Design and Synthesis of Pyrido[2,1-b][1,3,5]thiadiazine Library via Uncatalyzed Mannich-Type Reaction

ARTICLE *in* ACS COMBINATORIAL SCIENCE · SEPTEMBER 2014

Impact Factor: 3.03 · DOI: 10.1021/co5000807 · Source: PubMed

6 AUTHORS, INCLUDING:

Victor V Dotsenko
Vladimir Dal' Lugansk University (LPR)/Kuba…
122 PUBLICATIONS **509** CITATIONS
SEE PROFILE

K. A. Frolov
East Ukraine Volodymyr Dahl National Unive…
40 PUBLICATIONS **101** CITATIONS
SEE PROFILE

ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

Design and Synthesis of Pyrido[2,1-*b*][1,3,5]thiadiazine Library via Uncatalyzed Mannich-Type Reaction

Victor V. Dotsenko,*[,†,§] Konstantin A. Frolov,[†] Tatyana M. Pekhtereva,[‡] Olena S. Papaianina,[‡] Sergey Yu. Suykov,[‡] and Sergey G. Krivokolysko[†]

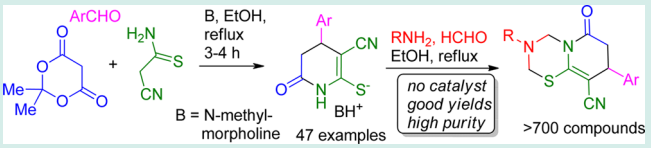
[†]ChemEx Laboratory, Vladimir Dal' East Ukrainian National University, 91034 Lugansk, Ukraine

[§]Kuban State University, 350040 Krasnodar, Russian Federation

[‡]L. M. Litvinenko Institute of Physical-Organic Chemistry and Coal Chemistry NAS of Ukraine, 83114 Donetsk, Ukraine

Supporting Information

ABSTRACT: This Research Article describes the synthesis of an over 700-member library of (8*R*/8*S*)-3-R-8-aryl-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazin-9-carbonitriles by uncatalyzed Mannich-type reaction of *N*-methylmorpholinium (4*R*/4*S*)-4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-thiolates with a set of primary amines and excessive HCHO. The scope and limitations of the reaction were studied. Starting thiolates were obtained in yields of 53−82% by multicomponent reaction of aromatic aldehydes, cyanothioacetamide, 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), and *N*-methylmorpholine, followed by heterocyclization of the resulting Michael adducts.



KEYWORDS: *uncatalyzed Mannich-type reaction, cyanothioacetamide, Meldrum's acid, tetrahydropyridine-2-thiolates, aminomethylation, pyrido[2,1-b][1,3,5]thiadiazines*

INTRODUCTION

1,3,5-Thiadiazines have attracted considerable attention over the years because of their biological activities and applications in medicine and agriculture (for reviews on the 1,3,5-thiadiazine chemistry, see refs 1−3). 1,3,5-Thiadiazines are known as antidermatophites,[4,5] antifungal and fungistatic agents,[6−14] antimicrobials and bactericides,[15−23] antifibrinolytic agents,[24−27] tuberculostatics,[28−31] etc. Thiadiazines are widely used as insecticides.[32] 2-*tert*-Butylimino-3-isopropyl-5-phenyl-3,4,5,6-tetrahydro-2*H*-l,3,5-thiadiazin-4-one, also known as buprofezin or Applaud (Figure 1), was found to be the most active growth regulator on the greenhouse whitefly (*Trialeurodes vaporariorum*) and the brown planthopper (*Nilaparvata lugens*), which is regarded as one of the most serious insect pests in rice fields.[33] Buprofezin acts on the insects by strong suppression of oviposition because of the inhibition of prostaglandin E2 biosynthesis[34] and by inhibition of chitin biosynthesis and integumentary cuticule deposition.[35,36] Recently, buprofezin has been found to be an acetylcholinesterase inhibitor in B-biotype *Bemisia tabaci*.[37] Another widely used compound is tetrahydro-3,5-dimethyl-1,3,5-thiadiazine-2-thione, also known under names Dazomet, Basamid, Mylone, Thiazone, Carbothialdine, or DMTT (Figure 1), which is a soil fumigant and used as a powerful insecticide, papermaking slimicide and nematicide, fungicide, and herbicide for cabbage, cucumber, maize, potato, and tomato plants.[38−44] Dazomet also behaves as a monodentate ligand toward some metal carbonyls.[45] In addition, Dazomet have been reported to possess an ovicidal effect on helminths eggs.[46] Another bioactive 1,3,5-thiadiazine, NIP-200 (3,5-dimethyl-4,6-diphenyl-tetrahydro-2*H*-1,3,5-thiadiazine-2-thione, Figure 1) is a potent hypolipidemic agent increasing the synthesis of bile acids as a result of the activation of cholesterol 7α-hydroxylase, the rate-limiting enzyme in the conversion of cholesterol to bile acids.[47] 3,5-Dibenzyltetrahydro-2*H*-1,3,5-thiadiazine-2-thione (D47, Dibenzthion) is an antimycotic agent useful for treatment of dermatomycoses.[48−51]

One of the most effective approaches to 1,3,5-thiadiazines is based on the double Mannich-type reaction of thioamides, dithiocarbamates or related *S*,*N*-binucleophilic species with primary amines and formaldehyde.[1−3] Cyclic thioamides (γ- and δ-thiolactams, 2-mercaptoazoles, -azines, or their 2-

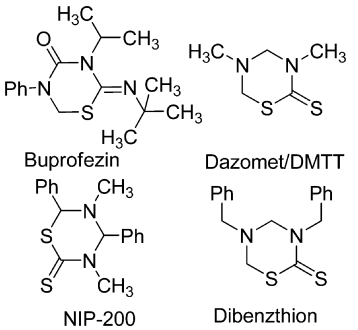


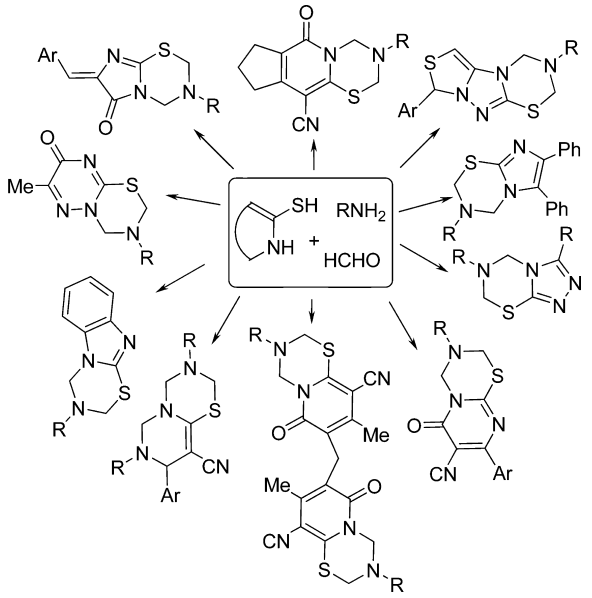
Figure 1. Biologically active 1,3,5-thiadiazines.

Received: May 16, 2014
Revised: August 1, 2014

   dx.doi.org/10.1021/co5000807 | *ACS Comb. Sci.* XXXX, XXX, XXX−XXX

thioxotautomers) can also be successfully employed in this reaction, giving rise to a variety of ring-condensed 1,3,5-thiadiazines. In fact, the related syntheses of 1,2,4-triazolo[3,4-*b*][1,3,5]thiadiazines,[52−60] imidazo[2,1-*b*][1,3,5]-thiadiazines,[61,62] 1,2,4-triazino[3,2-*b*][1,3,5]thiadiazines,[61] thiazolo[3′,4′:1,5][1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines,[63] 1,3,5-thiadiazino[3,2-*a*]benzimidazoles,[64] cyclopenta[*g*]pyrido-[2,1-*b*][1,3,5]thiadiazines,[65] *bis*(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)methanes,[66] pyrimido[2,1-*b*][1,3,5]thiadiazines,[67] and pyrimido[4,3-*b*][1,3,5]thiadiazines[68−70] have been reported (Scheme 1).

Scheme 1. Diversity of Ring-Condensed 1,3,5-Thiadiazines



However, despite the diversity and availability of ring-condensed 1,3,5-thiadiazines, their use and applicability is much less studied.[3] Thus, pyrazolo[1,5-*c*][1,3,5]thiadiazine-2-diones **1** (Figure 2) have been reported as effective fungicides[71−73] and photosynthetic electron transport inhibitors.[74,75] 1,2,4-Triazolo-[3,4-*b*][1,3,5]thiadiazines **2** were recognized as antibacterial agents,[52−55] while their oxo-analogs **3** showed moderate insecticidal activity.[76] In addition, 3-azacephalosporins **4** showed antibacterial activity,[77] and imidazo- and pyrimido-[2,1-*b*][1,3,5]thiadiazines **5** were recognized as insecticides.[78−80] Recently we found that pyrido[2,1-*b*][1,3,5]-thiadiazine **6** and related compounds showed significant inhibition against tick-borne encephalitis virus and Powassan virus.[81] Encouraged by this success, we turned our attention to the synthesis of related pyrido[2,1-*b*][1,3,5]thiadiazines in regard to library construction.

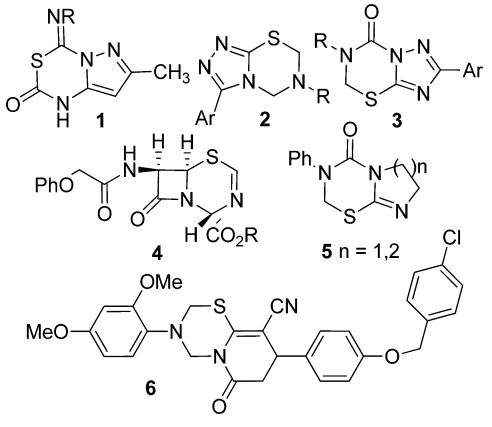
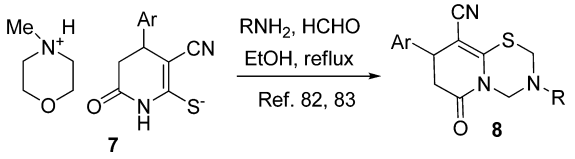


Figure 2. Biologically active ring-condensed 1,3,5-thiadiazines.

As we have shown in preliminary communications,[82,83] these pyrido[2,1-*b*][1,3,5]thiadiazines could be easily prepared by Mannich-type reaction of *N*-methylmorpholinium 4-aryl-6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates **7** with primary amines and excess formaldehyde (Scheme 2). This effective and

Scheme 2. Synthesis of Pyrido[2,1-*b*][1,3,5]thiadiazines 8



time-saving protocol is based on the use of inexpensive, readily available building blocks. In contrast to related double Mannich reactions,[52−60] no catalyst is required for this process. In most cases, the obtained pyrido[2,1-*b*][1,3,5]thiadiazines **8** were pure enough for analytical purposes that allowed us to exclude any purification steps. These results prompted us to study the scope and limitations of the reaction.

RESULTS AND DISCUSSION

In the current study, we report an optimized protocol for the synthesis of 700+ membered library of 3-*R*-8-aryl-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitriles **8**{*1*−*47*,*1*−*31*}, employing a small library of *N*-methylmorpholinium 4-aryl-6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates **7**{*1*−*47*} (Table 1), 37% aq. HCHO and a set of various primary amines **9**{*1*−*31*} (Figure 3). The required thiolates **7**{*1*−*47*} are easily accessible by one-pot condensation of aromatic aldehydes, cyanothioacetamide **10** and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **11** in the presence of *N*-methylmorpholine following the consequent cyclization of the isolable Michael adduct, *N*-methylmorpholinium 5-(3-amino-1-aryl-2-cyano-3-thioxopropyl)-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate **12**, as outlined in Scheme 3.[81−90] As the starting 1,4,5,6-tetrahydropyridine-2-thiolates **7** have been prepared as racemic mixtures of (4*R*)- and (4*S*)-enantiomers, all the pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitriles **8** also were obtained as mixtures of (8*R*)- and (8*S*)-isomers.

We found that 1,4,5,6-tetrahydropyridine-2-thiolates 7{*1*−*47*} easily react with primary amines **9**{*1*−*31*} and excess 37% aqueous formaldehyde under short-term heating in EtOH to give 3-*R*-8-aryl-6-oxo-3,4,7,8-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]-thiadiazine-9-carbonitriles **8**{*1*−*47*,*1*−*31*} (Scheme 3). Presumably, the reaction proceeds through the formation of non-isolable intermediate **13**. The order of mixing of the reactants does not exert a noticeable influence on the yields of the final products. Thus, when a suspension of thiolate 7{*2*} in EtOH was treated consecutively with 4.2 equiv of 37% HCHO and 1.1 equiv of $PhCH_2NH_2$ **9**{ *3*}, thiadiazine **8** {2,3} was obtained in 83% yield. Alternatively, when a hot solution of thiolate 7{*2*} in aq. EtOH was added to the mixture of HCHO and benzylamine in EtOH, thiadiazine **8** {2,3} yielded in 77%. EtOH is the solvent of choice since thiolates **7** were found to be

dx.doi.org/10.1021/co5000807 | ACS Comb. Sci. XXXX, XXX, XXX−XXX

Table 1. Diversity and Yields of 4-Aryl-6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates 7

entry	compound	Ar	yield	entry	compound	Ar	yield
1	7{1}	Ph	67[a]	24	7{24}	2-$NO_2C_6H_4$	57[d]
2	7{2}	2-MeC_6H_4	71[b]	25	7{25}	3-$NO_2C_6H_4$	64
3	7{3}	4-MeC_6H_4	71[a]	26	7{26}	4-$NO_2C_6H_4$	73
4	7{4}	4-EtC_6H_4	68	27	7{27}	4-$MeSC_6H_4$	83
5	7{5}	4-*i*-PrC_6H_4	70	28	7{28}	3-$PhCH_2OC_6H_4$	68[g]
6	7{6}	2-ClC_6H_4	73[c]	29	7{29}	4-$PhCH_2OC_6H_4$	78[g]
7	7{7}	4-ClC_6H_4	79	30	7{30}	5-Br-2-$MeOC_6H_3$	76
8	7{8}	2-FC_6H_4	76	31	7{31}	3-Br-4-$MeOC_6H_3$	73
9	7{9}	3-FC_6H_4	69	32	7{32}	2-furyl	55[f]
10	7{10}	4-FC_6H_4	71[d]	33	7{33}	5-Me-2-furyl	53
11	7{11}	3-BrC_6H_4	61	34	7{34}	2-thienyl	71[e]
12	7{12}	2-Cl-6-FC_6H_3	75	35	7{35}	3-Me-2-thienyl	57
13	7{13}	2,6-$Cl_2C_6H_3$	62	36	7{36}	4-HO-3-$MeOC_6H_3$	76
14	7{14}	2-$MeOC_6H_4$	78[h]	37	7{37}	4-HO-3-$EtOC_6H_3$	82
15	7{15}	4-$MeOC_6H_4$	72[e]	38	7{38}	4-EtO-3-$MeOC_6H_3$	69
16	7{16}	2-$EtOC_6H_4$	80[f]	39	7{39}	3-Br-4-HO-5-$MeOC_6H_2$	74
17	7{17}	3,4-$(MeO)_2C_6H_3$	70[a]	40	7{40}	3-Br-4-HO-5-$EtOC_6H_2$	69
18	7{18}	2,5-$(MeO)_2C_6H_3$	70[a]	41	7{41}	1-naphthyl	72[a]
19	7{19}	2,4-$(MeO)_2C_6H_3$	82[d]	42	7{42}	2-MeO-1-naphthyl	65
20	7{20}	2,3-$(MeO)_2C_6H_3$	70	43	7{43}	4-(4-$ClC_6H_4CH_2O$)C_6H_4	77[g]
21	7{21}	3,4-$(OCH_2O)C_6H_3$	79[a]	44	7{44}	4-$PhCH_2O$-3-$MeOC_6H_3$	75[g]
22	7{22}	2,4,5-$(MeO)_3C_6H_2$	71	45	7{45}	4-(2-$ClC_6H_4CH_2O$)C_6H_4	57
23	7{23}	3,4,5-$(MeO)_3C_6H_2$	67[a]	46	7{46}	4-$EtOC_6H_4$	65[a]
				47	7{47}	3-$MeOC_6H_4$	68

[a]Ref 89. [b]Ref 82. [c]Ref 84. [d]Ref 83. [e]Ref 85. [f]Ref 90. [g]Ref 81. [h]Ref 86.

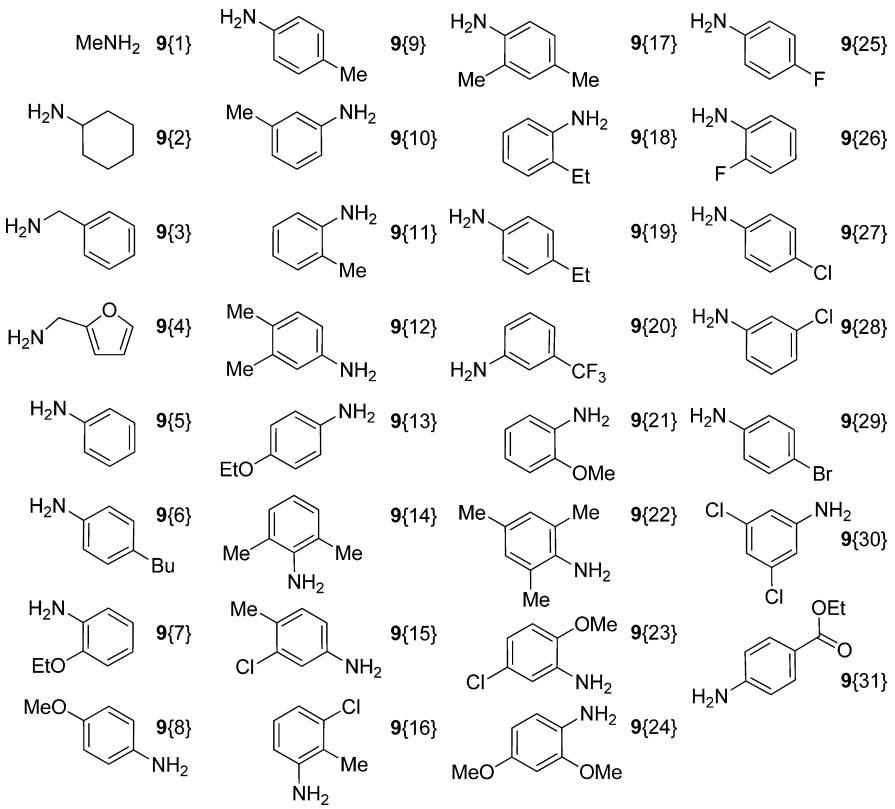
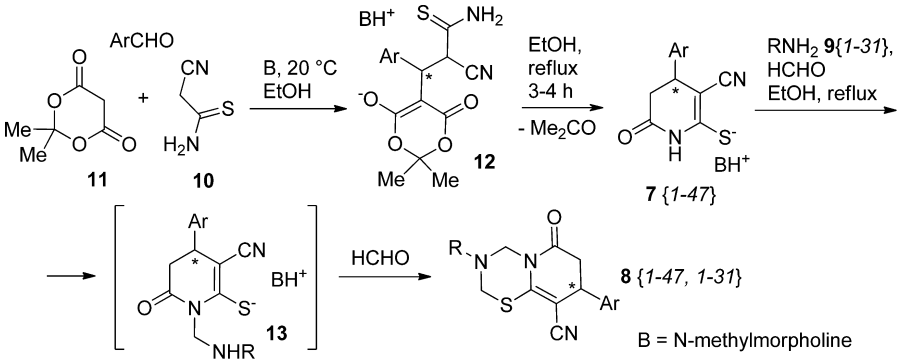


Figure 3. Diversity of primary amines **9**.

less soluble in higher alcohols, whereas lower yields of thiadiazines **8** were obtained with MeOH. Both aliphatic and aromatic primary amines reacted under these conditions. However, we did not succeed to obtain pyridothiadiazines **8** from anilines bearing strong electron-withdrawing substituents (e.g., NO_2, CN, Ac, PhC(O)) in ortho- or para-position to amino group, heterocyclic amines (e.g., Gewald's 2-amino-thiophenes, 2-aminopyridines, 2-aminothiazoles) and amino

dx.doi.org/10.1021/co5000807 | ACS Comb. Sci. XXXX, XXX, XXX–XXX

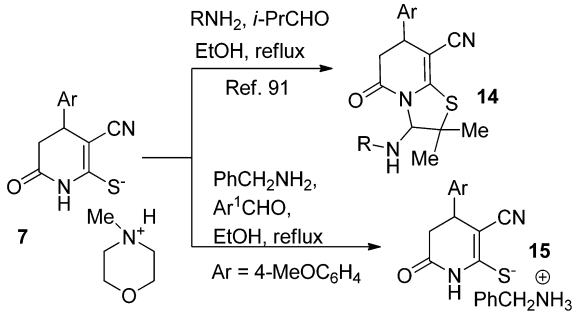
Scheme 3. Synthesis of Starting Thiolates 7 and Pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitriles 8



acids (α- and β-alanines). Unsatisfactory results were also obtained in the case of most sterically hindered amines, such as 2,6-dimethylaniline **9**{*14*}, 2-$MeOC_6H_4NH_2$ **9**{*21*}, 5-Cl-2-$MeOC_6H_3NH_2$ **9**{*23*}, 2-$CF_3C_6H_4NH_2$, *tert*-butylamine, and 2-ethyl-6-methylaniline. Meanwhile, 2-$EtOC_6H_4NH_2$ **9**{*7*}, mesidine **9**{*22*}, and 2-alkylanilines **9**{*11,16,17,18*} showed good reactivity.

The scope of the reaction is limited to the use of formaldehyde only. Under these conditions, aliphatic aldehydes are known to react in different ways: thus, as we have shown before,[91] the reaction of thiolates **7** with primary amines **9** and isobutyraldehyde leads to thiazolo[3,2-*a*]pyridines **14** (Scheme 4). The reaction of thiolate 7{*6*} with acetaldehyde and alkyl

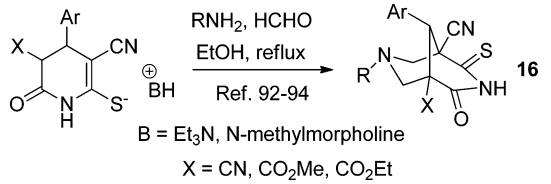
Scheme 4. Reaction of Thiolates 7 with Amines 9 and Various Aldehydes



amines led to appearance of cherry red coloration and resulted in the formation of tars, probably due to aldol-type condensations of CH_3CHO promoted by amines. The product of the reaction of thiolate 7{*15*} with *p*-toluidine and benzaldehyde consists of a red tarry mass, while the reaction with benzylamine and 4-ClC_6H_4CHO, 4-$MeOC_6H_4CHO$ or furfural afforded colorless crystalline solids, which appeared to be the same compound, benzylammonium salt **15**. The prolonged heating did not result in the formation of any Mannich-type products with thiolates **7**.

The structure of thiolate component is another key factor which has strong influence on the reaction outcome. As we have reported earlier,[92−94] those 1,4,5,6-tetrahydropyridine-2-thiolates that bear an electron-withdrawing group (C≡N, CO_2R) at C-5 position under the same conditions gave no 1,3,5-thiadiazine derivatives but readily underwent the double Mannich-type reaction at C-3 and C-5 to afford 3,7-diazabicyclo[3,3,1]nonanes **16** (Scheme 5). In contrast, the aminomethylation of thiolates 7 proceeds with high regioselectivity to give no C-3 attacked products, even in trace

Scheme 5. Aminomethylation of C-5 Substituted 1,4,5,6-Tetrahydropyridine-2-thiolates

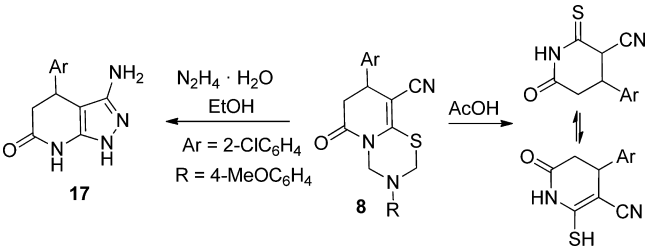


amounts. We were a bit surprised by the fact that the yields of pyrido[2,1-*b*][1,3,5]thiadiazines **8** are dependent on the nature of an aromatic substituent at C-4 position of starting thiolate **7**. The worst results were obtained with thiolates 7{*24−26,32,34*} (Ar = 2-NO_2Ph, 3-NO_2Ph, 4-NO_2Ph, 2-furyl, 2-thienyl).

Overall, pyridothiadiazines **8** were obtained in yields ranging from poor to excellent, depending mostly on the nature of primary amine and thiolate. Table S1 (Supporting Information) gives a few representative examples of how the yields of pyridothiadiazines **8** depend on the nature of the reagents.

N-Methylmorpholinium 4-aryl-6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates 7{*1−47*} are yellow or orange crystalline solids, soluble in hot aqueous EtOH but insoluble in acetone and cold EtOH. Pyridothiadiazines **8** are colorless or slightly yellowish crystalline solids, stable in neutral media, soluble in hot acetone, EtOAc, DMF or DMSO, but sparingly soluble in ether or alcohols. Compounds **8** are quite stable but decompose when treated with AcOH or diluted strong acids to form a complex mixture of *retro*-Mannich products. On the other hand, 1,3,5-thiadiazine ring may be cleaved with hydrazine hydrate to give after further heterocyclization the known[95] pyrazolopyridines of general structure **17**. Thus, when compound **8**{6,9} was reacted with excessive $N_2H_4{\cdot}H_2O$ in hot EtOH, pyrazolopyridine **17a** (Ar = 2-ClC_6H_4) was obtained in 36% yield (Scheme 6).

Scheme 6. Reactions of Pyridothiadiazines 8



dx.doi.org/10.1021/co5000807 | ACS Comb. Sci. XXXX, XXX, XXX−XXX

Starting 1,4,5,6-tetrahydropyridine-2-thiolates **7** and pyrido[2,1-*b*][1,3,5]thiadiazines **8** were characterized by ^{1}H NMR and IR spectroscopy. In the IR spectra of compounds **8**, strong absorptions at 1675−1690 and 2190−2205 cm^{-1} were detected because of the C═O and conjugated C≡N groups, respectively. 1D NMR (^{1}H NMR, ^{13}C NMR, ^{13}C DEPT NMR) and 2D NMR experiments (^{1}H−^{1}H COSY, ^{1}H,^{13}C-HMBC, and ^{1}H,^{13}C-HSQC) were used for the complete and unambiguous ^{1}H and ^{13}C chemical shift assignments for selected compound, 3-(2-furylmethyl)-8-(2,3-dimethoxyphenyl)-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitrile **8**{*20,4*} (Figure 4). Full set of data of homo- and heteronuclear correlations is given in the Supporting Information, Table S2.

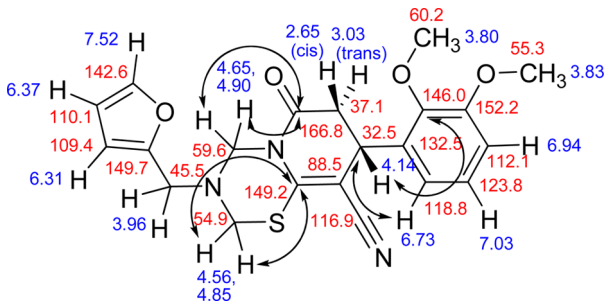


Figure 4. Assignment of signals and key ^{1}H−^{13}C HMBC correlations for compound **8**{*20,4*}.

In conclusion, an efficient and simple method for the preparation of 3-*R*-8-aryl-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitriles **8**{*1−47,1−31*} using readily available starting materials by Mannich-type reaction is reported. A small library of *N*-methylmorpholinium 4-aryl-6-oxo-3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates **7**{*1−47*}, 37% aq. HCHO and primary amines **9**{*1−31*} were used as starting compounds. The developed method requires no catalyst and usually gives acceptable yields of pure pyridothiadiazines.

EXPERIMENTAL PROCEDURES

The ^{1}H NMR and ^{13}C NMR spectra of thiolates **7** and pyridothiadiazines **8** were performed on Bruker DRX-500 instrument (500.13 and 125.76 MHz for ^{1}H and ^{13}C, respectively) in DMSO-d_6 using residual solvent peak (δ 2.49 ppm; 39.50 ppm for ^{1}H and ^{13}C, respectively) as reference or with Me_4Si as the internal standard. The ^{1}H NMR spectra of benzylammonium salt **15** were recorded on a Bruker DRX-400 instrument (400.40 MHz) and ^{1}H NMR spectrum of pyrazolopyridine **17a** was recorded on a Varian Gemini 200 instrument (199.975 MHz) in DMSO-d_6. NMR experiments for compound **8**{*20,4*} were performed on a Bruker Avance II 400 instrument (400.13 and 100.62 MHz for ^{1}H and ^{13}C respectively) in DMSO-d_6 or CCl_4−DMSO-d_6 with Me_4Si as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment of peak.

FT-IR spectra of thiolates **7** were recorded in KBr pellets using Thermo Nicolet Avatar 370 FT-IR Spectrometer. IR spectra of thiadiazines **8**, benzylammonium salt **15**, and pyrazolopyridine **17a** were recorded on an IKS-29 IR-spectrometer (LOMO, USSR).

LCMS analyses were obtained on a PE SCIEX API 150EX mass spectrometer (API-ES) following separation on a Shimadzu LC-10AD liquid chromatography system with Waters XBridge C18 3,5 μm (4.6 × 150 mm) column, equipped with Shimadzu SP D-10A UV−vis detector (220 and 254 nm) and Sedex 75 ELSD detector.

Elementary analyses were taken on a Carlo Erba Strumentazione 1106 Analyzer.

Melting points were measured on a Koefler hot stage and are uncorrected. The purity of the compounds were checked by TLC (thin layer chromatography) on Silufol UV 254 plates (sorbent, Silpearl, large-pore silicagel after Pitra with luminiscent indicator for UV 254 on the aluminum foil; binder, starch) in the acetone−hexane (1:1) system; spots were visualized with iodine vapors and UV light.

Synthesis of Starting *N*-Methylmorpholinium 4-Aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates 7{*1−47*}. *General Procedure.* The thiolates 7{*1−47*} were obtained in a manner analogous to reported procedures[81−90] as follows: A 0.5 L round-bottom flask fitted with an overhead stirrer was charged with the corresponding aromatic aldehyde (0.1 mol), cyanothioacetamide **10** (10.0 g, 0.10 mol) and EtOH (100 mL). *N*-Methylmorpholine (0.8−1.0 mL) was added, and the mixture was stirred for 1 h at 20 °C (yellow/orange crystalline 3-aryl-2-cyanoprop-2-enethioamides may precipitate from the solution). Then Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) **11** (15.0 g, 0.104 mol) and *N*-methylmorpholine (16.5 mL, 0.15 mol) were added, and the solution was stirred vigorously until the mixture became pale yellow and a white solid of the Michael adduct **12** precipitated. (If the precipitate does not appear within 20 min, the mixture was refluxed for 2−4 h and worked up as shown below.) The obtained slurry was stirred for 0.5 h. Then the flask was fitted with a reflux condenser. The mixture was refluxed to complete dissolution of the Michael adduct 12 and until evolution of CO_2 ceased (∼2−4 h). The solution was evaporated to a syrupy consistency and treated with dry acetone (100 mL). The crystalline precipitate of the corresponding thiolate **7** separates upon cooling to 15 °C and stirring (or seeding). The mixture was allowed to stand overnight, after which the solid was filtered off, washed with cold EtOH and acetone to give *N*-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates 7{*1−47*} in 53−83% yields. The compounds were used without further purification.

Synthesis of (8*R*/8*S*)-3-*R*-8-Aryl-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazin-9-carbonitriles 8{*1−47,1−31*}. *General Procedure.* Pyrido[2,1-*b*][1,3,5]thiadiazines **8** were prepared as follows: the corresponding thiolate 7{*1−47*} (2.5 mmol) was dissolved in 15−20 mL of warm EtOH; water (3−5 mL) may be added if appropriate. The obtained solution may be filtered through a paper filter to remove trace solids. To the solution, a primary amine **9**{*1−31*} (2.6−2.7 mmol, 1.04−1.08 equiv) and an excess of 37% aq. HCHO (5.0 mL, *d* = 1.08 g/mL, 66.6 mmol) were added, and the mixture was refluxed for 2−4 min under vigorous stirring until the product began to separate from the boiling solution. If no solid separated, the solution was allowed to cool to room temperature and left for 24−72 h. The crystalline solid was collected and washed with water, cold EtOH, ether, and then purified (if appropriate) by recrystallization. Selected data on the yields of pyrido[2,1-*b*][1,3,5]thiadiazines **8** are given in

dx.doi.org/10.1021/co5000807 | ACS Comb. Sci. XXXX, XXX, XXX−XXX

Table S1 (Supporting Information). Spectra of selected pyridothiadiazines **8** are given as PDF files in the archive (Supporting Information).

■ ASSOCIATED CONTENT

Supporting Information

Further details on the experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Victor_Dotsenko@bigmir.net.

Author Contributions

The study was initiated and designed by V.V.D. Compounds were synthesized and characterized by V.V.D. and K.A.F. NMR study was performed by S.Y.S., T.M.P., and O.S.P.; V.V.D. wrote the manuscript and Supporting Information. The study was supervised by S.G.K. All authors discussed and approved the publication of the manuscript.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Moody, C. J. Polyoxa, polythia and polyaza six-membered ring systems. In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 1984; pp 1039−1096.

(2) Smalley, R. K. 1,3,5-Oxadiazines and 1,3,5-thiadiazines. In *Comprehensive Heterocyclic Chemistry II*, Vol. 6; Boulton, A. J., Ed.; Elsevier: Oxford, U.K., 1996; pp 783−823.

(3) Shobana, N.; Farid, P. 1,3,5-Oxadiazines and 1,3,5-thiadiazines. In *Comprehensive Heterocyclic Chemistry III*, Vol. 9; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, U.K., 2008; pp 457−521.

(4) Manohar, V.; Murthy, S. V. K. N.; Sirsi, M.; Rao, G. R.; Rao, P. L. N. Antidermatophytic activity of 2-thiotetrahydro-1,3,5-thiadiazines and isothiocyanates. *J. Pharm. Sci.* **1975**, *64*, 164−165.

(5) Wurbach, G. Antimycotic effect and skin tolerance of synthetic mustard oil compounds. I. 2-Thion-tetrahydro-1,3,5-thiadiazines. *Dermatol. Monatsschr.* **1971**, *157*, 239−247 (In German)..

(6) Hussein, M. A.; El-Shorbagi, A. N.; Khallil, A. R. Synthesis and antifungal activity of 3,3′-ethylenebis(5-alkyl-1,3,5-thiadiazine-2-thiones). *Arch. Pharm., Pharm. Med. Chem.* **2001**, *334*, 305−308.

(7) Aboul-Fadl, T.; Hussein, M. A.; El-Shorbagi, A. N.; Khallil, A. R. New 2*H*-tetrahydro-1,3,5-thiadiazine-2-thiones incorporating glycine and glycinamide as potential antifungal agents. *Arch. Pharm., Pharm. Med. Chem.* **2002**, *335*, 438−442.

(8) Takubo, T.; Tadaoka, T. Synthesis and antifungal effect of tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives. *Yakugaku Zasshi* **1964**, *84*, 466−469 (in Japanese)..

(9) Smyth, H. F.; Carpenter, C. P.; Weil, C. S. Toxicologic studies on 3,5-dimethyltetrahydro-1,3,5,2*H*-thiadiazine-2-thione, A soil fungicide and slimicide. *Toxicol. Appl. Pharmacol.* **1966**, *9*, 521−527.

(10) Ertan, M.; Bilgin, A. A.; Palaska, E.; Yulug, N. Syntheses and antifungal activities of some 3-(2-phenylethyl)-5-substituted-tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones. *Arzneim. Forsch.* **1992**, *42*, 160−163.

(11) Ertan, M.; Ayyildiz, H. G.; Yulug, N. Synthesis and antifungal activities of some new tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones. *Arzneim. Forsch.* **1991**, *41*, 1182−1185.

(12) Rieche, A.; Hilgetag, G.; Martini, A.; Nejedly, O.; Schlegel, J. New compounds with bactericidal and fungicidal activity and which inhibit the growth of viruses. I. 2-Thiotetrahydro-1,3,5-thiadiazine ("carbothialdine") and dithiocarbamic acid salts. *Arch. Pharm.* **1960**, *293*, 957−967 (In German).

(13) Bhagat, S. K.; Deshmukh, S. P. Synthesis of 3-aryl-2-*tert*-butylimino-6-*p*-tolylimino-4-(S-tetra-*O*-benzoyl-D-glucopyranosyl)-2,3-dihydro-1,3,5-thiadiazine hydrochlorides and their antibacterial and antifungal studies. *J. Indian Chem. Soc.* **2005**, *82*, 1022−1024.

(14) Bhagat, S. K.; Deshmukh, S. P. On glucosylthioureides: Synthesis of 3-aryl-2-phenylimino-6-*p*-tolylimino-4-(*S*-tetra-*O*-benzoyl-D-glucopyranosyl)-2,3-dihydro-1,3,5-thiadiazines (hydrochlorides) and their antibacterial and antifungal studies. *J. Indian Chem. Soc.* **2003**, *80*, 654−655.

(15) El Bialy, S. A. A.; Abdelal, A. M.; El-Shorbagi, A. N.; Kheira, S. M. M. 2,3-Bis(5-Alkyl-2-thiono-1,3,5-thiadiazin-3-yl)propionic acid: One-pot domino synthesis and antimicrobial activity. *Arch. Pharm., Pharm. Med. Chem.* **2005**, *338*, 38−43.

(16) Sarac, S.; Ertan, M.; Balkan, A.; Yulug, N. Synthesis and antimicrobial activities of some new tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives of cefadroxil. *Arch. Pharm.* **1991**, *324*, 449−453.

(17) Ertan, M.; Tayhan, A. B.; Yulug, N. Synthesis and antimicrobial activities of some new tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives of ampicillin. *Arch. Pharm.* **1990**, *323*, 605−609.

(18) El-Shorbagi, A. N. New tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives as potential antimicrobial agents. *Arch. Pharm.* **2000**, *333*, 281−286.

(19) Deohate, P. P.; Berad, B. N. Synthesis and antimicrobial activity of 1,3,5-thiadiazines and their isomerism into 1,3,5-triazines. *Indian J. Chem.* **2005**, *44B*, 638−642.

(20) Ilhan, E.; Capan, G.; Ergenc, N.; Uzun, M.; Kiraz, M.; Kaya, D. Synthesis and antimicrobial activity of new tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives. *Farmaco* **1995**, *50*, 787−790.

(21) Ertan, M.; Sarac, S.; Yulug, N. Synthesis and antimicrobial activities of some new tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives of amoxicillin. *Arzneim. Forsch.* **1990**, *40*, 790−795.

(22) Balkan, A.; Ertan, M.; Sarac, S.; Yulug, N. Synthesis and antimicrobial activities of some new tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives of cephalexin. *Arzneim. Forsch.* **1990**, *40*, 1246−1249.

(23) Coburn, R. A.; Ho, C. H.; Bronstein, M. L. Synthesis and in vitro Antimicrobial Activity of 6-Substituted 2*H*-1,3,5-Thiadiazine-2,4(3*H*)-diones. *J. Med. Chem.* **1982**, *25*, 481−483.

(24) Ozçelik, A. B.; Ersan, S.; Ural, A. U.; Ozkan, S.; Ertan, M. Synthesis of 3-substituted-5-(4-carboxycyclohexylmethyl)-tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives as antifibrinolytic and antimicrobial agents. *Arzneim. Forsch.* **2007**, *57*, 554−559.

(25) Würbach, G.; Klöcking, H. P. 2-Thiontetrahydro-1.3.5-thiadiazines with antifibrinolytic properties. *Pharmazie* **1973**, *28*, 254−257.

(26) Klocking, H. P.; Wurbach, G. Antifibrinolytic and antimycotic properties of 2-thioxotetrahydro-1,3,5-thiadiazine. *Farmakol. Toxicol.* **1976**, *39*, 432−436 (in Russian)..

(27) Wurbach, G.; Klocking, H. P. On the fungistatic and antifibrinolytic effect of tetrahydro-1,3,5-thiadiazine-2-thiones. *Ann. Acad. Med. Lodzensis* **1974**, *15*, 147−151 (in Polish)..

(28) Tartler, G.; Weuffen, W.; Fröhling, P. Relations of chemical constitution and germ-killing action. 9. Tuberculostatic properties of a 2-thiotetrahydro-1,3,5,-thiadiazine in vitro. *Arch. Exp. Veterinarmed.* **1965**, *19* (3), 9−18 (in German)..

(29) Sriram, D.; Mallika, K. J.; Yogeeswari, P. Synthesis of Tetrahydro-2*H*-[1,3,5]-thiadiazine-5-(4-pyridylcarboxamido)-2-thione with antitubercular activity. *Sci. Pharm.* **2004**, *72*, 35−41.

(30) Aboul-Fadl, T.; Hassanin, K. Tetrahydro-2*H*-1,3,5-thiadiazine-5-(4-pyridylcarboxamide)-2-thione derivatives as prodrugs for isoniazid; synthesis, investigations and in vitro antituberculous activity. *Pharmazie* **1999**, *54*, 244−247.

(31) Katiyar, D.; Tiwari, V. K.; Tripathi, R. P.; Srivastava, A.; Chaturvedi, V.; Srivastava, R.; Srivastava, B. S. Synthesis and antimycobacterial activity of 3,5-disubstituted thiadiazine thiones. *Bioorg. Med. Chem.* **2003**, *11*, 4369−4375.

(32) Kagabu, S.; Murata, N.; Hibino, R.; Hanzawa, M.; Nishimura, K. Insecticidal and neuroblocking activities of thiamethoxam-type compounds in the american cockroach (*Periplaneta americana L.*). *J. Pestic. Sci.* **2005**, *30*, 111−115.

(33) For a brief review on the buprofezin, see: Kanno, H. An approach to a novel insect growth regulator buprofezin (Applaud). *Pure Appl. Chem.* **1987**, *59*, 1027−1032.
(34) Uchida, M.; Izawa, Y.; Sugimoto, T. Inhibition of prostaglandin biosynthesis and oviposition by an insect growth regulator, buprofezin, in *Nilaparvata lugens* Stål. *Pestic. Biochem. Physiol.* **1987**, *27*, 71−75.
(35) Izawa, Y.; Uchida, M.; Sugimoto, T.; Asai, T. Inhibition of chitin biosynthesis by buprofezin analogs in relation to their activity controlling *Nilaparvata lugens* Stål. *Pestic. Biochem. Physiol.* **1985**, *24*, 343−347.
(36) Uchida, M.; Asai, T.; Sugimoto, T. Inhibition of cuticle deposition and chitin biosynthesis by a new insect growth regulator, buprofezin, in *Nilaparvata lugens* Stål. *Agric. Biol. Chem.* **1985**, *49*, 1233−1234.
(37) Cottage, E. L. A.; Gunning, R. V. Buprofezin inhibits acetylcholinesterase activity in B-biotype *Bemisia tabaci*. *J. Mol. Neurosci.* **2006**, *30*, 39−40.
(38) Smith, M. S.; Weeraratna, C. S. Influence of some biologically active compounds on microbial activity and on the availability of plant nutrients in soils II. Nitrapyrin, dazomet, 2-chlorobenzamide and tributyl-3-chlorobenzylammonium bromide. *Pestic. Sci.* **1975**, *6*, 605−615.
(39) Goksøyr, J. Chemical and fungicidal reactions of 3,5-dimethyltetrahydro-1,3,5-thiadiazine-2-thione (3,5-D). A comparison with sodium *N*-methyl dithiocarbamate and methyl isothiocyanate. *Acta Chem. Scand.* **1964**, *18*, 1341−1352.
(40) Fu, C. H.; Hu, B. Y.; Chang, T. T.; Hsueh, K. L.; Hsu, W. T. Evaluation of dazomet as fumigant for the control of brown root rot disease. *Pest. Manage. Sci.* **2012**, *68*, 959−962.
(41) Munnecke, D. E.; Martin, J. P. Release of methyl isothiocyanate from soils treated with mylone (3,5-dimethyltetrahydro-1,3,5-2*H*-thiadiazine-2-thione). *Phytopathology* **1964**, *54*, 941−945.
(42) Drescher, N.; Otto, S. Uber den abbau von dazomet im boden. *Residue Rev.* **1968**, *23*, 49−54.
(43) Barnard, A. J.; Hornby, D. The effects of dazomet and nitrogen fertilizer on successive crops of maize (*Zea mays L.*) grown for either grain or forage. *J. Agric. Sci.* **1982**, *98*, 7−15.
(44) Morrell, J. J.; Sexton, C. M.; Lebow, S. The effect of pH on decomposition of Mylone (dazomet) and tridipam to fungitoxic methylisothiocyanate in wood. *Wood Fiber Sci.* **1988**, *20*, 422−430.
(45) Sert, S.; Ercag, A.; Sentürk, O. S.; Sterenberg, B. T.; Udachin, K. A.; Özdemir, Ü.; Sarikahya, F. U. Photochemical reactions of metal carbonyls $[M(CO)_6$ (M = Cr, Mo, W), $Re(CO)_5Br$, $Mn(CO)_3Cp]$ with 3,5-dimethyl-tetrahydro-2*H*-1,3,5-thiadiazine-2-thione (DTTT) and the crystal structure of $[W(CO)_5(DTTT)]$. *Polyhedron* **2003**, *22*, 1689−1693.
(46) Babaeva, R. I. The effect of thiazon on helminth eggs in soil. *Meditsinskaya Parazitologiya i Parazitarnye Bolezni (Medical Parasitology and Parasitic Diseases)* **1989**, *2*, 25−27 (in Russian)..
(47) Sakashita, M.; Toyoda, K.; Kitahara, M.; Tsuruzoe, N.; Nakayama, S.; Oguchi, K. Mechanisms of the hypolipidemic effect of NIP-200 in rats. *Jpn. J. Pharmacol.* **1993**, *62*, 87−91.
(48) Meinhof, W. Experimental studies and clinical experiences with the new antimycotic agent dibenzthion (3,5-dibenzyl-tetrahydro-1,3,5-thiadiazine-2-thione). *Z. Haut. Geschlechtskr.* **1962**, *33*, 124−131 (In German).
(49) Meinhof, W.; Jannasch, G. Therapeutic experiences with dermatological preparations of the antimycotic dibenzthion. *Z. Haut. Geschlechtskr.* **1963**, *34*, 172−179 (In German)..
(50) Paldrok, H. Dibenzthion (3,5-dibenzyltetrahydro-1,3,5-thiadiazine-2-thione), A new drug for dermatomycoses. *Sven. Lakartidn.* **1964**, *61*, 2922−2926 (in Swedish)..
(51) Weuffen, W. Testing of antimycotic active substances on the model of experimental cockscomb epidermophytosis. I. Methods and testing of 3,5-dibenzyl-2-thion-tetrahydro-1,3,5-thiadiazine (D 47). *Mykosen* **1968**, *11*, 33−39 (In German)..
(52) Wang, Z. Y.; Shi, H. X.; Shi, H. J. Novel synthesis of condensed heterocyclic systems containing 1,2,4-triazole ring. *Synth. Commun.* **2001**, *31*, 2841−2848.
(53) Wang, Z. Y.; You, T. P.; Shi, H. J.; Shi, H. X. Synthesis of 3,6-disubstituted tetrahydro-*s*-triazolo[3,4-*b*][1,3,5]thiadiazines. *Molecules* **1996**, *1*, 89−92, http://www.mdpi.net/molecules/list96.htm.
(54) Wang, Z. Y.; You, T. P.; Shi, H. J.; Shi, H. X. Studies on double Mannich reaction of 3-aryl-5-mercapto-1,2,4-triazoles. *Gaodeng Xuexiao Huaxue Xuebao* **1997**, *18* (4), 550−553; (in Chinese) *Chem. Abstr.* **1997**, *127*, 95265t.
(55) Shi, H. X.; Shi, H. J.; Wang, Z. Y. Synthesis & bioactivity of chiral 3,5-disubstituted-s-triazolo[3,4-*b*]-2,4-dihydro-1,3,5-thiadiazines. *Youji Huaxue* **2000**, *20* (3), 344−347; (In Chinese) *Chem. Abstr.* **2000**, *133*, 120280c.
(56) Hozein, Z. A.; Sarhan, A. A. O.; El-Sherief, H. A. H.; Mahmoud, A. M. A convenient one-pot synthesis of pyrazolo[3,4-*d*]pyrimidines and *s*-triazolo[3,4-*b*][1,3,5]thiadiazines. *Z. Naturforsch. B* **1997**, *52*, 1401−1412; *Chem. Abstr* **1998**, *128*, 88906v.
(57) Shi, H. J.; Shi, H. X.; Wang, Z. Efficient one-pot synthesis of *s*-triazolo[3,4-*b*]-[1,3,5]thiadiazines containing a chiral side chain by double Mannich type reaction. *J. Heterocycl. Chem.* **2001**, *38*, 929−932.
(58) Shi, H. J.; Wang, Z. Y.; Shi, H. X. Synthesis and study of 3-methyl-5-aryl-s-triazolo[3,4-b]-2H,4H-1,3,5-thiadiazines. *Chimia* **1997**, *51*, 529; *Ref. Zhurn. Khim.* **1998**, No. 13ZH272.
(59) Shi, H.; Wang, Z.; Shi, H. Novel synthesis of chiral 5-aryltriazolo[3,4-*b*]-3-α-phenylethyl-2,4-2*H*-1,3,5-thiadiazines by bis-Mannich reaction. *Synth. Commun.* **1999**, *29*, 2027−2034.
(60) Sarfraz, T. B.; Husain, S. A.; Murtaza, N.; Siddiqui, B. S. Potential antibacterial agents part V. Synthesis and structural characterization of some new 3-aryl-7*H*,6-(aryl)-5*H*-1,2,4-triazolo-[3,4-*b*]-1,3,5-thiadiazines. *Pak. J. Sci. Ind. Res.* **2000**, *43*, 334−337.
(61) Hozein, Z. A. Intramolecular Mannich reaction for synthesis of imidazo-[2,1-*b*]-1,3,5-thiadiazines and 1,2,4-triazino[3,2,-*b*]-1,3,5-thiadiazines. *J. Chem. Res.* **2000**, *3*, 99.
(62) Frolov, K. A.; Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. Mannich reaction in the synthesis of N,S-containing heterocycles. Part 1. Synthesis of novel derivatives of imidazo[2,1-*b*][1,3,5]-thiadiazine. *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 2226−2228.
(63) Yadav, L. D. S.; Vaish, A.; Sharma, S. New fungitoxic fused-ring synthetics incorporating azoles and azines in different combinations. *J. Agric. Food Chem.* **1994**, *42*, 811−813.
(64) Sarhan, A. A. O.; Abdel-Hafez, S. H.; El-Sherief, H.; Aboel-Fadl, T. Utility and synthetic uses of Mannich reaction: An efficient route for synthesis of thiadiazino-[1,3,5][3,2-*a*]benzimidazoles. *Synth. Commun.* **2006**, *36*, 987−996.
(65) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. The synthesis of cyclopenta[*c*]pyridine (2-pyrindene) derivatives. *Monatsh. Chem.* **2008**, *139*, 271−275.
(66) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. An efficient Mannich-type synthesis of bis(pyrido[2,1-*b*][1,3,5]thiadiazin-7-yl)-methanes. *Monatsh. Chem.* **2008**, *139*, 657−661.
(67) Dotsenko, V. V.; Krivokolysko, S. G.; Rusanov, E. B.; Litvinov, V. P. The Mannich reaction in the synthesis of N,S-containing heterocycles. Part 5. Synthesis and structures of new pyrimido[2,1-*b*][1,3,5]thiadiazine derivatives. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 1437−1440.
(68) Dotsenko, V. V.; Frolov, K. A.; Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. A convenient Mannich-type one-pot synthesis of pyrimido[6,1-*b*][1,3,5]thiadiazines. *Monatsh. Chem.* **2006**, *137*, 1089−1098.
(69) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. The Mannich reaction in the synthesis of N,S-containing heterocycles. Part 6. New approaches to the synthesis of pyrimido[4,3-*b*][1,3,5]-thiadiazine derivatives. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 1474−1476.
(70) Dotsenko, V. V.; Frolov, K. A.; Krivokolysko, S. G.; Litvinov, V. P. The Mannich reaction in the synthesis of N,S-containing heterocycles. Part 10. Recyclization of stable cyclic Michael adducts, *N*-methylmorpholinium 6-*R*-6-hydroxy-1,4,5,6-tetrahydropyridine-2-thiolates, to pyrimido[4,3-*b*][1,3,5]thiadiazines under conditions of aminomethylation reaction. *Russ. Chem. Bull., Int. Ed.* **2009**, *58*, 1479−1483.

(71) Mares, D.; Romagnoli, C.; Andreotti, E.; Forlani, G.; Guccione, S.; Vicentini, C. B. Emerging antifungal azoles & effects on *Magnaporthe grisea*. *Mycol. Res.* **2006**, *110*, 686−696.
(72) Mares, D.; Romagnoli, C.; Vicentini, C. B.; Sacchetti, G.; Bruni, A. Antifungal screening of seven new azole derivatives. *Microbios* **1996**, *86* (348), 185−193.
(73) Vicentini, C. B.; Forlani, G.; Manfrini, M.; Romagnoli, C.; Mares, D. Development of new fungicides against *Magnaporthe grisea*: Synthesis and biological activity of pyrazolo[3,4-*d*][1,3]thiazine, pyrazolo[1,5-*c*][1,3,5]thiadiazine, and pyrazolo[3,4-*d*]pyrimidine derivatives. *J. Agric. Food Chem.* **2002**, *50*, 4839−4845.
(74) Vicentini, C. B.; Mares, D.; Tartari, A.; Manfrini, M.; Forlani, G. Synthesis of pyrazole derivatives and their evaluation as photosynthetic electron transport inhibitors. *J. Agric. Food Chem.* **2004**, *52*, 1898−1906.
(75) Vicentini, C. B.; Guccione, S.; Giurato, L.; Ciaccio, R.; Mares, D.; Forlani, G. Pyrazole derivatives as photosynthetic electron transport inhibitors: new leads and structure−activity relationship. *J. Agric. Food Chem.* **2005**, *53*, 3848−3855.
(76) Liu, S. Y.; Qian, X. H.; Chen, J.; Song, G. H. Novel fused heterocycles: Synthesis and activity of 5,6-dihydro-7-thia-1,3,3*a*,5-tetraazainden-4-one and 1-thia-3,4*a*,9-triazafluoren-4-one derivatives. *Monatsh. Chem.* **2000**, *131*, 953−957.
(77) Aratani, M.; Hashimoto, M. Synthesis of 3-azacephalosporins. *J. Am. Chem. Soc.* **1980**, *102*, 6171−6172.
(78) Farooq, S.; Streibert, H.-P. Imidazo- and pyrimido-1,3,5-thiadiazin-4-ones. U.S. Patent 4,443,445 1984; www.espacenet.com.
(79) Farooq, S.; Streibert, H.-P. Imidazo- and pyrimido-1,3,5-thiadiazin-4-ones. Great Britain Patent 2,106,513 1983; www.espacenet.com.
(80) Farooq, S.; Streibert, H.-P. Imidazo- and pyrimido-1,3,5-thiadiazin-4-ones. Swiss Patent CH654,002 1986. www.espacenet.com.
(81) Osolodkin, D. I.; Kozlovskaya, L. I.; Dueva, E. V.; Dotsenko, V. V.; Rogova, Yu. V.; Frolov, K. A.; Krivokolysko, S. G.; Romanova, E. G.; Morozov, A. S.; Karganova, G. G.; Palyulin, V. A.; Pentkovski, V. M.; Zefirov, N. S. Inhibitors of tick-borne flavivirus reproduction from structure-based virtual screening. *ACS Med. Chem. Lett.* **2013**, *4*, 869−874.
(82) Dotsenko, V. V.; Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. Synthesis and structure of pyrido[2,1-*b*][1,3,5]thiadiazine derivatives. *Doklady Chem.* **2003**, *389* (4−6), 92−96.
(83) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. The Mannich reaction in the synthesis of N,S-containing heterocycles. 11. Synthesis of 3,3′-(1,4-phenylene)-bis(8-aryl-6-oxo-3,4,7,8-tetrahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3,5]thiadiazine-9-carbonitriles). *Russ. Chem. Bull., Int. Ed.* **2012**, *61*, 131−135.
(84) Nesterov, V. N.; Krivokolysko, S. G.; Dyachenko, V. D.; Dotsenko, V. V.; Litvinov, V. P. Synthesis, properties, and structures of ammonium 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates. *Russ. Chem. Bull., Int. Ed.* **1997**, *46*, 990−996.
(85) Dyachenko, V. D.; Krivokolysko, S. G.; Litvinov, V. P. A new method for the synthesis of *N*-methylmorpholinium 4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates and their properties. *Russ. Chem. Bull., Int. Ed.* **1997**, *46*, 1758−1762.
(86) Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P. *N*-Methylmorpholinium 4-aryl-5-cyano-3-methoxycarbonyl-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates: synthesis and properties. *Russ. Chem. Bull., Int. Ed.* **2001**, *49*, 487−489.
(87) Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. Synthesis, structure, and alkylation of N-methylmorpholinium 5-[2-cyanoethyl-1-(4-hydroxy-3-methoxyphenyl)-2-thiocarbamoyl]-2,2-dimethyl-6-oxo-1,3-dioxa-4-cyclohexen-4-olate. *Chem. Heterocycl. Compd.* **2002**, *38*, 1269−1275.
(88) Krivokolysko, S. G.; Dyachenko, V. D.; Litvinov, V. P. Synthesis and alkylation of *N*-methylmorpholinium 5-cyano-4-(3- and 4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates. *Russ. Chem. Bull., Int. Ed.* **1999**, *48*, 2308−2311.
(89) Dotsenko, V. V.; Krivokolysko, S. G.; Chernega, A. N.; Litvinov, V. P. Fused sulfur-containing pyridine systems. 1. Synthesis and structures of tetrahydropyridothienopyridinone and tetrahydropyridothiopyranopyridinone derivatives. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 969−977.
(90) Dotsenko, V. V.; Lebedeva, I. A.; Krivokolysko, S. G.; Povstyanoi, M. V.; Povstyanoi, V. M.; Kostyrko, E. O. Reaction of ethyl 4-aryl-6-bromomethyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylates with *N*-methylmorpholinium 3-cyano-1,4-dihydro- and 3-cyano-1,4,5,6-tetrahydropyridine-2-thiolates. *Chem. Heterocycl. Compd.* **2012**, *48*, 462−469.
(91) Dotsenko, V. V.; Krivokolysko, S. G. The Mannich reaction in the synthesis of N,S-containing heterocycles. 14. Unexpected formation of thiazolo[3,2-*a*]pyridines in the aminoalkylation of *N*-methylmorpholinium 4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates by isobutyraldehyde and primary amines. *Chem. Heterocycl. Compd.* **2012**, *48*, 672−676.
(92) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. Aminomethylation of 1,2,3,4-tetrahydropyridine-6-thiolates: A novel approach to synthesis of 3,7-diazabicyclo[3.3.1]nonane derivatives. *Chem. Heterocycl. Compd.* **2005**, *41*, 1428−1429.
(93) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. A double Mannich-type reaction in the 1,4,5,6-tetrahydropyridine-2-thiolate series: A convenient approach to functionalized 3,7-diazabicyclo[3.3.1]nonane derivatives. *Monatsh. Chem.* **2007**, *138*, 489−494.
(94) Dotsenko, V. V.; Krivokolysko, S. G.; Litvinov, V. P. The Mannich reaction in the synthesis of N,S-containing heterocycles. 8. Aminomethylation of 3,5-dicyano-6-oxo-1,4,5,6-tetrahydropyridine-2-thiolates as a method for the synthesis of new functionally substituted 3,7-diazabicyclo[3.3.1]nonane derivatives. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2482−2486.
(95) Rodrigues-Santos, C. E.; Echevarria, A. Convenient syntheses of pyrazolo[3,4-*b*]pyridin-6-ones using either microwave or ultrasound irradiation. *Tetrahedron Lett.* **2011**, *52*, 336−340.