Disulfide^a

The general reaction scheme shows the conversion of an acid hydrazide (R-C(=O)-NH-NH₂) to an oxadiazole derivative (152-167) under conditions *i*. The product is an oxadiazole ring where the carbonyl carbon is substituted with the R group from the acid hydrazide.

Sl. No.	R	Product	Ref.	Yield %	Sl. No.	R	Product	Ref.	Yield %
1.			34	61–68	9.			116	95
2.			103	83.3	10.			117	69
3.			104	59	11.			118	90
4.			33,111	83	12.			119	70
5.			112	65–68	13.			120	79–84
6.			113	71	14.			121	56.4
7.			114	74	15.			122, 123	82
8.			115	60	16.			108	86

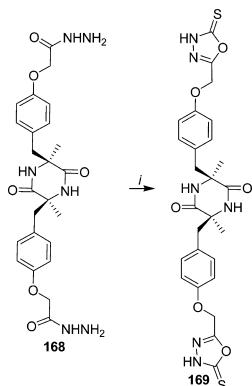
^a(i) CS₂, alcholic KOH, or NaOH.

side chain (R₁) to the methyl ester was accomplished via a metal–halogen exchange of the corresponding alkylbromide to give the α -ketooxadiazole 138 in 20–73% yields (Scheme 44).^{109,110}

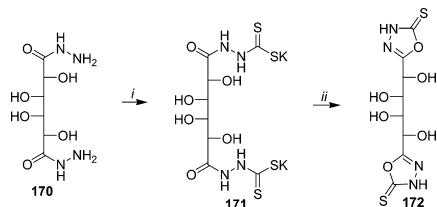
Cyclocondensation of acid hydrazides 106, 118, 123, and 139–151 with carbon disulfide in alcholic KOH or NaOH under

reflux conditions gave the respective oxadiazole derivatives 152–167 (Table 1).

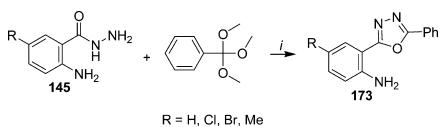
The dicarbohydrazide 168 was reacted with carbon disulfide and ethanolic KOH to obtain the corresponding oxadiazole derivative 169 in 48% yield (Scheme 45).¹²⁴

Scheme 45^a^a(i) CS₂, EtOH/KOH.

The dipotassium salt of galactaric acid bis-hydrazidocarbodi-thioic acid **171**, obtained on condensation of galactaric acid bis-hydrazide **170** with carbon disulfide in the presence of ethanolic potassium hydroxide at ambient temperature, underwent base-catalyzed dehydrosulfurative cyclization on heating with ethanolic potassium hydroxide to form 82% of 1,4-bis(*S*-thioxo-1,3,4-oxadiazolin-2-yl)-galacto-tetritol structure **172** (Scheme 46).¹²⁵

Scheme 46^a^a(i) CS₂, EtOH/KOH; (ii) KOH/EtOH.

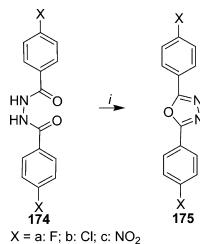
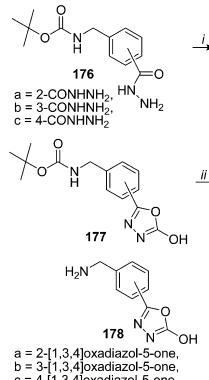
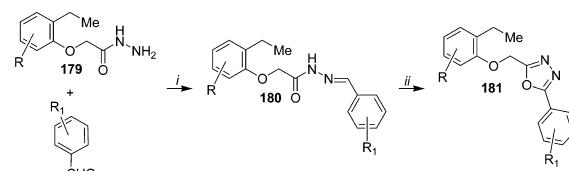
2,5-Diaryl-1,3,4-oxadiazoles **173**, obtained in 39–53% yields, were synthesized by refluxing the hydrazides **145** with trimethyl orthobenzoate (Scheme 47).¹²⁶

Scheme 47^a^a(i) MeOH, reflux, 24–48 h.

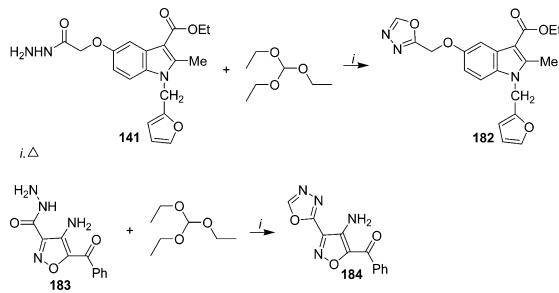
Thermal cyclodehydration of hydrazide 1,4-bis(4-aryl)-hydrazide **174** in *N*-cyclohexyl-2-pyrrolidone (CHP) yielded the oxadiazole-containing monomer, 2,5-bis(aryl)-1,3,4-oxadiazoles **175**, with 70–88% yields (Scheme 48).¹²⁷

Cyclization of hydrazides **176** in dry DMF at 0 °C containing triethylamine followed by addition of 1,1'-carbodiimidazole (CDI) afforded the *N*-boc-protected benzylamine oxadiazole intermediates **177**. The final *N*-boc deprotection in the presence of 4 M HCl afforded the [1,3,4]oxadiazol-2-one benzylamine building blocks **178** in 88–91% yields (Scheme 49).¹²⁸

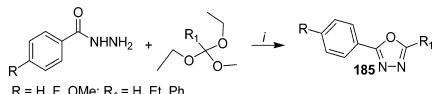
Schiff bases **180** underwent cyclization in the presence of iodobenzene diacetate (IBD) to yield 70–75% of oxadiazoles **181** (Scheme 50).¹²⁹

Scheme 48^a^a(i) CHP, 250 °C.Scheme 49^a^a(i) CDI, TEA, DMF, 0 °C to rt, 16 h; (ii) HCl, dioxane, rt, 8 h.Scheme 50^aR = 4-Me, 5-Cl, H, 4-Cl; R₁ = H, 2-OH, 4-NO₂, 4-Cl, 3-OMe, 4-OH^a(i) EtOH; (ii) PhI(OAc)₂.

A group of researchers have utilized triethylorthoformate to synthesize oxadiazole derivatives. Indole carbohydrazide **141** was heated with triethylorthoformate to form 69% of oxadiazole derivative **182** (Scheme 51).¹¹³ Similarly, reaction of **183** with triethylorthoformate underwented smooth cyclization to yield 82% of 4-amino-5-benzoyl-3-oxadiazolo[1,3,4]isoxazole **184** (Scheme 51).¹³⁰

Scheme 51^a^a(i) (Ac)₂O, Δ.

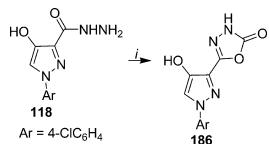
One-pot solvent-free synthesis of 1,3,4-oxadiazoles **185** by condensation of acid hydrazide and triethyl orthoalkanates under microwave irradiation was reported by Varma et al.¹³¹ (Scheme 52). This green protocol was catalyzed efficiently by solid

Scheme 52^a

^a(i) Nafion NR50, MWI.

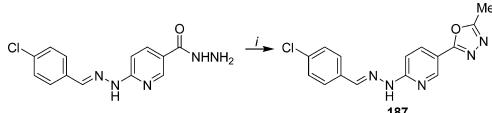
supported NafionNR50 to have excellent yields (80–90%). A novel and efficient synthesis of 2-styryl-1,3,4-oxadiazoles (yields 95–98%) by cyclocondensation of cinnamic acid hydrazide and triethyl orthoesters under microwave irradiation is also reported by Kudelko and co-workers.¹³²

Rostom et al.¹⁰³ explored the synthesis of oxadiazole derivative **186** (60% yield) from acid hydrazide **118** by one-pot cyclization of the latter in the presence of 1,1'-carbonyldiimidazole (CDI) in dry tetrahydrofuran (THF) (Scheme 53).

Scheme 53^a

^a(i) CDI, THF.

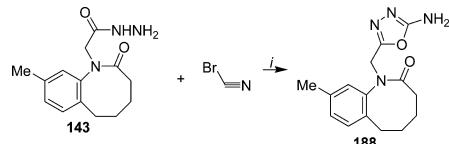
1,3,4-Oxadiazole derivative **187** was obtained with 64% yield from 6-(2-(4-chlorobenzylidene)hydrazino)nicotinic hydrazide by a [4 + 1] cyclocondensation reaction with triethylorthoacetate (Scheme 54).¹³³

Scheme 54^a

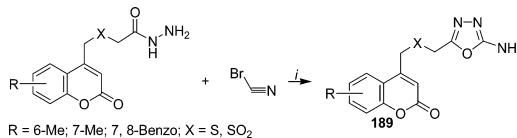
^a(i) MeC(OEt)_3 , reflux, 16 h.

Sureshbabu et al.¹³⁴ reported the synthesis of S-linked 1,3,4-oxadiazole-tethered N^{α} -protected peptidomimetics under sonication using acid hydrazides as synthetic precursor.

A group of researchers used cyanogen bromide as a source of single carbon for synthesis of the amino oxadiazole derivatives (Schemes 55 and 56). Treatment of hydrazide **143** with cyanogen bromide at 80–85 °C produced oxadiazole **188** in 73% yield (Scheme 55).¹¹⁵ Similarly, 2-oxo-2*H*-chromen-4-yl

Scheme 55^a

^a(i) MeOH, reflux, 80–85 °C.

Scheme 56^a

^a(i) MeOH, reflux, 60 °C.

acetohydrazide when treated with cyanogen bromide generated the amino oxadiazole derivative **189** in 78–87% yields (Scheme 56).¹³⁵ Kagthara and co-workers also utilized cyanogen bromide for condensation of benzoyl hydrazide **14** to form 90% of 1,3,4-oxadiazoles.³⁹

A series of 1,3,4-oxadiazole derivatives was formed from condensation of acid hydrazides with aromatic acids in phosphorus oxychloride (Table 2).

Adapting a similar procedure, Husain et al.¹⁴² also reported the synthesis of 1,3,4-oxadiazole derivatives from acid hydrazides.

Schwarz and co-workers¹⁴³ reported the synthesis of oxadiazole from acyl hydrazides **190**. When POCl_3 was employed in refluxing acetonitrile to effect cyclodehydration of **190a**, smooth conversion to a new heteroaromatic product was observed, which was considered to be either compound **194a** or **192**, via a second dehydration. Two mechanistic possibilities for double dehydration of **190a** were considered (Scheme 57). In scenario A, cyclodehydration to an hydrazido-oxazole **191** would be followed by attack of the carbonyl and dehydration to afford *1H*-pyrazolo[4,3-*d*]oxazole **192**, which is ruled out.¹⁴⁴ However, scenario B proceeded through formation of the oxadiazole amide **193a**, and subsequent dehydration of this intermediate by POCl_3 afforded exclusively imidazo[5,1-*b*][1,3,4]oxadiazole **194a** in 76% isolated yield. Following the same path, imidazo[5,1-*b*][1,3,4]oxadiazole **194b** was obtained in 73% yield. In addition, when 2-methylalanine was employed as the core subunit in acyclic precursor **195** only the oxadiazole amide **196** was obtained in 65% yield as cyclodehydration to the imidazo-oxadiazole was precluded by the presence of a quaternary carbon atom (Scheme 58).¹⁴³ Similarly, methylation of the amide nitrogen as in **197** afforded a substrate unable to participate in the second dehydration event, resulting in exclusive formation of 32% of **198**.

Various conjugated polymers with 1,3,4-oxadiazole structures show diverse characteristics such as thermal and chemical stability in addition to mechanical strength and rigidity, allowing them to be used in carbon fibers, high-performance fibers, reinforcing materials, and gas separation membranes.^{145,146} It is understood that oxadiazole shows such characteristics because its structures resemble the characteristics of phenyl structures.¹⁴⁷ Hence, recently, there has been much study on applying conjugated polymers with oxadiazole structures to electrooptics. Specifically, related to development of the multilevel structure of OLED (ITO/HTL/EL/ETL/metal) it is studied and developed widely as ETL.¹⁴⁸ In view of this, Lee et al.¹⁴⁹ synthesized oxadiazole polymer **202** (80% yield) with bipyridyl groups via thermal dehydrative cyclization of precursor polymer **201** using phosphorus oxychloride, which have an n-type semiconducting property due to electron deficiency and chelating efficiency because of the bipyridine scaffold (Scheme 59).

1-(5-Chloro-2-methoxyphenyl)-5-methyl-1*H*-pyrazole-4-carboxyhydrazide **203** on reaction with proper substituted benzoyl chlorides in the presence of pyridine yielded compounds **204**,

Table 2. Synthesis of 1,3,4-Oxadiazoles from Acid Hydrazides and Aromatic Acids

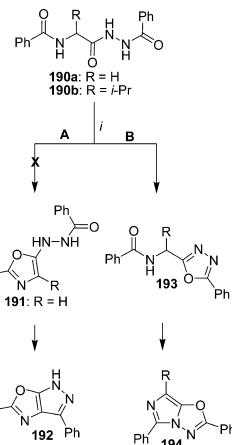
Sl. No.	Hydrazide	Aromatic acids	Product	Ref.	Yield %
1.		RCOOH R = Ph, 4-ClC ₆ H ₄ , 4-BrC ₆ H ₄ , 4-MeC ₆ H ₄ , 4-OMeC ₆ H ₄		136	59- 74
2.		RCOOH R = Ph, 4-BrC ₆ H ₄ , 2-ClC ₆ H ₄ , 4-ClC ₆ H ₄ , 2-OH C ₆ H ₄ , 2-OMeC ₆ H ₄		39	68- 79
3.		PhCOOH		103	75
4.			137	68- 80	
5.		RCOOH R = Ph, 4-MeC ₆ H ₄ , o-MeC ₆ H ₄ , p-OMeC ₆ H ₄ , o-ClC ₆ H ₄ , p-ClC ₆ H ₄ , o-HOC ₆ H ₄ , p-HOC ₆ H ₄ , p-NO ₂ C ₆ H ₄		138	81- 87
6.		RCOOH R = Ph, p-NH ₂ C ₆ H ₄ , o-NH ₂ C ₆ H ₄ , o-OH-C ₆ H ₄ , 6-methoxyquinolin-2-yl		139	63- 89
7.		R = 4-Me, 2-Me, 2-Cl, 4-Cl-2-Me, 4-Cl-3-Me		140	70- 81
8.			141	65	

which when heated with phosphorus oxychloride gave the respective oxadiazoles **205** in 66–80% yields (Scheme 60).¹⁵⁰

N'-(2-Cyano-3-(2,4-dichlorophenyl)acryloyl)benzohydrazide underwent ring closure upon refluxing with phosphorous oxychloride to give the oxadiazole derivative **206** in 75% yield (Scheme 61).¹⁵¹

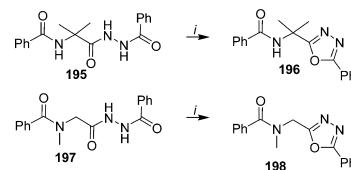
Condensation of hydrazinoisonicotinic acid hydrazide **144** with *p*-fluorobenzaldehyde yielded the benzylidene derivative **207**, which on further treatment with anhydrous sodium acetate in refluxing glacial acetic acid gave oxadiazole **208** in 85% yield. Acetylation of **208** with acetic anhydride afforded 70% of the oxadiazole derivative **209**. On the other hand, treatment of compound **207** with acetic acid in the presence of sodium acetate and bromine gave oxadiazole **210** in 85% yield (Scheme 62).¹¹⁶

Scheme 57^a



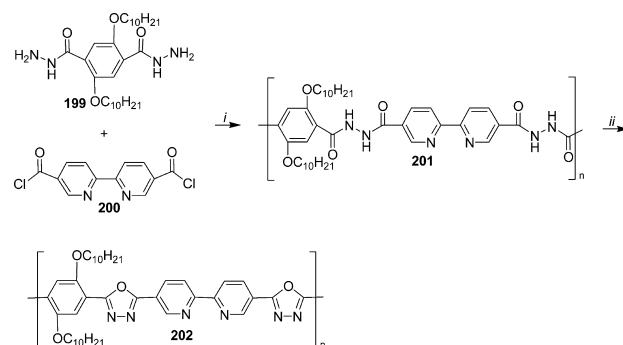
^a(i) POCl₃, MeCN.

Scheme 58^a



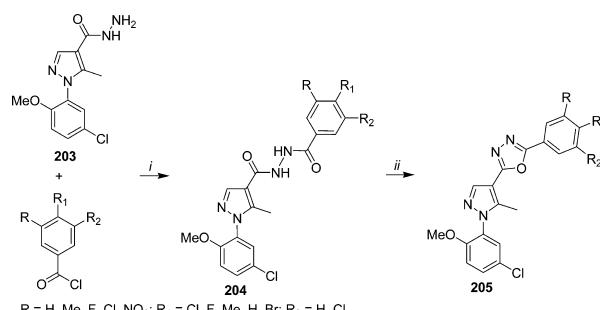
^a(i) POCl₃, MeCN.

Scheme 59^a



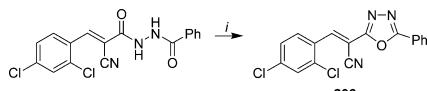
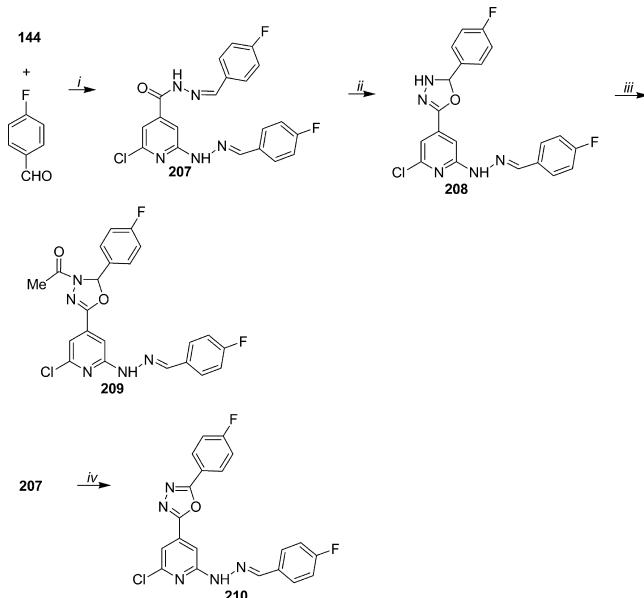
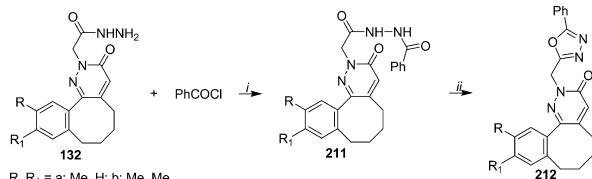
^a(i) TEA, CHCl₃; (ii) POCl₃.

Scheme 60^a



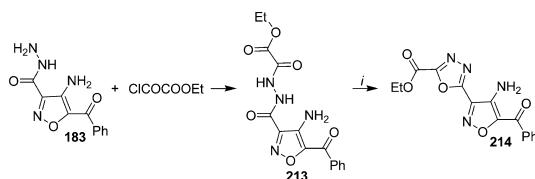
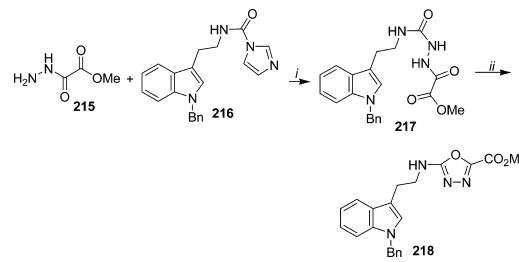
^a(i) Dichloromethane, pyridine; (ii) POCl₃, 120 °C.

Dehydrative ring closure of the intermediate **211** with thionyl chloride furnished the corresponding oxadiazole derivatives **212** in 28–30% yield (Scheme 63).¹⁰⁶

Scheme 61^a^a(i) SOCl_2 .Scheme 62^a^a(i) EtOH; (ii) AcOH/AcONa; (iii) Ac_2O ; (iv) AcOH/ Br_2 , AcONa.Scheme 63^a^a(i) TEA, DMF; (ii) SOCl_2 .

Treatment of the hydrazide 183 with ethyloxalyl chloride in the presence of anhydrous pyridine produced the corresponding ethyl{2-[(4-amino-5-benzoylisoxazol-3-yl)carbonyl]hydrazine} (oxo)acetate 213, which was readily cyclized to ethyl-5-(4-amino-5-benzoylisoxazol-3-yl)-[1,3,4]oxadiazole-2-carboxylate 214 (68% yield) under acidic conditions with thionyl chloride (Scheme 64).¹³⁰

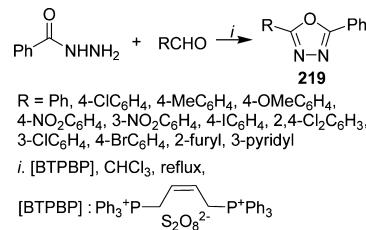
The 1,3,4-oxadiazole 218 bearing the tethered indole dipolarophile was prepared from 1-benzyltryptamine¹⁵² (Scheme 65) in a three-step sequence. Treatment of urea 216

Scheme 64^a^a(i) SOCl_2 .Scheme 65^a^a(i) AcOH, THF; (ii) TsCl , TEA.

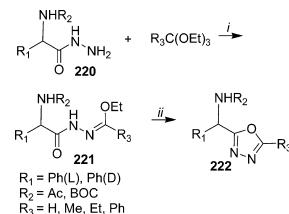
with methyl oxalyl hydrazide 215¹⁵³ provided 217. Dehydration of 217 on treatment with TsCl and TEA afforded the oxadiazole 218 (81% for two steps).¹⁵⁴

Badri et al.¹⁵⁵ reported an efficient, one-pot, solution-phase preparation of 2,5-disubstituted-1,3,4-oxadiazoles 219 (60–81% yields) directly from the acyl hydrazide and aromatic aldehydes using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant under nonaqueous and aprotic conditions (Scheme 66).

Scheme 66



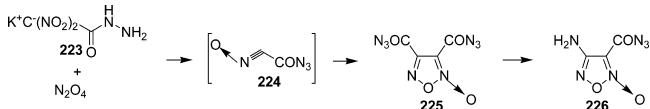
The two enantiomers of *N*-protected hydrazides of phenylglycine 220 were subjected to heating with an excess of triethyl orthoesters ($R_3 = \text{H, Me, Et, Ph}$) to yield the acyclic derivatives of 1-(alkanecarbonyl)-2-ethoxymethylenehydrazines 221 as the only products. Introduction of an acidic solvent (glacial acetic acid) to the reaction mixture resulted in formation of 2,5-disubstituted-1,3,4-oxadiazoles 222 in low to moderate yields (38–80%) (Scheme 67).¹⁵⁶

Scheme 67^a^a(i) AcOH; (ii) AcOH.

Kulikov and co-workers¹⁵⁷ reported the synthesis of 4-amino 1,2,5-oxadiazole 226 on treatment of potassium salt of dinitroacetic acid hydrazide 223 with N_2O_4 via intermediate formation of azidocarbonyl-formonitrile oxide 224 and diazide 225. The low-yield diazide 225 underwent Curtius rearrangement of one of two azidocarbonyl groups to give a low yield of amino 1,2,5-oxadiazole 226 (16%) (Scheme 68).

Use of hydrazides as amine components in the Petasis 3-component coupling reaction (CCR) had been investigated by

Scheme 68



Nielsen et al.¹⁵⁸ (Table 3). Hydrazido alcohols **227** were obtained from reaction of hydrazides, boronic acids, and

Table 3. BTC-Mediated Oxadiazolone and Oxazolidinone Formation

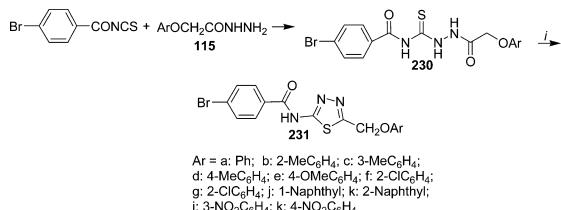
entry	R ₁	R ₂	Oxadiazolone product (yield %) ^a	Oxazolidinone product (yield %) ^a
1.			85	65
2.			86	92
3.			87	84
4.			88	88

^aIsolated yield after flash column chromatography.

hydroxyaldehyde. The resulting hydrazido alcohols **227** were selectively converted into oxazolidinone **228** and oxadiazolone ring systems **229** via triphosgene-mediated cyclization processes by slow addition of 1 equiv of bis(trichloromethyl)carbonate (BTC) and fast addition of a large excess of BTC, respectively.

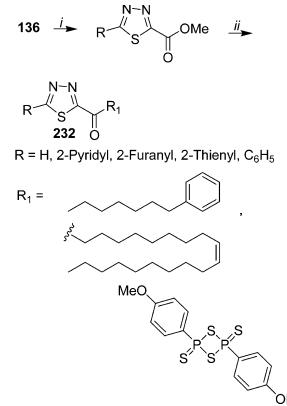
3.3.2. Thiadiazoles and Their Fused Derivatives. 1,3,4-Thiadiazoles are a class of heterocycles which have attracted significant interest in medicinal chemistry, and they have a wide range of pharmaceutical and biological activities including antibacterial,^{159–162} antifungal,^{161,162} antitubercular,^{163–165} analgesic,¹⁶⁶ antiinflammatory,^{161,162,166} and leishmanicidal¹⁶⁷ agents.

4-Bromobenzoyl isothiocyanate on treatment with aryloxyacetic acid hydrazides **115** gave 1,4-disubstituted thiosemicarbazides **230**, which when refluxed with glacial acetic acid underwent intramolecular dehydrative cyclization to afford the corresponding substituted 1,3,4-thiadiazoles **231** in 90–97% yields (Scheme 69).¹⁶⁸

Scheme 69^a

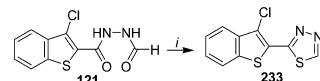
^a(i) Reflux, AcOH.

The diacyl hydrazide **136** underwent cyclization upon treatment with Lawesson's reagent, i.e., 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide, to yield methyl 1,3,4-thiadiazole-2-carboxylates, which underwent subsequent addition of the requisite side chain (R_1) to the methyl ester via a metal–halogen exchange of the corresponding alkylbromide to give the α -ketothiadiazoles **232** in low to moderate yields (Scheme 70).^{109,110}

Scheme 70^a

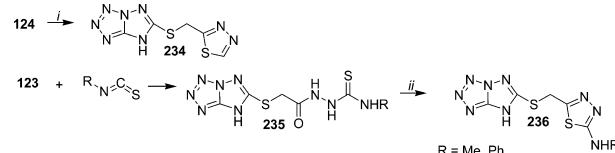
^a(i) Lawesson's reagent; (ii) R₁Li or R₁MgBr.

2-(3-Chloro-1-benzothien-2-yl)-1,3,4-thiadiazole **233** was obtained in 53% yield on treatment of 3-chloro-2-(*N*-formyl acid hydrazide)benzo[b]thiophene **121** with phosphorus pentasulphide under refluxing xylene solution (Scheme 71).³²

Scheme 71^a

^a(i) P₂S₅, xylene, reflux.

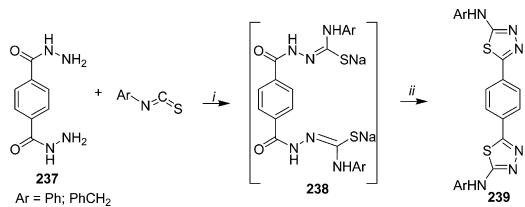
Refluxing acetylhydrazine **124** with phosphorus pentasulfide in toluene formed 1,3,4-thiadiazole **234** in 61% yield, while dehydrocyclization of thiosemicarbazide **235** with phosphoryl trichloride gave the thiadiazole **236** with 53–54% yields (Scheme 72).¹⁰⁴

Scheme 72^a

^a(i) P₂S₅, toluene; (ii) POCl₃.

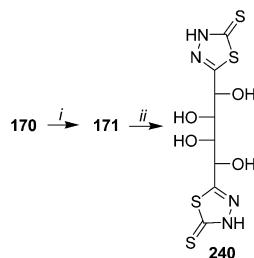
Refluxing terephthalic acid hydrazide **237** with phenyl/benzyl isothiocyanate in DMF in the presence of sodium hydride and concentrated hydrochloric acid formed nonisolable intermediate **238**, which was subsequently refluxed with phosphoryl chloride to give bis-thiadiazoles **239** with yields as follows: Ar = Ph (87%) and PhCH₂ (92%) (Scheme 73).¹⁶⁹

Dipotassium salt of galactaric acid bis-hydrazidocarbodithioic acid **171** underwent acid-catalyzed dehydrocyclization with

Scheme 73^a

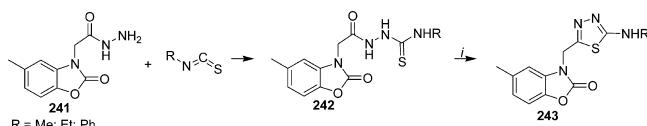
^a(i) NaH/DMF, conc HCl; (ii) POCl₃.

sulfuric acid in methanol at room temperature to give 1,4-bis(S-thioxo-1,3,4-thiadiazolin-2-yl)-galacto-tetritol **240** (82% yield) (Scheme 74).¹²⁵

Scheme 74^a

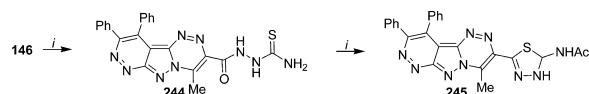
^a(i) CS₂, EtOH/KOH; (ii) H₂SO₄/MeOH.

1,3,4-Thiadiazoles **243** were obtained in 47–93% yields by cyclization of thiosemicarbazides **242** with orthophosphoric acid (Scheme 75).¹⁷⁰

Scheme 75^a

^a(i) H₃PO₄.

Hydrazide **146**, when heated with either ammonium thiocyanate or potassium thiocyanate, afforded the 4-methyl-9,10-diphenylpyridazino [3',4':3,4]pyrazolo[5,1-*c*]-1,2,4-triazine-3-carbothiosemicarbazide **244**. The cyclodehydration of **244** in the presence of acetyl chloride led to formation of 2-acetylamino-1,3,4-thiadiazole derivative **245** in 57% yield (Scheme 76).¹¹⁸ Similarly, Para et al.¹⁷¹ also reported the

Scheme 76^a

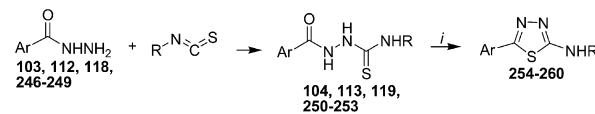
^a(i) NH₄SCN or KSCN; (ii) AcCl.

synthesis of different amino-1,3,4-thiadiazoles from different 3,4,5-*n*-trialkoxybenzoylthiosemicarbazides in the presence of acetyl chloride.

Reaction of acid hydrazide **103**, **112**, **118**, and **246–249** with alkyl/aryl isothiocyanate yielded the corresponding thiosemicarbazides **104**, **113**, **119**, and **250–253**. Dehydrative cyclization

of thiosemicarbazide derivatives in cold concentrated sulfuric acid resulted formation of 1,3,4-thiadiazole **254–260** (Table 4).

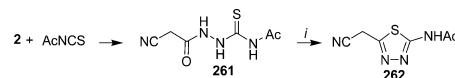
Table 4. Synthesis of 1,3,4-Thiadiazoles 254–260 by Dehydrative Cyclization of Thiosemicarbazides



Sl. No.	Ar	Product	Ref.	Yield %
1.	F-phenyl-4-fluorophenyl-OH 103		98	45–93
2.	N(Me)-imidazole-2-yl-Ar' 112 Ar' = 4-ClC ₆ H ₄		101	75–80
3.	N(Me)-imidazole-2-yl-Ar' 118 Ar' = 4-ClC ₆ H ₄		103	90
4.	2,3-dichlorophenyl-4-chlorophenyl-S 246		172	54–59
5.	2,3-dimethyl-4-phenyl-piperidin-2-one 247		173	50
6.	2,3-dimethyl-4-phenyl-piperidin-2-one 248 Ar' = 3,4-Me ₂ C ₆ H ₃		174	72–84
7.	2-bromo-4-(2-bromophenyl)-5-methyl-1,3-dihydro-2H-1,4-diazepine-2-thione 249		175	97–98

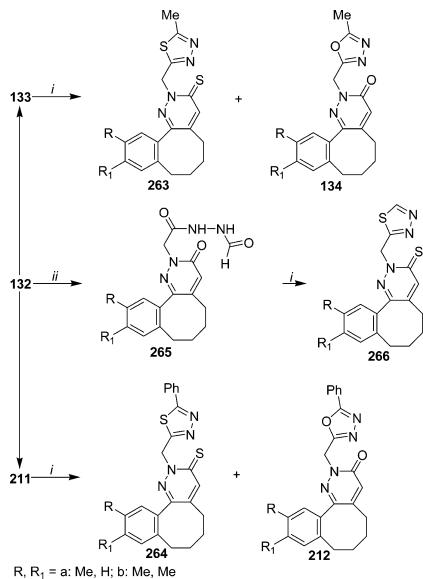
Condensation of acetyl isothiocyanate with hydrazide **2** gave thiocarbamoyl derivative **261**, which underwent intramolecular cyclization in refluxing acetic acid to produce 55% of *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)acetamide **262** (Scheme 77).¹⁷⁶

N-Acetyl derivative **133** of pyridazinyl-2-acetylhydrazide **132** on reaction with phosphorus pentasulfide afforded thiadiazolo compound **263** with 26–30% yields along

Scheme 77^a

^a(i) AcOH.

with oxadiazolo derivative **134** as a minor product. Similarly, the intermediate **211** when treated with phosphorus pentasulfide furnished 30–35% of thiadiazoles **264** along with oxadiazolo derivative **212** as a minor product. On the other hand, treatment of hydrazide **132** with formic acid yielded **265**, which on dehydrative ring closure by treatment with phosphorus pentasulfide in xylene afforded thiadiazole derivative **266** in low yields (23–25%) (Scheme 78).¹⁰⁶

Scheme 78^a

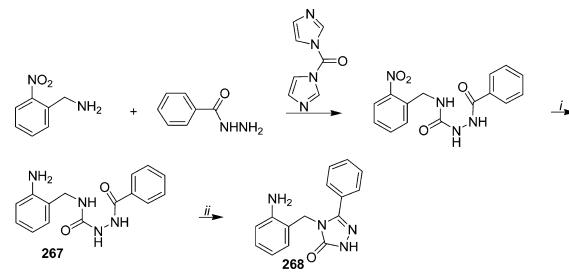
^a(i) P₂S₅, xylene; (ii) HCOOH.

3.3.3. Triazoles and Their Fused Derivatives. 1,2,4-Triazoles and their derivatives represent an interesting class of compounds possessing a wide spectrum of biological activities. A large number of 1,2,4-triazole-containing ring systems exhibit antibacterial,^{177–182} antifungal,^{179–183} antitubercular,^{184–186} analgesic,^{187,188} antiinflammatory,^{189–191} anticancer,^{192,193} anticonvulsant,^{194,195} antiviral,^{196,197} insecticide,¹⁹⁸ antidepressant,¹⁹⁹ and central nervous system (CNS)¹⁵⁹ activities. Moreover, there are a number of antimicrobial compounds containing a 1,2,4-triazole ring in their structures such as Fluconazole, Itraconazole, Voriconazole, Rauconazole, and Posaconazole that are important antifungal drugs.²⁰⁰

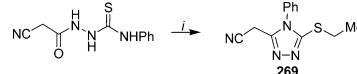
Reaction of 2-nitrobenzylamine with 1,1'-carbonyldiimidazole and benzhydrazide formed the 1-benzoyl-4-(2-nitrobenzyl)-semicarbazide. Catalytic hydrogenation of the nitro group in the presence of 10% palladium on charcoal gave the corresponding 1-benzoyl-4-(2-aminobenzyl)semicarbazide derivative **267**. Cyclization of amino derivative **267** in 5% potassium carbonate led to formation of 75% of 4-(2-aminobenzyl)-3-phenyl-4,5-dihydro[1,2,4]triazol-5-one **268** (Scheme 79).²⁰¹

3-Ethylsulfanyl-5-cyanomethyl-4-phenyl-1,2,4-triazole **269** was prepared in 90% yield by reaction of 1-cyanoacetyl-4-phenylthiosemicarbazide with ethyl iodide in DMF and in the presence of anhydrous potassium carbonate at room temperature (Scheme 80).²⁰²

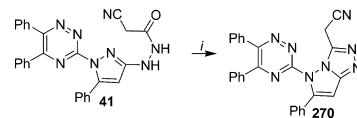
[5-(5,6-Diphenyl-1,2,4-triazin-3-yl)-6-phenyl-5*H*-pyrazolo[5,1-*c*][1,2,4]triazol-3-yl] acetonitrile **270** was obtained in 70% yield on refluxing the hydrazide **41** in glacial acetic acid and anhydrous sodium acetate (Scheme 81).²⁰³

Scheme 79^a

^a(i) H₂/Pd; (ii) K₂CO₃.

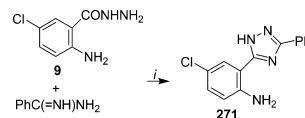
Scheme 80^a

^a(i) EtI, K₂CO₃/DMF.

Scheme 81^a

^a(i) AcONa, AcOH.

Francis et al.³⁷ studied the synthesis of 3-(2-amino-5-chlorophenyl)-5-phenyl-1,2,4-triazole **271** (62% yield) on reaction of 2-amino-5-chlorobenzohydrazide **9** with benzamidine (Scheme 82).

Scheme 82^a

^a(i) PhCl, EtOH, reflux.

Reaction of acid hydrazide **4**, **103**, **106**, **112**, **118**, **123**, **139**, **247**, **249**, and **272–278** with isothiocyanate derivatives resulted in formation of the corresponding thiosemicarbazides **279**, **104**, **107**, **113**, **119**, **280**, **281**, **251**, **253**, and **282–288**. Alkaline cyclization of the thiosemicarbazides using sodium hydroxide afforded the 1,2,4-triazolin-3-thiones **289–304** (Table 5).

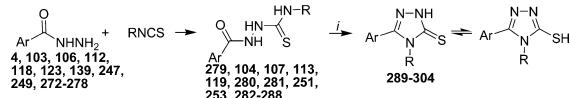
Hydrazide **2** treated with different ethoxycarbonylhydrazones **305** to generate respective 3-alkyl-4-carbethoxyamino-5-cyano-methyl-4*H*-1,2,4-triazole derivatives **306** in 58–73% yields (Scheme 83).²¹²

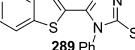
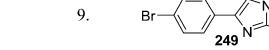
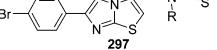
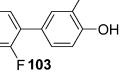
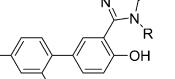
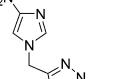
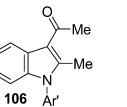
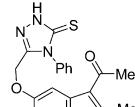
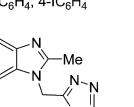
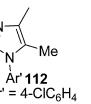
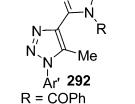
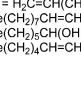
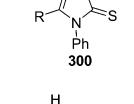
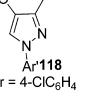
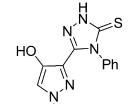
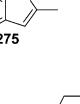
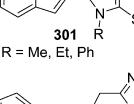
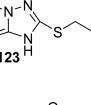
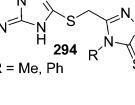
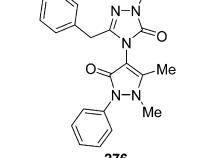
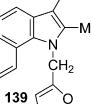
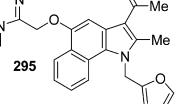
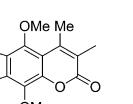
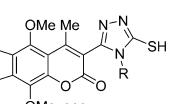
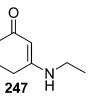
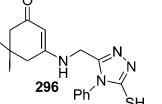
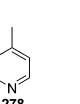
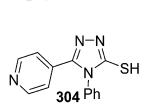
Reaction of **2** with lactim ether produced 89% of 1-cyanomethyl-4*H*,5,6-dihydro-1,2,4-triazolo[4,3-*a*]-benz[f]-azepine **308** (Scheme 84).²¹³

Hydrazinolysis of 1,3,4-oxadiazole¹¹¹ moiety **154** yielded 48% of 4-amino-4*H*-1,2,4-triazole-3-thiol structure **309** (Scheme 85).¹⁰⁴ A series of 1,2,4-triazole derivatives prepared following a similar procedure was reported by Mohan,²¹⁴ Dhiman,²¹⁵ Mostafa,¹²⁵ Demirbas,^{208,210} Kumar,²¹⁶ Prasad,²¹⁷ Seleim,²¹⁸ and Vainilavicius et al.²¹⁹

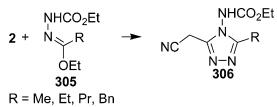
Reaction of terephthalic acid hydrazide **237** with phenyl/benzyl isothiocyanate and phenyl isocyanate in DMF in the presence of sodium hydride gave the nonisolable intermediates

Table 5. Synthesis of 1,2,4-Triazolin-3-thiones 289–304 by Alkaline Cyclization of Thiosemicarbazides

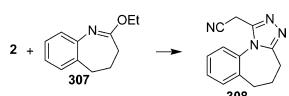


Sl. No.	Ar	Product	Ref.	Yield %	Sl. No.	Ar	Product	Ref.	Yield %
1.			32	48	9.			175	94-99
2.			98	67-90	10.			203	70-85
3.			34	53-64	11.			204,2	89-92
4.			101	63	12.			206	67-85
5.			103	85-90	13.			207	91-98
6.			104	61-71	14.			208	76-87
7.			33	83	15.			209	70
8.			173	60	16.			210,2	83

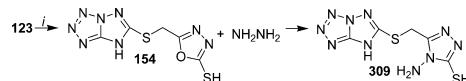
Scheme 83



Scheme 84



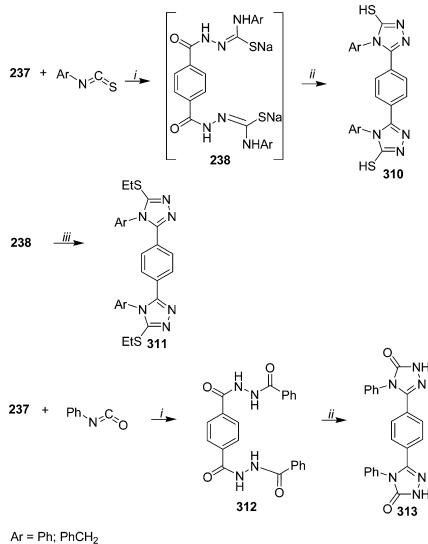
Scheme 85^a



^a(i) CS₂, alcholic KOH.

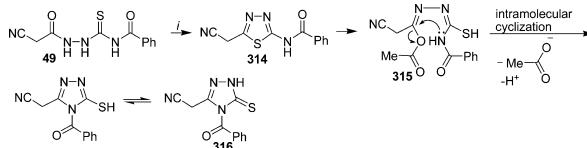
238 and **312**, respectively, which upon cyclization with NaOH furnished the corresponding bis-1,2,4-triazoles **310** and 5,5'-(1,4-phenylene)bis(4-phenyl-3-oxo-1,2,4-triazole) **313** in 65–69% and 64% yields, respectively. Furthermore, reaction of **238** with ethyl iodide at room temperature catalyzed by anhydrous

potassium carbonate yielded 58–62% of the triazole product **311** (Scheme 86).¹⁶⁹

Scheme 86^a

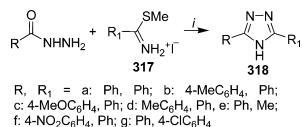
^a(i) NaH/DMF, conc HCl; (ii) NaOH; (iii) EtI/K₂CO₃.

Refluxing hydrazide **49** in acetic acid initially produced 1,3-thiadiazole derivative **314**, which underwent ring opening under the prevailing reaction conditions and then ring closing of the intermediate **315** to afford the 1,2,4-triazole thione **316** in 86% yield (Scheme 87).⁶⁷

Scheme 87^a

^a(i) AcOH, reflux, 5 h.

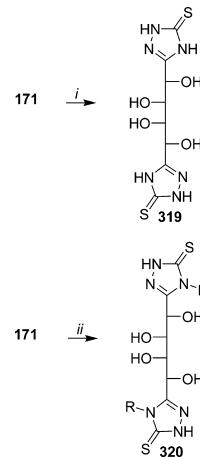
Three-component condensation reaction of acid hydrazides, S-methyl isothioamide hydroiodides **317**, and ammonium acetate on the surface of silica gel under microwave irradiation gave the corresponding 3,5-disubstituted-1,2,4-triazoles **318** in 66–91% yields (Scheme 88).²²⁰

Scheme 88^a

^a(i) NH₄⁺OAc⁻, SiO₂, TEA, MW.

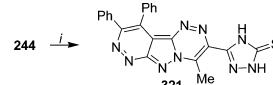
Condensative cyclization with concomitant dehydrosulfuration and dehydration of the salt of galactaric acid bis-hydrazidocarbodithioic acid **171** has been accomplished by heating with ammonium acetate to give 71% of the 1,4-bis(S-thioxo-1,2,4-triazolin-3-yl)-galacto-tetritol **319**, and 1,4-bis(4-acetyl-5-thioxo-1,2,4-triazolin-3-yl)-galacto-tetritol **320a** (74% yield) and 1,4-bis(4-methyl-5-thioxo-1,2,4-triazolin-3-yl)-galac-

to-tetritol **320b** (77% yield) were achieved on heterocyclization of the dithioate **171** with acetamide and methylamine, respectively (Scheme 89).¹²⁵

Scheme 89^a

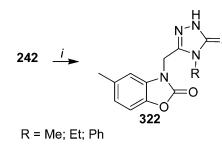
^aR = a, Me; b, Ac (i) AcONH₄; (ii) RNH₂.

The thiosemicarbazide **244** was cyclized under a basic condition to produce the 1,2,4-triazole-3-thione derivative **321** in 83% yield (Scheme 90).¹¹⁸ A series of 1,2,4-triazole derivatives following a similar procedure was reported by Mohan²¹⁴ and Zhang et al.¹³⁶

Scheme 90^a

^a(i) NaOH.

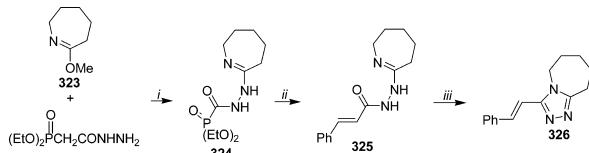
Reaction of thiosemicarbazides **242** with triethylamine in ethanol underwent smooth cyclization through dehydration to afford 1,2,4-triazole-5(4H)-thione **322** in 82–97% yields (Scheme 91).¹⁷⁰

Scheme 91^a

^a(i) TEA, EtOH.

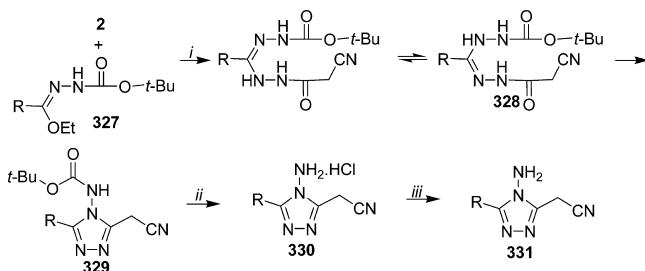
Condensation of 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine **323** with diethoxyphosphinyl acetic acid hydrazide in methylene chloride at room temperature provided the amidrazone **324**. Subsequently, the Horner–Emmons reaction was carried out with benzaldehyde in NaOEt/EtOH at room temperature to give 3-phenyl-*N'*-(4,5,6,7-tetrahydro-3*H*-azepin-2-yl)acrylic acid hydrazide **325**. Cyclodehydration of **325** was accomplished in refluxing toluene with a catalytic amount of acetic acid to afford *trans*-3-styryl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-*a*]azepine **326** in 71% yield (Scheme 92).²²¹

Compound **327** was reacted with cyanoacetic acid hydrazide to obtain the corresponding 3-alkyl-4-*tert*-butoxycarbonylamino-

Scheme 92^a

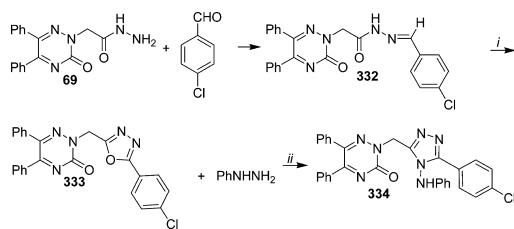
^a(i) CH₂Cl₂, rt; (ii) NaOEt/EtOH, PhCHO; (iii) AcOH (cat.), toluene, reflux.

5-cyanomethyl-4*H*-1,2,4-triazoles **329** in 37–81% yields via the intermediates **328**. Compounds **329** were converted to the corresponding 3-alkyl-4-amino-5-cyanomethyl-4*H*-1,2,4-triazole hydrochlorides **330** in good yields in the presence of 6 N HCl, which on further treatment with 2 N KOH led to formation of 3-alkyl-4-amino-5-cyanomethyl-4*H*-1,2,4-triazoles **331** (44–79% yields) (Scheme 93).²²²

Scheme 93^a

^a(i) Oil bath 115 °C; (ii) 6N HCl; (iii) 2N KOH.

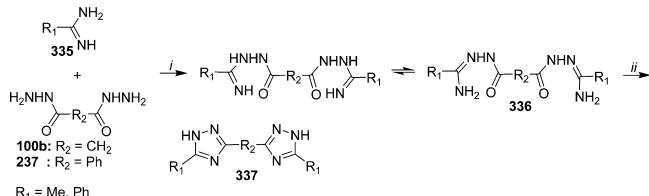
Treatment of hydrazone **332** of *N*-triazino-2-acetic acid hydrazide **69** with FeCl₃–ethanol afforded 1,3,4-oxadiazole **333**, which on condensation with phenylhydrazine through ANRORC (addition of the nucleophile, ring opening, and ring closure) gave 65% of 1,2,4-triazole **334** (Scheme 94).⁷⁴

Scheme 94^a

^a(i) FeCl₃/EtOH; (ii) EtOH.

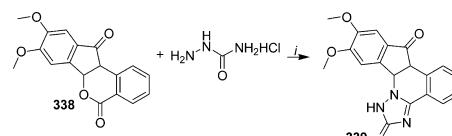
The intermediate acylamidrazone **336** were obtained from reactions of acetamidine or benzamidine **335** with an malonodihydrazide **100b** or terephthalobishydrazide **237** in the presence of sodium ethoxide and underwent thermal cyclization to form the corresponding 1,2,4-triazoles **337** in moderate to high yields (R₁, R₂ = Me, CH₂ (92%); Me, Ph (89%); Ph, CH₂ (93%); Ph, Ph (88%)) (Scheme 95).²²³

[1,2,4]Triazolo[2,3-*a*]isoquinoline derivative **339** was obtained as the sole product in fairly good yield (80%) upon treatment of compound **338** with semicarbazide hydrochloride (Scheme 96)²²⁴ via nucleophilic ring opening and nitrogen attack at the carbonyl group of the δ -lactone (tetrahedral

Scheme 95^a

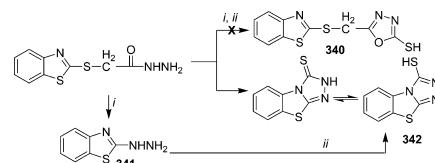
^a(i) EtOH/rt, 24 h; (ii) Δ .

mechanism) followed by 1,5-exo-trig cyclization with elimination of water.

Scheme 96^a

^a(i) Py, Δ .

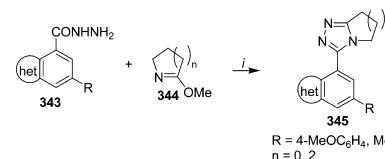
2-Benzothiazolylthioacetyl hydrazide generally when reacted with CS₂ in ethanolic KOH unexpectedly formed *s*-triazolo[3, 4-*b*]benzothiazole-3-thiol **342** instead of 5-substituted-1,3,4-oxadiazol-2-thiol **340**. Alternatively, the authors successfully obtained **342** through the isolated intermediate 2-benzothiazolylhydrazine **341** generated via intramolecular addition–elimination reaction of the substrate 2-benzothiazolylhydrazide in the presence of ethanolic KOH. Hydrazine **341** reacted with KOH and CS₂ further to convert into *s*-triazolo[3, 4-*b*]-benzothiazole-3-thiol **342** (Scheme 97).²²⁵

Scheme 97^a

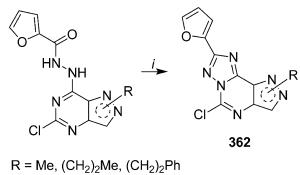
^a(i) Ethanolic KOH; (ii) CS₂, KOH.

Hydrazides **343** underwent the standard combinatorial transformations including cyclo-*o*-methyl amide coupling with **344** in refluxing 2-propanol to form 1,2,4-triazoles **345** (Scheme 98)²²⁶ in moderate to good yields.

Reaction of α -hydroxyacid hydrazides **346** and orthoesters in ethanol–acetic acid solution had been studied to obtain a series of 4-acylamino-1,2,4-triazoles **349** as the final products in 25–64% yields by Zielinski and co-workers²²⁷ via intermediates **347** and **348** (Scheme 99).

Scheme 98^a

^a(i) 2-Propanol.

Scheme 106^a

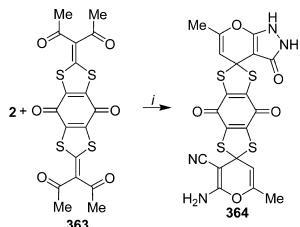
R = Me, $(\text{CH}_2)_2\text{Me}$, $(\text{CH}_2)_2\text{Ph}$

^a(i) HMDS, BSA, 120 °C, 18 h.

anticoagulant, anticancer, and antianaphylactic activity.²³⁶ Moreover, pyrans are useful intermediates for synthesis of various compounds.^{237–240}

Furthermore, pyrans represent building blocks of a series of natural products,²⁴¹ and consequently, numerous methods have been reported for synthesis of these compounds.

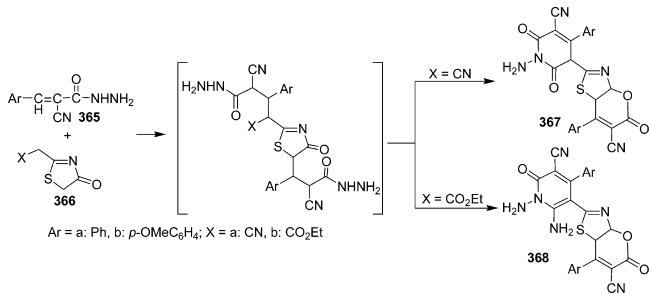
Treatment of bisdithiolo benzoquinone 363 with 2 in a 1:2 molar ratio in refluxing ethanol containing piperidine as a catalyst gave 63% of dispiro[dipyrano-(2,4':6,4'')-bidithiolo-(4,5-b:4',5'-e)-4,8-benzoquinone] derivative 364 (Scheme 107).²⁴²

Scheme 107^a

^a(i) EtOH/piperidine, reflux, 4.5 h.

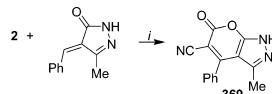
Pyran[2,3-*d*]-thiazole derivatives 367 was obtained in 86–91% yields from addition of two molecules of 2-cyanomethyl-2-thiazolin-4-one 366a (*X* = CN) to one molecule of each of the benzylidene derivatives of cyanoacetic acid hydrazide 365 with loss of one molecule of hydrazine. Analogously, 366b (*X* = CO₂Et) reacted with 365 to give 84–86% of the pyran[2,3-*d*]-thiazoles 368 (Scheme 108).²⁴³

Scheme 108



A yield of 78% of 3-Methyl-6-oxo-4-phenyl-1,6-dihydropyran-[2,3-*c*]pyrazole-5-carbonitrile 369 was prepared via cyclocondensation of 2 with 4-benzylidene-3-methyl-2-pyrazolin-5-one (Scheme 109).²⁴³

3.4.2. Pyridine and Their Fused Derivatives. The pyridine nucleus is an important heteroaromatic class of compounds with a wide range of activities, and it is present in many drugs, vitamins, food-flavoring agents, plant products, dyes, rubber products, adhesives, insecticides, and herbicides.

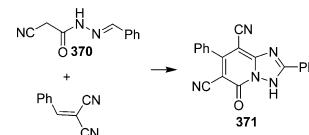
Scheme 109^a

^a(i) Δ.

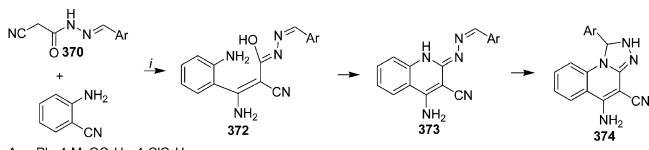
cides.^{244,245} In view of these findings, it was contemplated to design and synthesize some new pyridine derivatives.

Reaction of *N*-arylmethylened-2-cyanoacetohydrazides 370 when treated with benzylidenemalononitrile afforded 72% of [1,2,4]triazolo[1,5-*a*]pyridin-5(3H)-one derivative 371 (Scheme 110).²⁴⁶

Scheme 110

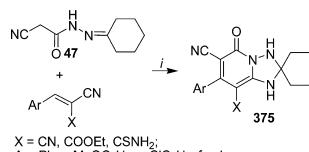


Anthrilonitrile was fused with different *N*-arylidenes 370 of cyanoacetohydrazide 2 in the presence of triethylamine to afford triazolo[4,3-*a*]quinoline derivatives 374 in 60–75% yields through the initial Thorpe–Ziegler addition²⁴⁷ of the methylene group of 370 to the CN group of anthrilonitrile to afford the acyclic intermediates 372 followed by loss of a water molecule to afford the intermediates 373, which in turn undergo further cyclization via addition of the NH to the activated C=N to give the final products 374 (Scheme 111).²⁴⁸

Scheme 111^a

^a(i) TEA, oil bath at 170 °C.

Refluxing hydrazone derivative 47 and appropriate arylidenes of activated nitriles in ethanolic piperidine yielded spiro[cyclohexane-1,2'-[1,2,4]triazolo[1,5-*a*]pyridine]-S'-(1'H)-one derivatives 375 (Scheme 112).^{66,249}

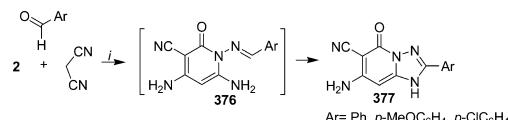
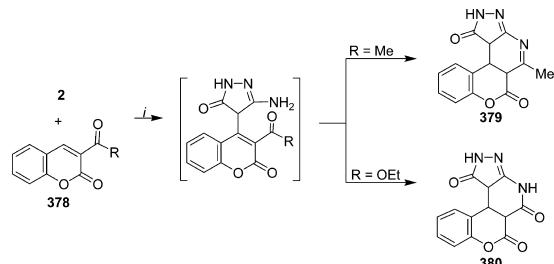
Scheme 112^a

X = CN, COOEt, CSNH₂; Ar = Ph, *p*-MeOC₆H₄, *p*-ClC₆H₄, furyl

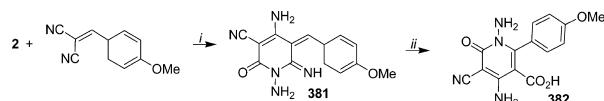
^a(i) EtOH, piperidine.

One-pot synthesis of [1,2,4]triazolo[1,5-*a*]pyridin-5(1H)-one derivatives 377 was reported in 82–89% yields by reaction of 2 with malononitrile and aromatic aldehyde (Scheme 113).²⁵⁰

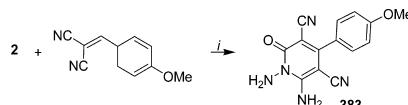
Treatment of 2 with 3-acetyl- and 3-carboethoxy coumarin 378 in ethanol containing a catalytic amount of piperidine under reflux afforded pyrazolo[3,4-*b*]pyridine-1,6-dione 379 and 380 in 70% and 60% yields, respectively (Scheme 114).²⁴⁸

Scheme 113^a^a(i) Py, EtOH.Scheme 114^a^a(i) EtOH, piperidine, reflux.

Cyclocondensation of hydrazide **2** with (4-methoxybenzylidene)malononitrile in ethanol in the presence of triethylamine afforded 1-aminopyridine derivative **381**, which underwent hydrolysis followed by ring opening and recyclization on refluxing in 95% aqueous ethanol and triethylamine to give 70% of 1,4-diamino-5-cyano-2-(4-methoxyphenyl)-6-oxo-1,6-dihdropyridine-3-carboxylic acid **382** (Scheme 115).²⁵¹

Scheme 115^a^a(i) EtOH/TEA; (ii) EtOH (95%)/TEA, Δ .

Martin and co-workers reinvestigated cyclocondensation of **2** with (4-methoxybenzylidene)malononitrile either at room or reflux temperature in absolute or 96% ethanol to achieve 1,6-diamino-4-(4-methoxyphenyl)-3,5-dicyano-2-pyridone **383** (Scheme 116).²⁵²

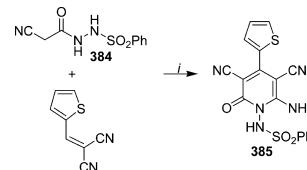
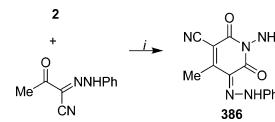
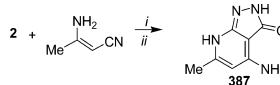
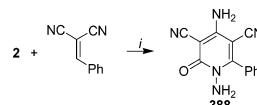
Scheme 116^a^a(i) EtOH/TEA, 24 h, Δ .

Reaction of cyanoaceto-*N*-arylsulfonylhydrazide **384** with 2-((thiophen-2-yl)methylene) malononitrile furnished 90% of *N*-phenylsulfonylamino-2-pyridone **385** (Scheme 117).²⁵³

Treatment of **2** with phenylhydrazone-3-oxobutyronitrile yielded pyridine-2,6-dione derivative **386** (65% yield) (Scheme 118).^{254,255}

Cyclocondensation of **2** with β -aminocrotononitrile produced pyrazolo[3,4-*b*]pyridine derivative **387** in 75% yield (Scheme 119).²⁵⁶

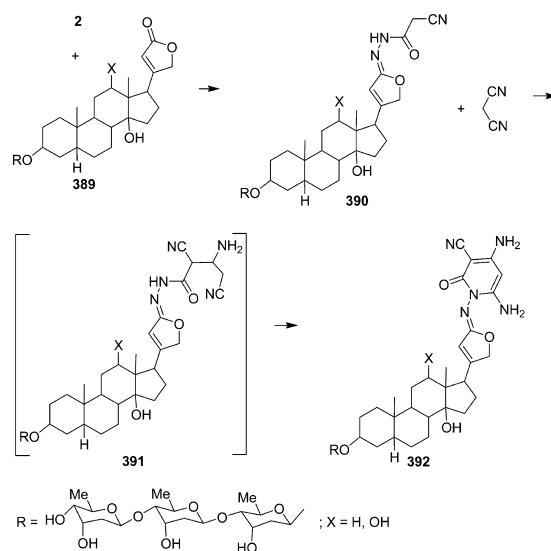
Reaction of **2** with benzylidenemalononitrile provided pyridone derivative **388** (Scheme 120).²⁵⁷

Scheme 117^a^a(i) EtOH/piperidine.Scheme 118^a^a(i) EtOH/TEA.Scheme 119^a^a(i) NaOMe, MeOH; (ii) AcOH.Scheme 120^a^a(i) EtOH/TEA.

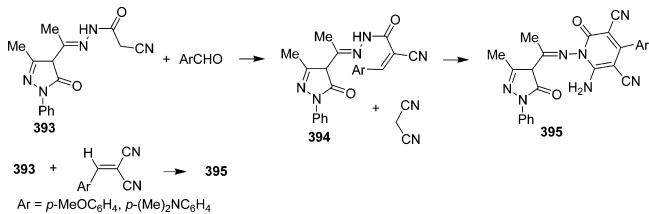
Treatment of **390** with malononitrile gave the pyridine adducts **392** in 78–88% yields via formation of the intermediate **391** (Scheme 121).²⁵⁸ The reaction pathway in later is believed to be through intramolecular cycloaddition of the amidic –NH group to the terminal –C≡N function.

Condensation of **393** with aromatic aldehydes furnished the acrylonitriles **394** (Scheme 122). Treatment of the latter compounds with malononitrile gave the aminopyridine deriva-

Scheme 121

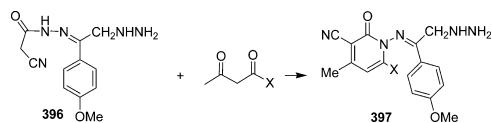


Scheme 122



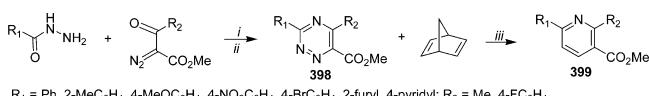
tives 395 in 68–72% yields. Further support for the proposed structure 395 was prepared independently through addition of acetonitrile derivative 393 to the activated double bond in benzylidene malononitrile derivatives under Michael reaction conditions (Scheme 122).²⁵⁹ Similarly, Mohareb et al.²⁶⁰ reported the synthesis of pyridines from α-cyanocinnamone or ethyl α-cyanocinnamate.

Reaction of compound 396 with either acetylacetone or ethyl acetoacetate gave the 6-oxopyridine derivatives 397 (yields X = Me (55%) and OEt (54%)) (Scheme 123).²⁶¹ A similar method was adapted by Abu-Hashem et al.²⁶² to prepare pyridine derivatives.

Scheme 123^a

^aX = Me, OEt.

Hydrazides with methyl 2-diazo-3-oxobutanoate was converted into 1,2,4-triazines 398 in the presence of copper(II) acetate as the catalyst followed by treatment with ammonium acetate in acetic acid. Subsequent hetero-Diels–Alder reaction^{263–267} of triazines 398 with norbornadiene gave pyridines 399 in 40–94% yields (Scheme 124).²⁶⁸

Scheme 124^a

R₁ = Ph, 2-MeC₆H₄, 4-MeOC₆H₄, 4-NO₂C₆H₄, 4-BrC₆H₄, 2-furyl, 4-pyridyl; R₂ = Me, 4-FC₆H₄.

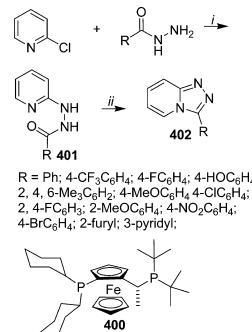
^a(i) Cu(OAc)₂, CH₂Cl₂, MW, 80 °C, 10 min; (ii) NH₄OAc, AcOH, MW, 100 °C; (iii) PhCl, reflux, 24 h.

A palladium-catalyzed addition of hydrazides to 2-chloropyridine in DMF and a phosphine ligand Josiphos 400 formed 1,2,4-triazolo[4,3-*a*]pyridines 402 in 47–91% yields, which occurred chemoselectively at the terminal nitrogen atom of the hydrazide, followed by dehydration in acetic acid under microwave irradiation (Scheme 125).²⁶⁹

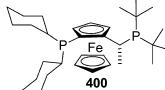
Interaction of compound 2-cyano-*N'*-[1-(2,5-dimethoxyphenyl)]ethylideneacetohydrazide with ethyl α-cyanocinnamate derivatives, malononitrile, and ethyl cyanoacetate gave the dihydropyridine derivatives 403, 404, and 405 in 59–81%, 82%, and 77% yields, respectively (Scheme 126).²⁷⁰

3.5. Synthesis of Six-Membered Rings with Two Heteroatoms

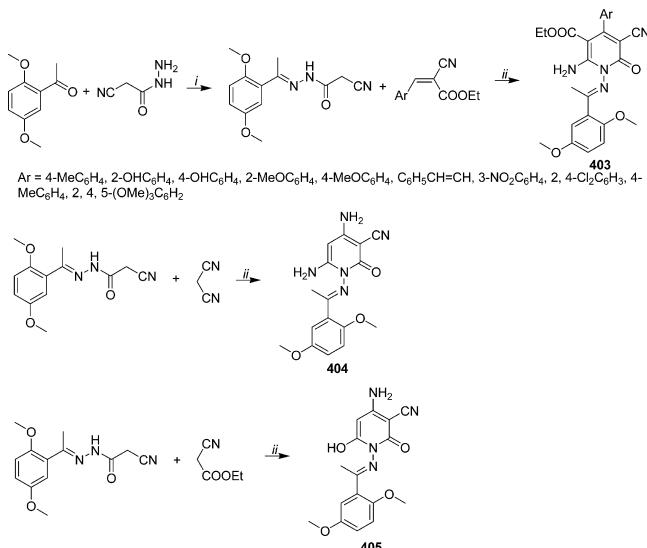
3.5.1. Pyridazine and Their Fused Derivatives. The pyridazinone derivatives show wide biological activity. They constitute the pyridazinone class of herbicides, which are

Scheme 125^a

R = Ph; 4-CF₃C₆H₄; 4-FC₆H₄; 4-HOC₆H₄; 2, 4, 6-Me₂C₆H₂; 4-MeOC₆H₄; 4-ClC₆H₄; 2, 4-FC₆H₃; 2-MeOC₆H₄; 4-NO₂C₆H₄; 4-BrC₆H₄; 2-furyl; 3-pyridyl;



^a(i) Pd₂(dba)₃ (1–2.5%), Josiphos 400, NaHCO₃, DMF, 100 °C, 15 h; (ii) AcOH, 180 °C, MW, 0.5 h.

Scheme 126^a

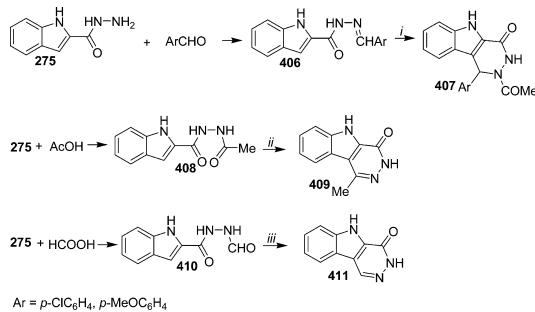
^a(i) Dioxane, reflux, 2 h; (ii) dioxane, TEA, reflux, 4 h.

carotenoid biosynthesis inhibitors,²⁷¹ and also act as fungicide and insecticides.²⁷² Even more important, the pyridazin-3(2H)-one ring is present in many compounds that possess a variety of pharmacological properties and therefore play the role of a pharmacophore viz. cardiotonic,²⁷³ antihypertensive,²⁷⁴ anti-nociceptive,²⁷⁵ antifungal,²⁷⁶ and antiulcer²⁷⁷ agents.

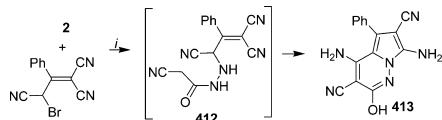
Refluxing hydrazone derivatives 406 of indole-2-carboxylic acid hydrazide 275 in acetyl chloride afforded the corresponding indolo[2,3-*d*]pyridazine derivatives 407 in 76–81% yields. Acetylation of indole-2-carboxylic acid hydrazide 275 in acetic acid afforded 2-acetylhydrazinocarbonylindole 408, which underwent cyclization in POCl₃ to form 43% of indolo[3,2-*b*]pyridazine derivative 409. On the other hand, refluxing 275 in formic acid afforded the *N*-formyl derivative 410. By ring closure of 410 upon heating, indolo[3,2-*b*]pyridazine derivative 411 was obtained in 43% yield (Scheme 127).²⁰⁷

Reaction of 2 with 2-phenyl-1,1,3-tricyano-3-bromopropene in a basic medium gave the nonisolable acyclic intermediate 412, which underwent cyclization via addition of the active methylene to the CN group to afford the 69% of pyrrolo[1,2-*b*]pyridazine derivative 413 (Scheme 128).²⁷⁸

Refluxing hydrazide 2 with aceanthraquinone in acetic acid produced 414, which when treated with potassium hydroxide was converted into 10,11-dihydro-10-oxo-aceanthryleno[1,2-

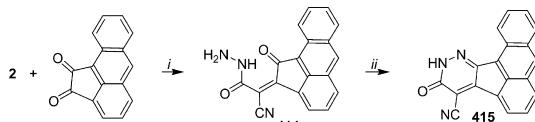
Scheme 127^a

^a(i) MeCOCl; (ii) POCl₃; (iii) Δ , 10 min, EtOH, reflux, 3 h.

Scheme 128^a

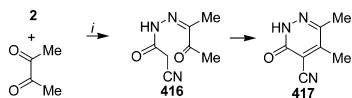
^a(i) TEA, DMF.

c] pyridazine-9-carbonitrile derivative **415** in 50% yield (Scheme 129).²⁷⁹

Scheme 129^a

^a(i) AcOH; (ii) KOH.

One-pot reaction of **2** with biacetyl yielded pyridazin-3-one derivative **417** in quantitative yield (94%) via cyclocondensation of the unisolated hydrazone derivative **416** (Scheme 130).²⁸⁰

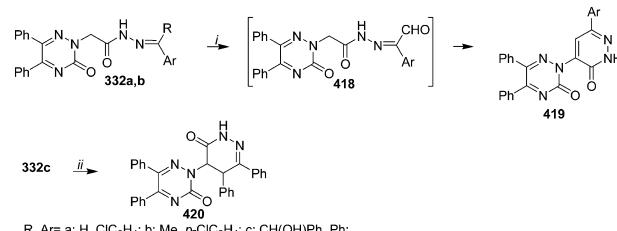
Scheme 130^a

^a(i) EtOH, rt.

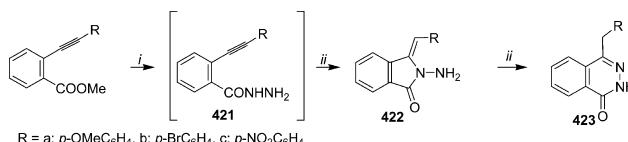
Oxidation of hydrazones **332a,b** of *N*-triazino-2-acetic acid hydrazide **69** using SeO₂ led to formation of arylpyridazine-3(2*H*)-ones **419** in 90–95% yields. Also, hydrazone **332c** underwent cyclization in sodium ethoxide, resulting in formation of pyridazine-3(2*H*)-one **420** in 78% yield (Scheme 131).⁷⁴

Ethynylbenzoates on heating with hydrazine hydrate in ethanol directly led to the cyclization products **422** (67–90%) without intermediate accumulation of hydrazides **421** (Scheme 132). On refluxing, *N*-amino lactams **422** in ethanolic potassium hydroxide underwent rearrangement to give a 6-exoproduct benzopyridazinones **423a** and **423b** in 65% and 75% yields, respectively. Only lactam **422c** with a strong acceptor nitro substituent did not undergo recyclization even under more prolonged heating with KOH (Scheme 132).²⁸¹

3.5.2. Pyrimidine and Their Fused Derivatives. Pyrimidine is a key structural component in life molecules, and its derivatives are considered privileged structures in medicinal

Scheme 131^a

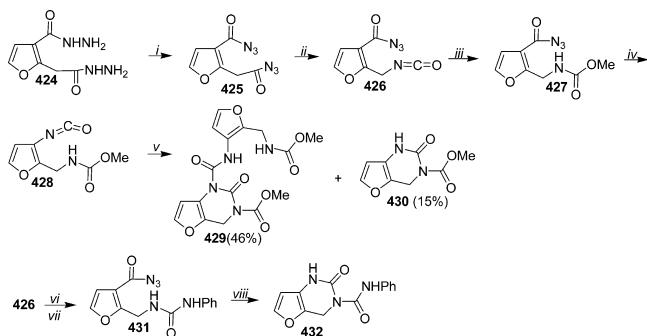
^a(i) SeO₂, dioxane; (ii) NaOEt.

Scheme 132^a

^a(i) NH₂NH₂; (ii) KOH, EtOH.

chemistry.^{282–290} It is therefore logical to explore the synthesis of pyrimidine heterocycles.

2-(2-Hydrazino-2-oxoethyl)-3-furohydrazide **424** was reacted with NaNO₂ and HCl to give the corresponding 2-(2-azido-2-oxoethyl)-3-furoyl azide **425**, which was allowed to heat in benzene at 35–40 °C to effect the transformation of the alkyl acyl azide functionality to the corresponding monoisocyanate, 2-(isocyanatomethyl)-3-furoyl azide **426** (Scheme 133).²⁹¹ Treat-

Scheme 133^a

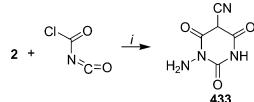
^a(i) NaNO₂, HCl·H₂O, 0–5 °C; (ii) benzene, 35–40 °C; (iii) MeOH; (iv) benzene, reflux; (v) benzene, reflux; (vi) benzene, 35–40 °C, 48 h; (vii) aniline, rt, 5 min, 84%; (viii) THF, reflux, 16 h.

ment of the formed isocyanate **426** in benzene with MeOH gave the urethane **427** in 70% yield. The urethane **427** containing an acyl azide functionality was again subjected to Curtius rearrangement by refluxing in benzene under nitrogen atmosphere to bring about its quantitative transformation to **428**. The expected intramolecular cyclization product **430** was unfortunately only formed in 15%. The major product **429** (46%) was formed by addition of the NH in **430** to the initially formed isocyanate **428**. In order to hinder the intermolecular addition reaction between **428** and **430**, the author decided to increase the nucleophilicity of the NH group in **428** and force the system to undergo intramolecular cyclization. For this reason, isocyanate **426** generated at 35–40 °C in benzene was trapped with aniline to give **431** in 84% yield. Curtius rearrangement of the acyl azide

431, carried out in dry tetrahydrofuran, afforded the pyrimidinone derivative 432 in 71% yield.

1-N-Amino-3-cyanobarbituric acid 433 was synthesized in 70% yield by reaction of chlorocarbonylisocyanate with 2 (Scheme 134).²⁹²

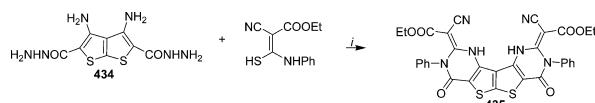
Scheme 134^a



^a(i) Dioxane/TEA.

Reaction of hydrazide 434 with ethyl 2-cyano-3-mercaptopropanoate under PTC conditions produced 40% of bis[ethyl(4-oxo-3-phenyl-1(*H*)-thieno(2,3'-pyrrolidin-2-ylidene) cyanoacetate] 435 via nucleophilic attack of the NH group of the *N*,*S*-acetal at the carbonyl carbon with elimination of a hydrazine molecule followed by intramolecular cyclization through elimination of an H_2S molecule (Scheme 135).²⁹³

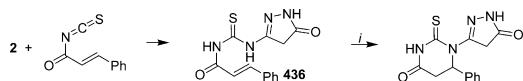
Scheme 135^a



^a(i) K₂CO₃, TBAB.

Cinnamoyl isothiocyanate reacts with 2 to give the corresponding cinnamoyl thiourea 436, which underwent cyclization to give the corresponding 1-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-6-phenyl-2-thioxotetrahydropyrimidin-4(1*H*)-one 437 in 60% yield (Scheme 136).²⁹⁴

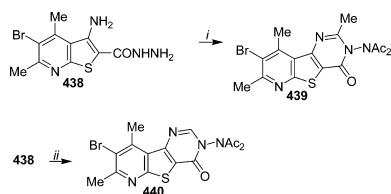
Scheme 136^a



^a(i) NaOEt.

3-Amino-5-bromo-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbohydrazide 438 on reaction with freshly distilled acetic anhydride and formic acid furnished 55% of 8-bromo-3-diacylamino-2,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one 439 and 63% of 8-bromo-7,9-dimethyl-3-formylaminopyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one 440, respectively (Scheme 137).²⁹⁵

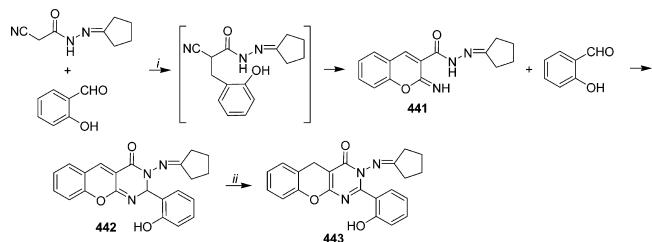
Scheme 137^a



^a(i) Ac₂O, 138 °C; (ii) HCOOH, 100 °C.

Knoevenagel condensation of salicylaldehyde with cyclopentylidene hydrazide leads to formation of the coumarine imine 441, which on attack by the second molecule of salicylaldehyde generated pyrimidin-4(5*H*)-one derivative 442 in 70% yield. Base-catalyzed rearrangement of 442 gave the pyrimidin-4(5*H*)-one derivative 443 in 71% yield (Scheme 138).²⁹⁶

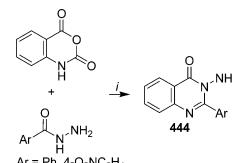
Scheme 138^a



^a(i) EtOH, H₂O; (ii) piperidine.

Condensation of the anhydride with the hydrazides of arencarboxylic acids in the presence of *p*-toluenesulfonic acid gave the 2-aryl-3-amino-4-quinazolones 444 (yield Ar = Ph (37%) and 4-NO₂C₆H₄ (39%)) (Scheme 139).²⁹⁷

Scheme 139^a

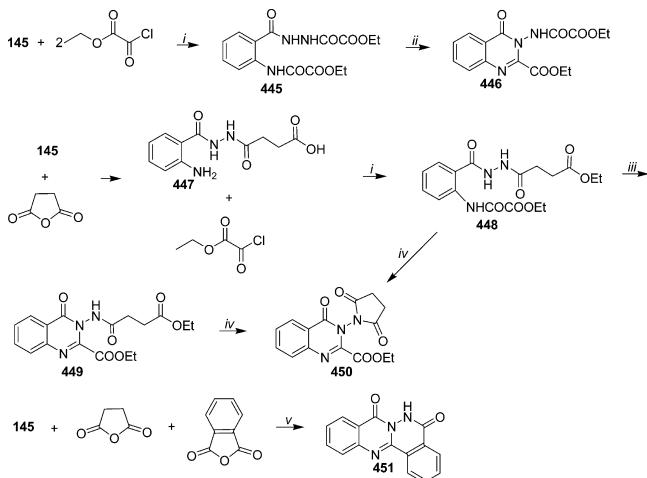


^a(i) AcOH, PTSA, boiling, 9 h.

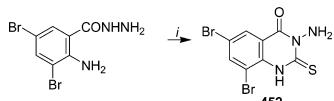
Acylation of anthranilic acid hydrazide 145 with 2 equivalent of ethoxalyl chloride formed diester 445, which readily underwent cyclization in the presence of acetic anhydride to ethyl 3-[ethoxy(oxo)acetylaminoo]-4-oxo-3,4-dihydroquinazoline-2-carboxylate 446 with 51% yield. On the other hand, ethyl 4-oxo-3-(2,5-dioxopyrrolidin-1-yl)-3,4-dihydroquinazoline-2-carboxylate 450 was synthesized starting from 4-[2-(2-aminobenzoyl)hydrazino]-4-oxobutanoic acid²⁹⁸ 447, which on reaction with ethoxalyl chloride gave oxamate 448. Oxamate 448 on heating in acetic acid afforded the derivative 449, which on further treatment with acetic anhydride furnished 68% of quinazolin-4-one 450. Ethyl 4-oxo-3-(2,5-dioxopyrrolidin-1-yl)-3,4-dihydroquinazoline-2-carboxylate 450 can also be obtained in 73% yield directly from ester 448 without isolation of ester intermediate 449 by the action of acetic anhydride (Scheme 140).^{299,300} Compound 451³⁰¹ was obtained in 83% yield by successive acylation of hydrazide 145 with succinic and phthalic anhydrides in acetic acid (Scheme 140).

Cyclization of 2-amino-3,5-dibromobenzohydrazide with carbon disulfide afforded 51% of quinazolin-4-one derivative 452 (Scheme 141).³⁰²

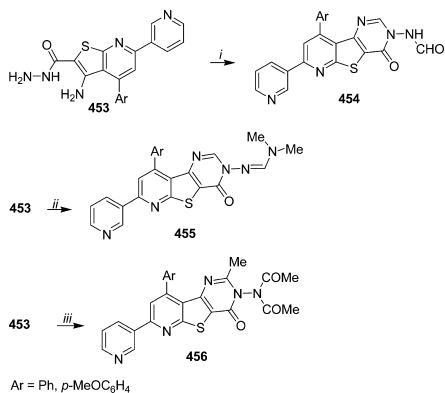
Reactions of 3-amino-4-(4-methoxyphenyl)-6-pyridin-3-ylthieno[2,3-*b*]pyridine-2-carbohydrazide 453 with formic acid, dimethylformamide-dimethylacetal, and acetic anhydride were carried out separately to afford the corresponding pyridothenopirimidines 454, 455, and 456, respectively, in 70–87% yields (Scheme 142).³⁰³

Scheme 140^a

^a(i) AcOH, TEA; (ii) Ac₂O, Δ; (iii) AcOH, Δ; (iv) Ac₂O; (v) AcOH.

Scheme 141^a

^a(i) CS₂/EtOH, NaOH.

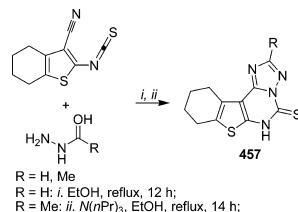
Scheme 142^a

^a(i) HCOOH; (ii) DMF/DMA; (iii) Ac₂O.

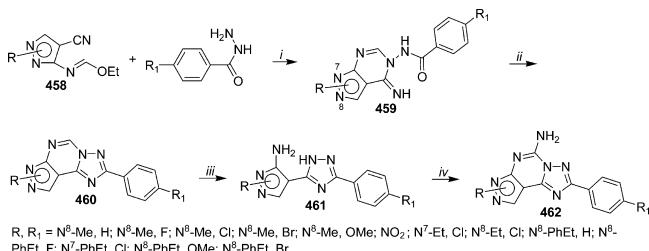
Reaction of 2-isothiocyanato-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]-thiophene with formic acid hydrazide (R = H) and acetic hydrazide (R = Me) afforded the respective 5-thioxo-4,6,8,9,10,11-hexahydro-benzo[*b*]thiopheno[2,3-*d*]-1,2,4-triazolo[1,5-*c*]pyrimidines 457 (yield R = H (76%) and Me (78%)). Formation of 457 proceeds by attack of the terminal amino group of hydrazide onto the isothiocyanate then to the nitrile function for cyclization and subsequent attack of the imino group onto the amide for annelation (Scheme 143).³⁰⁴

Imidate derivatives of pyrazole 458 were reacted with the appropriate (para-substituted)benzoic acid hydrazide in refluxing 2-methoxyethanol to afford the intermediates 459, which subsequently were subjected to a thermally induced cyclization in diphenyl ether at 260 °C to give 460. Hydrolysis of 460 in 20% HCl gave rise to the corresponding hydrolyzed intermediates 461, which were consequently converted into the 5-amino-7- or 8-(substituted)-2-[(para-substituted)phenyl]pyrazolo[4,3-*e*]-

Scheme 143



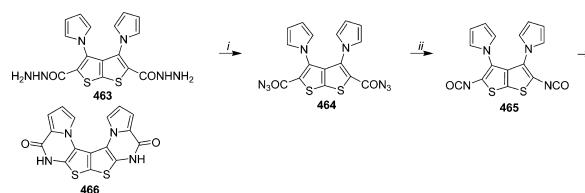
1,2,4-triazolo[1,5-*c*]pyrimidine derivatives 462 (17–54% yields) in the presence of 1-methyl-2-pyrrolidinone, cyanamide, and *p*-toluenesulfonic acid monohydrate (Scheme 144).³⁰⁵

Scheme 144^a

^a(i) MeO(CH₂)₂OH; (ii) Ph₂O, 260 °C, flash chromatography; (iii) HCl, reflux; (iv) NH₂CN, 1-methyl-2-pyrrolidinone, *p*-TsOH.

3.5.3. Piperazine and Their Fused Derivatives. Piperazines are a significant class of organic compounds for clinical chemistry.³⁰⁶ Piperazines have been reported in gene transfer reactions,³⁰⁷ and quaternary piperazinium salts have shown spasmolytic, anthelmintic, and germicidal activity. Some piperazine derivatives possess high biological activity for multidrug resistance in cancer and malaria.^{308,309}

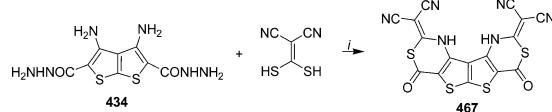
3,4-Di(pyrrol-1'-yl)thieno[2,3-*b*]thiophene-2,5-dicarbohydrazide 463 was converted to 2,5-dicarbazido-3,4-di(pyrrol-1'-yl)thieno(2,3-*t*)thiophene 464 on treatment with nitrous acid, which was easily decomposed at 170 °C through a Curtius rearrangement, and subsequent ring closure produced the corresponding bis[thienopyrrolopiperazine] 466 in 90% yield via the intermediacy of isocyanate derivative 465 (Scheme 145).²⁹³

Scheme 145^a

^a(i) NaNO₂/HCl; (ii) 170 °C, Δ.

3.5.4. Thiazine and Their Fused Derivatives. Among the heterocycles, 1,3-thiazines are a class of compounds with biological activity, such as antimicrobial,³¹⁰ antitumor,³¹¹ antioxidant,³¹² calcium channel modulators,³¹³ and antipyretic.^{314,310} In view of these observations it was considered of interest to synthesize some new thiazine derivatives of biological importance.

Treatment of 3,4-diaminothieno(2,3-*b*)thiophene-2,5-dicarbohydrazide **434** with *S,S*-acetals under PTC conditions afforded bis[(coxo-1*H*-thieno(2,3-*b*)-1',3'-thiazin-2'-ylidene) malononitrile **467** (29% yield) via nucleophilic attack of the SH group of the *S,S*-acetal at the carbonyl group with elimination of a hydrazine molecule and subsequent intramolecular cyclization via elimination of hydrogen sulfide molecule (Scheme 146).²⁹³

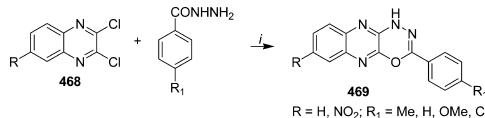
Scheme 146^a

^a(i) K_2CO_3 , TBAB.

3.6. Synthesis of Six-Membered Rings with Three Heteroatoms

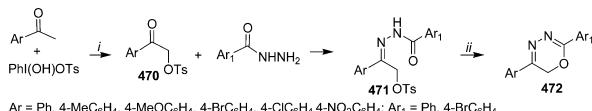
3.6.1. Oxadiazine and Their Fused Derivatives. A diversity of biological effects is associated with oxadiazines³¹⁵ bearing heteroatoms at 1,2,4- or 1,3,4-positions. 1,3,4-Oxadiazine derivatives exhibit cardiovascular, antibacterial, plant growth regulating, miticidal and nematocidal, acridical, insecticidal, and anticonvulsive activities.^{316,317} In addition, oxadiazines are useful intermediates³¹⁸ in the synthesis of tenidap prodrugs or β -lactam antibiotics, in particular, into the synthesis of carbapenems and penems.^{319,320} 4-Substituted 5,6-dihydro-2-*o*-hydroxyphenyl-4*H*-1,3,4-oxadiazine-5-ones³²¹ were reported in the literature as potential psychopharmacological drugs. The promising therapeutic potential of this class of compounds prompted researchers to synthesize novel derivatives of several 1,3,4-oxadiazines.

Dubey and co-workers reported the reaction of 2,3-dichloroquinoxaline **468** with aromatic acid hydrazides in acetonitrile containing K_2CO_3 as base and triethylbenzylammonium chloride (TEBAC) as phase transfer catalyst, which resulted in formation of oxadiazinoquinoxalines **469** in moderate yields (Scheme 147).³²²

Scheme 147^a

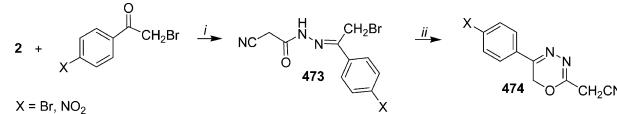
^a(i) K_2CO_3 , TEBAC, MeCN, Δ .

Reaction of acetophenone with [hydroxyl(tosyloxy)iodo]-benzene (HTIB) formed **470**, which on condensation with benzoic acid hydrazides afforded the acid hydrazones **471** which underwent requisite cyclization on addition of K_2CO_3 to yield 2,5-diphenyl-6*H*-1,3,4-oxadiazine **472** in 58–71% yields (Scheme 148).³²³

Scheme 148^a

^a(i) MeCN; (ii) K_2CO_3 .

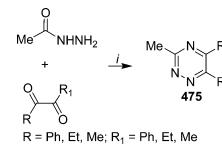
The hydrazide-hydrazone derivatives **473** of **2** underwent cyclization in sodium ethoxide solution to give the 2-(5-(4-bromoaryl)-6*H*-1,3,4-oxadiazin-2-yl)acetonitrile derivatives **474** (yields X = Br (81%) and NO_2 (77%)) (Scheme 149).³¹⁸

Scheme 149^a

^a(i) 1,4-Dioxane, reflux 2 h; (ii) NaOEt /EtOH, reflux on water bath for 4 h, HCl till pH 6.

3.6.2. Triazine and Their Fused Derivatives. 1,2,4-Triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities.³²⁴ Synthesis of 1,2,4-triazines and their derivatives is well documented,^{325–328} and their methods of preparation are numerous and varied.

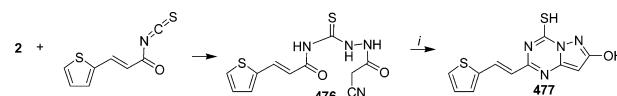
1,2,4-Triazines **475** were obtained in 61–93% yields from the one-pot condensation reaction of acid hydrazide, ammonium acetate, and dicarbonyl compounds on the surface of silica gel in the presence of triethylamine under microwave irradiation (Scheme 150).³²⁹ Lindsley et al.³³⁰ also reported a one-pot 3-

Scheme 150^a

^a(i) NH_4OAc , SiO_2 , TEA, MW.

component condensation under microwave irradiation of an acyl hydrazide-tethered indole to form a triazine, unnatural β -carboline alkaloids in good isolated yields from ammonium acetate followed by an inverse-electron demand Diels–Alder reaction.

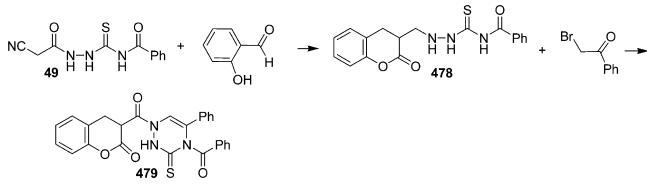
Nucleophilic addition reaction of 3-thiophen-2-yl-acryloylisothiocyanate with hydrazide **2** afforded thiocarbamoyl derivative **476**, which gave 55% of pyrazolo[1,5-*a*][1,3,5]triazine derivative **477** on treatment with 5% potassium hydroxide (Scheme 151).³³¹

Scheme 151^a

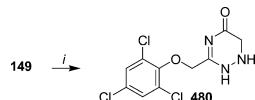
^a(i) 5% KOH.

Reaction of hydrazide **49** with salicyldehyde afforded the coumarin derivative **478**, which on further treatment with phenacyl bromide afforded 70% of 1,2,4-triazine-3-thione derivative **479**. The reaction is assumed to follow a 1,4-dinucleophilic attack by the aminothioxomethylhydrazine moiety on the α -haloketone (Scheme 152).⁶⁷

Scheme 152



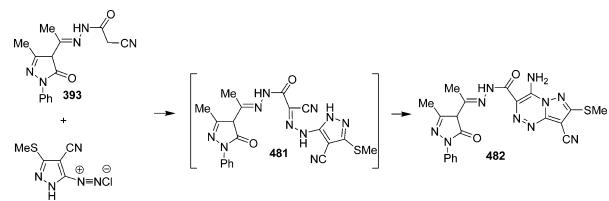
1,2,4-Triazine **480** was synthesized in 63% yield by condensation of hydrazide **149** with chloroacetamide (Scheme 153).¹²¹

Scheme 153^a

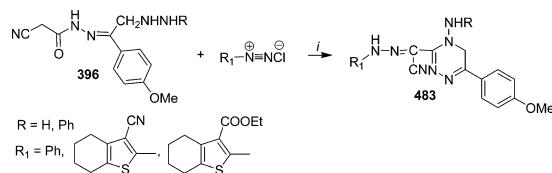
^a(i) Chloroacetyl chloride, DMF.

Coupling of **393** with pyrazole-5-diazonium chloride yielded polycondensed heterocyclic pyrazolo[*S,1-c*]-1,2,4-triazine **482** (60% yield) via the nonisolable hydrazone intermediate **481** (Scheme 154).²⁵⁹

Scheme 154



Reaction of hydrazone derivative **396** with diazonium chlorides formed the triazine derivative **483** in 54–82% yields (Scheme 155).²⁶¹

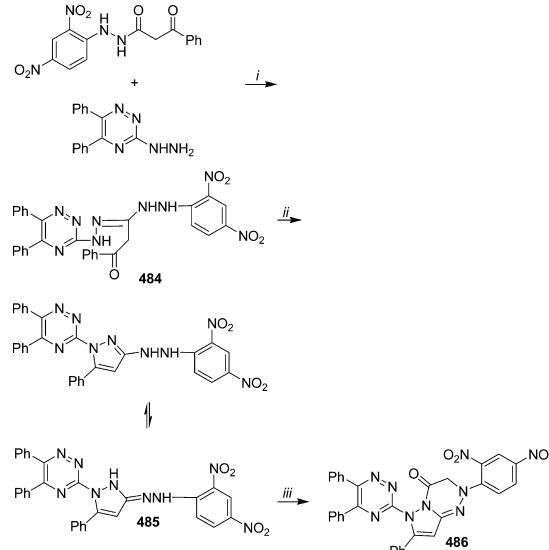
Scheme 155^a

^a(i) EtOH, NaOH.

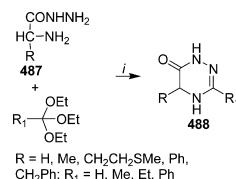
Condensation of *N'*-(2,4-dinitrophenyl)-3-oxo-3-phenylpropanehydrazide with triazine gave the corresponding hydrazone **484**, which underwent cyclization on heating with glacial acetic acid in the presence of anhydrous sodium acetate to form pyrazole derivative **485**. Alkylation of **485** using ethyl bromoacetate led to formation of 65% of 2-(2,4-dinitrophenyl)-6-(5,6-diphenyl-1,2,4-triazin-3-yl)-7-phenyl-2,3-dihydropyrazolo[*S,1-c*][1,2,4]triazin-4(6*H*)-one **486** (Scheme 156).⁶³

Neunhoeffer et al.³³² reported the cyclization of amino acid hydrazides **487** with orthocarboxylates to form 1,2,4-triazin-6(1*H*)-ones **488** in 16–84% yields (Scheme 157).

Katritzky and co-workers reported the synthesis of *N*-Cbz-1,2,4-triazine-derived α -amino acids **490** with 61–68% yields

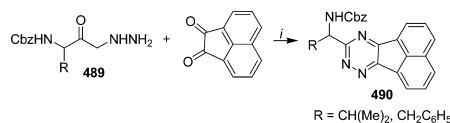
Scheme 156^a

^a(i) EtOH, reflux, 1 h; (ii) anhyd AcONa/AcOH, reflux, 1 h; (iii) BrCH₂COOEt, 5% ethanolic KOH.

Scheme 157^a

^a(i) DMF.

using *N*-Cbz-amino acid hydrazides **489** and 1,2-acenaphthene-dione in the presence of ammonium acetate under microwave irradiation (Scheme 158).³³³

Scheme 158^a

^a(i) NH₄OAc, MW irradiation.

4. CONCLUSION

This review describes the high synthetic potential of various acid hydrazides for synthesis of five- and six-membered polyfunctional heterocyclic compounds that have been published in the last three decades. Many pharmaceutically active heterocycles have been obtained based on the reaction of acid hydrazides particularly concerning Gewald reaction, Curtius rearrangement, Dimroth rearrangement, Horner–Emmons reaction, and Reid–Heindel reaction. Essentially esters, organic acid halides, lactones, lactims, and cyclic anhydrides are potential resources for generation of variety of acid hydrazides as key synthon components for preparation of numerous diverse heterocycles. Reaction of hydrazides with most other various reagents like isocyanate, isothiocyanate, carbondisulfide, aldehydes, and ketones, both cyclic and acyclic, for synthesis of heterocycles

occurs through nucleophilic addition, substitution, addition–elimination, and ANRORC (addition of the nucleophile, ring opening, and ring closure) mechanisms under basic, acidic, or neutral reaction conditions. Most of these reagents are accessible from easily or commercially available low-cost starting materials. This review has also demonstrated the salient feature to development of an environmentally benign microwave-irradiated experimental procedure for heterocyclic synthesis from this basic acid hydrazide unit. The synthetic methods illustrated in this review can be extended to the synthesis of natural heterocycles and also suggest that acid hydrazides can be a promising building block in combinatorial synthesis of functionalized heterocyclic compounds used for design of novel highly effective pharmaceutical drugs with a broad spectrum of bioresponses. In certain cases, reports on the low yield of bioactive heterocycles in this review could be overcome by prospective synthetic chemists with this continued investigation and new approaches for broad methodology and elaborated experimental techniques could be explored for its enhancement for preparation of a library of such polyfunctional heterocycles to provide a useful aid to medicinal chemistry.

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Notes

The authors declare no competing financial interest.

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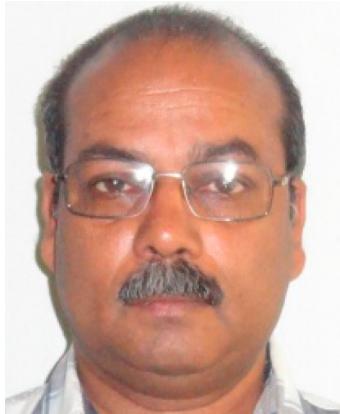
Anita Pati was born in Sambalpur, Odisha, India, in 1977. She obtained her M.Sc. degree in 2002, and M.Phil. degree in 2003, from Sambalpur University, India. During her Ph.D. she worked with Prof. R. K. Behera in the area of organic synthesis and after receiving her Ph.D. degree from Sambalpur University in August 2010, she joined the group of Dr. Dillip Kumar Chand and Dr. Santosh J. Gharpure, Indian Institute of Technology Madras, Chennai, India, to pursue her postdoctoral research work in the area of supramolecular Chemistry. After the successful completion of her postdoctoral research training, presently she is working as an Assistant Professor in the School of Applied Sciences (Chemistry), KIIT University, Bhubaneswar. Her research interest includes organic synthesis, new synthetic methods and supramolecular chemistry.



Manabendra Patra was born in Cuttack, India. He received his M.Sc. (1991) and M.Phil. (1993) degrees from the PG Department of Chemistry, Sambalpur University, India. He studied micellar chemistry during his M.Phil. work. He obtained his Ph.D. degree on polymer kinetics under the guidance of Professor B. K. Sinha from Sambalpur University in 1999. In the same year he joined the group of Professor Rajani Kanta Behera as a Research Associate working on organic synthesis. At present, he is an Assistant Professor at the National Institute of Science and Technology, Berhampur, Orissa. His research interest is in on surface chemistry and organic synthesis.



Rajani K. Behera was born in 1952 in Kalahandi District of Odisha, India. He received his M.Sc. degree in 1974 and Ph.D. degree in 1980 from Sambalpur University. After working at Government College, he became a Lecturer at Sambalpur University and subsequently became a Reader in 1991 and Professor in 1999. He worked with Professor G. R. Newkome at the University of South Florida on the synthesis of dendrimers from 1988 to 1991. He has one patent in the United States and another in Canada to his credit. His research interests include synthesis of heterocycles, macromolecules, and dendrimers.



Ajaya Kumar Behera was born in Nayagarh District of Odisha, India, in 1962. He received his M.Sc. degree from Utkal University in 1984 and M.Phil. and Ph.D. degrees from Berhampur University in 1990 and 1996, respectively. After working for a few years at Government College, he joined the PG Department of Chemistry, Sambalpur University, in 1997 as Senior Lecturer and became Reader in 2003. His research interest includes synthesis of pharmacologically active heterocycles, spiroheterocycles, and natural products.

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ABBREVIATIONS

aq	aqueous
bpy	2,2'-bipyridine
Bn	benzyl
Boc	tert-butyloxycarbonyl
t-Bu	tert-butyl
BTC	bis(trichloromethyl)carbonate
TPBP	1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate
BSH	bis(trimethylsilyl)acetamide
CCR	component coupling reaction

CDI	1,1'-carbonyldiimidazole
CDK	cyclin-dependent kinase
CHP	N-cyclohexyl-2-pyrrolidone
conc	concentrate
cycl	cyclization
DCM	dichloromethane
dil	dilute
DMA	dimethylacetal
DMF	N,N-dimethyl formamide
EDCl	ethylenediamine chloride
Et	ethyl
ETL	electron transport layer
h	hour
HOBT	1-hydroxy benzotriazole
HTIB	[hydroxyl(tosyloxy)iodo]benzene
HTL	hole transport layer
HMDS	hexamethyldisilazane
IBD	iodobenzene diacetate
IBX	iodoxybenzoic acid
INH	isonicotinic acid hydrazide
ITO	indium tin oxide
MAO	monoamine oxidase
Me	methyl
min	minute
MW	microwave
NMP	N-methyl-2- pyrrolidone
OLED	organic light-emitting diode
PEG	Polyethylene glycol
Ph	phenyl
PPA	polyphosphoric acid
PTC	phase transfer catalyst
PTSA	p-toluenesulfonic acid
PTSCI	p-toluene sulphonyl chloride
i-pr	isopropyl
py	pyridine
rt	room temperature
SPS	solid-phase synthesis
TEA	triethylamine
THF	tetrahydrofuran
TEBAC	triethyl benzylammonium chloride
Δ	heating

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