



Cite this: RSC Adv., 2015, 5, 81608

Received 26th July 2015
 Accepted 15th September 2015
 DOI: 10.1039/c5ra14795f
www.rsc.org/advances

Synthetic approaches and functionalizations of imidazo[1,2-a]pyrimidines: an overview of the decade

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Imidazo[1,2-a]pyrimidine has been receiving significant attention in the synthetic chemistry community through different chemosynthetic methodologies *viz.*, multicomponent reactions, condensation reactions, intramolecular cyclizations, tandem reaction, carbon–hydrogen, carbon–carbon, carbon–nitrogen bond formation, aza-Michael–Mannich reaction, chiral compounds synthesis etc. The mechanisms for the selected reactions are also discussed to observe the formation of this heterocyclic moiety. This review comprehensively summarizes the recently reported various synthetic approaches along with its functionalization at 3-positions to construct this privileged scaffold for further use in the development of new chemosynthetic strategies and drug development due to its wide range of applications in medicinal chemistry.

Introduction

Over the past few decades, the bulk of chemists' interest has been on heterocyclic compounds and their various derivatives as well as their applications in the pharmaceutical and chemical fields. Nitrogen containing heterocyclic moieties has received considerable attention because of their potential utility in medicinal chemistry.¹ Research concerning many kinds of heterocyclic compounds, such as imidazo[1,2-a]pyrazines,²

imidazo[1,2-a]pyridines³ and so on, has been the subject of numerous recent reviews. Imidazo[1,2-a]pyrimidines are also a prevalent and important fused heterocyclic system containing three nitrogen atoms. Being, the structural similarity to purines,⁴ imidazo[1,2-a]pyrimidine exhibited a broad range of pharmacological profile *viz.*, anticancer,⁵ antiviral,⁶ antimicrobial,⁷ antibacterial,⁸ antifungal,⁹ anti-inflammatory,¹⁰ GABA receptor ligands,¹¹ local anaesthetic and calcium channel blocking activity.¹² It has also found its application for use as azo dyes,¹³ fabric whiteners,¹⁴ insecticidal, acaricidal and nematicidal agents.¹⁵ It has also been found to be a key structural element of divaplon¹⁶ and fasipron¹⁷ as a potential

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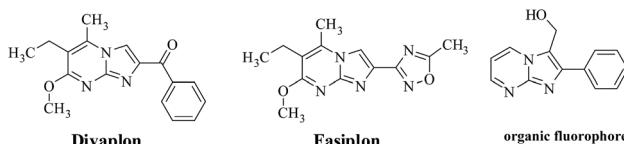


Fig. 1 Imidazo[1,2-a]pyrimidine based preclinical drug candidates and organic fluorophore.

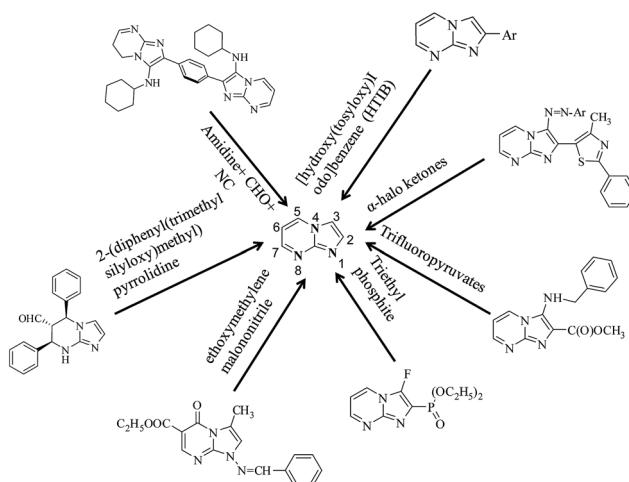


Fig. 2 Access to imidazo[1,2-a]pyrimidine from various reactants.

anxiolytic and anticonvulsant agent whose use was abated in clinical practice.¹⁸ To further explore its applications, this scaffold also act as organic fluorophore being used as biomarkers and photochemical sensors (Fig. 1).¹⁹ Thus, we realize there is a necessity for a comprehensive review to summarize the enormous amount of scattered literature about imidazo[1,2-a]pyrimidines into classifications to facilitate the imidazo[1,2-a]pyrimidines research. In this review, we give an overview to the synthesis of the imidazo[1,2-a]pyrimidines ring and its derivatives on the basis of multicomponent reactions, condensation reactions, intramolecular cyclizations, aza-Michael–Mannich reaction *etc.* that has been reported in the



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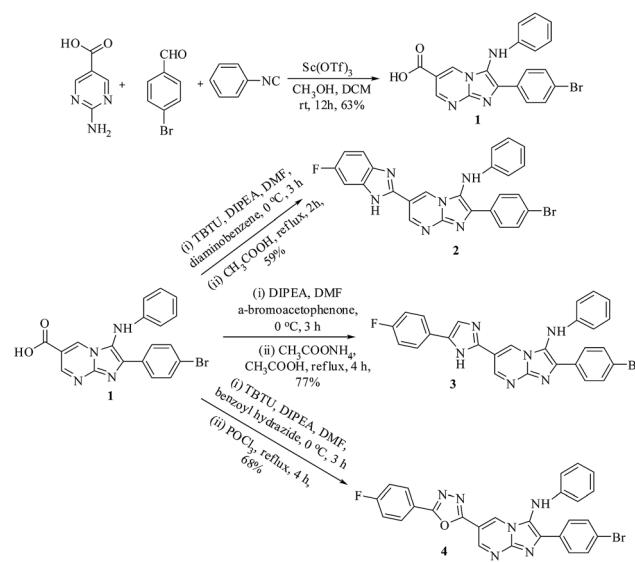
decade (Fig. 2). In addition, this review also tracks the history of all the reactions involved to represent the reactivity of imidazo[1,2-a]pyrimidines at 3-positions.

Multicomponent reactions (MCR)

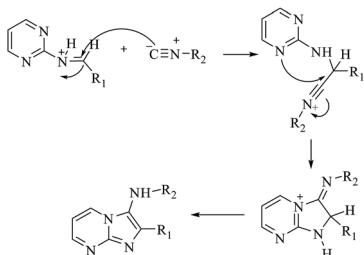
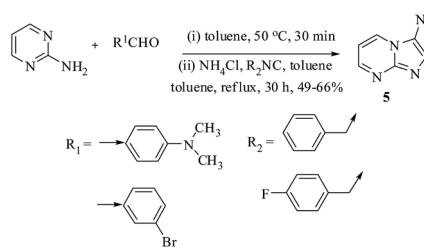
Multicomponent reaction of 2-aminopyrimidine, aldehyde and isocyanide

Al-Tel *et al.* in 2010 reported the post Groebke–Blackburn multicomponent reaction through [4 + 1] cycloaddition of 5-carboxy-2-aminopyrimidine, *p*-bromobenzaldehyde and phenyl isocyanide in the presence of catalytic amount of Sc(OTf)₃ to afford 6-carboxyimidazo[1,2-a]pyrimidine **1**. Coupling reaction of **1** with 1,2-diaminobenzene using TBTU in DMF/CH₃COOH gave benzimidazole substituted imidazo[1,2-a]pyrimidine **2** in 59% isolated yield. Reaction of **1** with α -bromoacetophenone at 0 °C in DMF gave phenyl imidazole substituted imidazo[1,2-a]pyrimidine **3** in 77% isolated yield. Moreover, coupling reaction of **1** with benzoyl hydrazide using *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) and diisopropylethylamine (DIPEA) in DMF followed by phosphorous oxychloride to access oxadiazole substituted imidazo[1,2-a]pyrimidine **4** in 68% yield (Scheme 1).²⁰

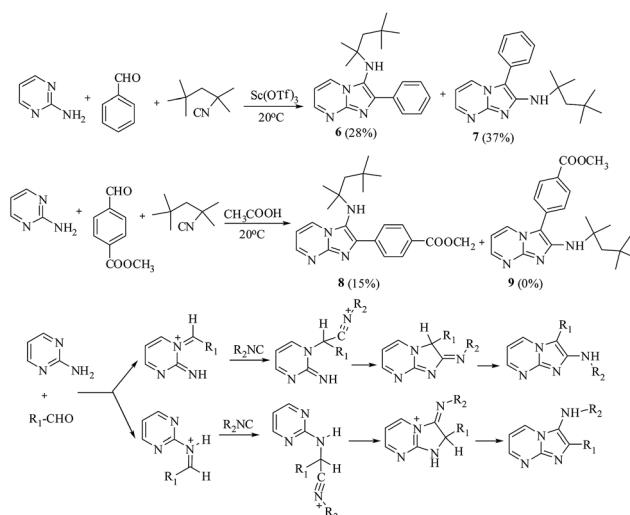
Krasavin and coworkers established the protocol for the synthesis of imidazo[1,2-a]pyrimidines through multicomponent reaction of 2-aminopyrimidine, aldehydes and isonitriles in non polar solvent. This protocol suppressed the formation of side products with the formation of 2,3-disubstituted imidazo[1,2-a]pyrimidines as solo isolated product. Reaction of 2-aminopyrimidine with different aldehydes and isonitriles in the presence of ammonium chloride in toluene afforded the combinatorial library of 3-arylamino-2-substituted imidazo[1,2-a]pyrimidine **5** in 49–66% yields. The reaction proceeded through the formation of a Schiff base of 2-aminopyrimidine with aldehyde followed by insertion of isonitrile that provided



Scheme 1 Synthesis and reactivity of trisubstituted imidazo[1,2-a]pyrimidines.



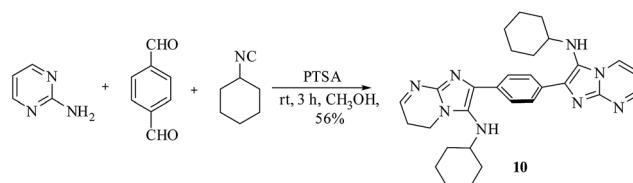
Scheme 2 MCR with aryl isonitriles.



Scheme 3 Synthesis of 2,3-disubstituted imidazo[1,2-a]pyrimidines.

nucleophilic ring nitrogen, which finally cyclized to form imidazo[1,2-a]pyrimidines (Scheme 2).²¹ Reaction of 2-aminopyrimidine with benzaldehyde and 2-isocyano-2,4,4-trimethylpentane catalyzed by scandium triflate at 20 °C gave mixtures of regioisomeric 3-amino 6 and 2-amino imidazo[1,2-a]pyrimidine 7 in 28% and 37% yields respectively. However, reaction of 2-aminopyrimidine with methyl 4-formylbenzoate and 2-isocyano-2,4,4-trimethylpentane in the presence of acetic acid at 20 °C gave only compound 8 in 15% yield (Scheme 3).²²

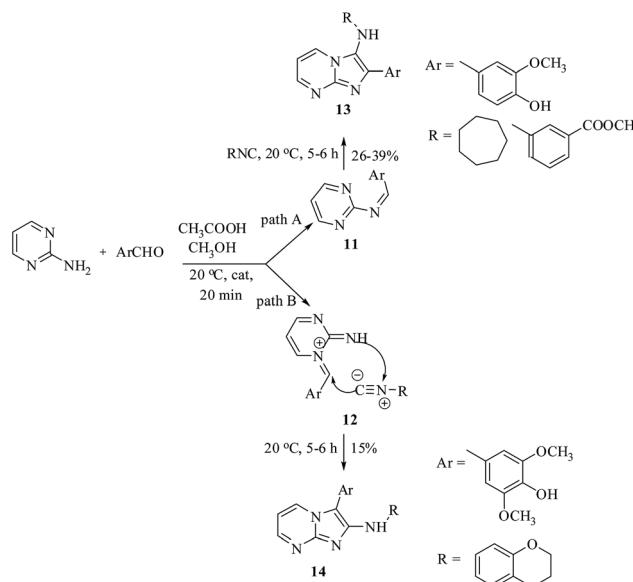
Shaabani and coworkers synthesized bis imidazo[1,2-a]pyrimidines at 2-position through one pot multicomponent reaction. Pseudo five component condensation reaction of 2-aminopyrimidine with terephthaldehyde and isocyanide in the presence of catalytic *p*-toluenesulphonic acid in methanol at room temperature for 3 h afforded *N*-cyclohexyl-2-(4-(3-(cyclohexylamino)imidazo[1,2-a]pyrimidin-2-yl)phenyl)imidazo[1,2-a]pyrimidin-3-amine 10 in 56% yield (Scheme 4).²³



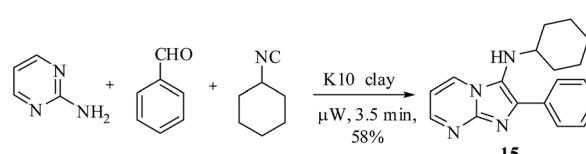
Scheme 4 Synthesis of bis imidazo[1,2-a]pyrimidines.

Voskressensky and coworkers reported the first Groebke-Blackburn multicomponent reaction of 2-aminopyrimidine with 4-hydroxybenzaldehyde and isocyanide. Reaction of 2-aminopyrimidine and aldehyde in the presence of acetic acid and methanol obtained Schiff base 11 through pathway A and heating at 80 °C obtained Schiff base 12 through pathway B. Compound 11 and 12 were further reacted with different isocyanides to afford respective 2-aryl-3-amino substituted imidazo[1,2-a]pyrimidine 13 in 26–39% yields and 3-aryl-2-amino substituted imidazo[1,2-a]pyrimidine 14 in 15% yield (Scheme 5).²⁴

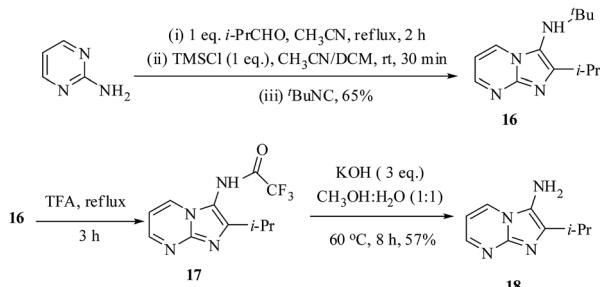
Synthesis of imidazo[1,2-a]pyrimidine 15 in 58% yield has been achieved through microwave assisted multicomponent reaction of 2-aminopyrimidine with benzaldehyde and cyclohexyl isocyanide in the presence of recyclable montmorillonite under solvent free conditions for 3.5 min (Scheme 6).²⁵



Scheme 5 Acid catalyzed synthesis of imidazo[1,2-a]pyrimidine.



Scheme 6 Clay catalyzed synthesis of imidazo[1,2-a]pyrimidine.

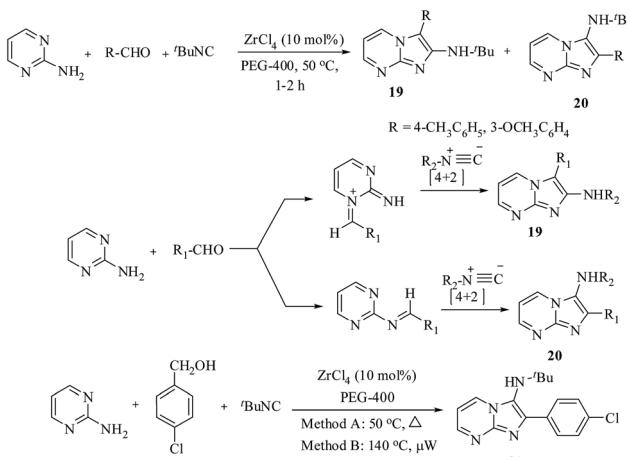


Scheme 7 Synthesis and reactivity of 3-aminoimidazo[1,2-a]pyrimidine.

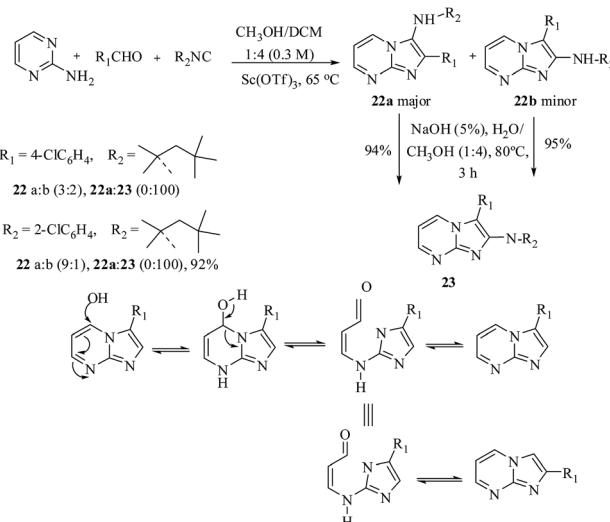
Krasavin and coworkers developed tertiary butyl isocyanide as a convertible reagent in Groebke–Blackburn multicomponent reaction. Two step multicomponent reactions of 2-aminopyrimidine with isopropyl aldehyde and tertiary butyl isocyanide in the presence of trimethylsilyl chloride (TMSCl) in a mixture of acetonitrile and DCM gave **16** in 65% yield followed by reaction with trifluoroacetic acid (TFA) provided trifluoroacetamide derivative **17**. The subsequent removal of trifluoroacetamide group with potassium hydroxide afforded 3-amino-2-isopropyl imidazo[1,2-a]pyrimidine **18** in 57% yield (Scheme 7).²⁶

Guchhait and coworkers reported an efficient and regioselective Ugi type multicomponent synthesis of *N*-fused 2- and 3-amino imidazo[1,2-a]pyrimidines. Reaction of 2-aminopyrimidine with varying aldehydes and tertiary butyl isocyanide, catalyzed by 10 mol% of zirconium chloride in polyethylene glycol (PEG)-400 afforded mixture of 2- and 3-amino imidazo[1,2-a]pyrimidine **19** and **20** in 78–80% and 9–11% yields respectively.²⁷ Later on, this group carried out the reaction of 2-amino pyrimidine with *p*-chlorobenzaldehyde and tertiary butyl isocyanide catalyzed by zirconium chloride in PEG-400 with heating at 50 °C (method A) and microwave irradiation at 140 °C (method B) to afford *N*-*tert*-butyl-2-(4-chlorophenyl)imidazo[1,2-a]pyrimidin-3-amine **21** (Scheme 8).²⁸

Carballares and coworkers developed two step procedure for regioselective synthesis of 3-substituted-2-aminoimidazo[1,2-a]



Scheme 8 ZrCl₄ catalyzed synthesis of imidazo[1,2-a]pyrimidines.



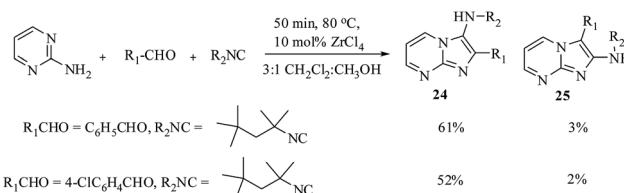
Scheme 9 Regioisomeric synthesis of 2-amino imidazo[1,2-a]pyrimidines.

pyrimidines. Multicomponent reaction of 2-aminopyrimidine with different aldehydes as well as isocyanides catalyzed by scandium triflate in DCM and methanol yielded mixture of 2-substituted **22a** and 3-substituted aminoimidazo[1,2-a]pyrimidines **22b** in 94–95% yields. Dimroth rearrangement of mixture of **22a** and **22b** using 5% NaOH afforded final access to only one regioisomer **23** in excellent yield (Scheme 9).²⁹

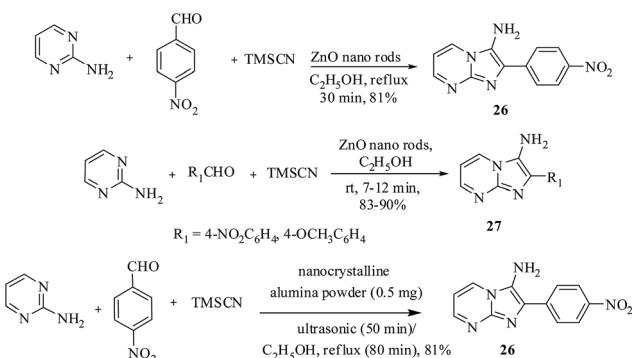
Chen and coworkers developed an efficient protocol for regioselective synthesis of 3-amino imidazo[1,2-a]pyrimidine **24** under continuous flow conditions. Use of Lewis acid catalyst Zr⁴⁺ with continuous flow synthesis led to the regioselective formation of 3-aminoisomer **24** in comparison to 2-regiosomer **25** with shorter reaction time. Library of compound was synthesized with multicomponent reaction of 2-aminopyrimidine, different aldehyde as well as isocyanide components catalyzed by zirconium chloride in dichloromethane : methanol (3 : 1) using this approach (Scheme 10).³⁰

Multicomponent reaction of 2-aminopyrimidine, aldehyde and trimethylsilylcyanide

Sadjadi and coworkers developed ZnO nano rods as an efficient catalyst for synthesis of imidazo[1,2-a]pyrimidines. Reaction of 2-aminopyrimidine with 4-nitrobenzaldehyde and trimethylsilylcyanide in the presence of ZnO nano rods as catalyst for



Scheme 10 Continuous flow synthesis of imidazo[1,2-a]pyrimidines.



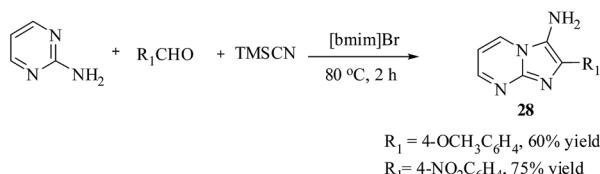
Scheme 11 Nanorods catalyzed synthesis of imidazo[1,2-a]pyrimidines.

30 min afforded 2-(4-nitrophenyl)imidazo[1,2-a]pyrimidin-3-amine **26** in 81% yield. Use of 0.5 mg of ZnO nano rods instead of bulk ZnO gave a good yield of product.³¹ However, multicomponent reaction of 2-aminopyrimidine with different aldehydes and trimethylsilyl cyanide catalyzed by ZnO nano rods under ultrasonic radiations for 5–15 min afforded 3-amino-2-substituted imidazo[1,2-a]pyrimidine **27** in 83–90% yields.³² They also reported the synthesis of imidazo[1,2-a]pyrimidine **26** from one step three component reaction of 2-aminopyrimidine with 4-nitrobenzaldehyde and trimethylsilyl cyanide catalyzed by 0.5 mg nano crystalline alumina powder. The reaction conditions were eco-friendly having a good percentage of yield (81%) and were performed under short reaction times, *i.e.* in 50 min with ultrasonic radiations, and in 80 min under refluxing conditions (Scheme 11).³³

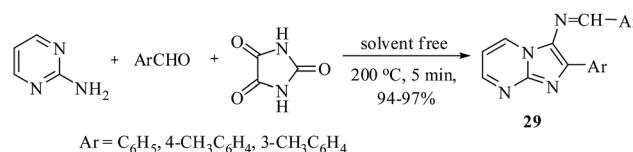
One pot multicomponent condensation reaction of 2-aminopyrimidine with different aldehydes and trimethylsilyl cyanide in the presence of catalytic amount of ionic liquid [bmim]Br as a promoter afforded 3-amino-2-substituted imidazo[1,2-a]pyrimidine **28** in 60–75% yields with relatively shorter reaction time (Scheme 12).³⁴

Multicomponent reaction of 2-aminopyrimidine, aldehyde and imidazoline-2,4,5-trione

Adib and coworkers reported the one pot multicomponent synthesis of 2-aryl-3-amino imidazo[1,2-a]pyrimidines. Solvent free three component condensation of 2-aminopyrimidine with varying aldehydes and imidazoline-2,4,5-trione at 200 °C for 5 minutes afforded *N*-arylidene-2-arylimidazo[1,2-a]pyrimidin-3-amine **29** in 94–97% yields (Scheme 13).³⁵



Scheme 12 Ionic liquid catalyzed synthesis of imidazo[1,2-a]pyrimidine.



Scheme 13 Solvent free three component synthesis of imidazo[1,2-a]pyrimidines.

Multicomponent reaction of 2-aminopyrimidine, isocyanide and formaldehyde equivalent (MP-CO₃)

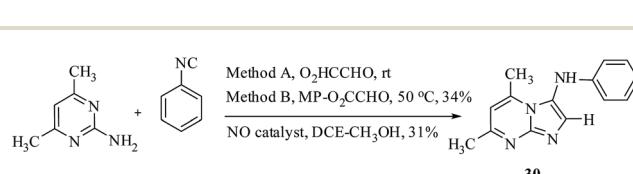
Kercher and coworkers developed one pot three component reaction for the synthesis of 3-arylaminoimidazo[1,2-a]pyrimidines. Condensation of 2-amino-4,6-dimethyl pyrimidine with phenylisocyanide and aldehydes using MP-glyoxylate (macro-porous) formaldehyde equivalent without the use of any catalyst afforded 5,7-dimethyl-N-phenylimidazo[1,2-a]pyrimidin-3-amine **30** in 34% (method A) and 31% (method B) yields. Glyoxylic acid could either be used in solution form or immobilized on MP-carbonate (Scheme 14).³⁶

Biginelli-type multicomponent reaction between 2-aminopyrimidine, aldehyde and pyrimidinetrione

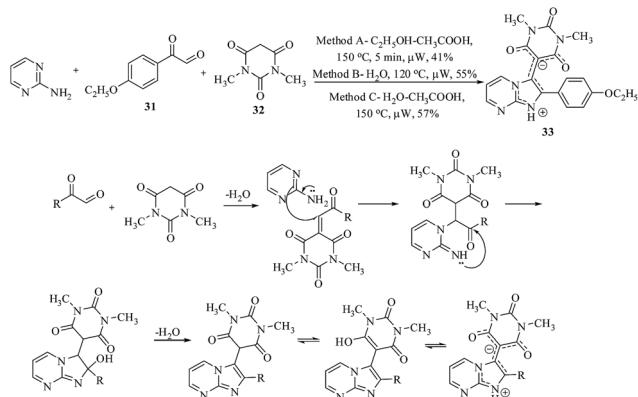
Gorobets and coworkers in 2014 reported the novel microwave assisted Biginelli-type multicomponent reaction of 2-aminopyrimidine with 2-(4-ethoxyphenyl)-2-oxoacetaldehyde **31** and 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione **32** in ethanol-acetic acid at 150 °C (condition A), water at 120 °C (condition B) and water-acetic acid at 150 °C (condition C) for 5 min to afford 5-(2-(4-ethoxyphenyl)imidazo[1,2-a]pyrimidin-1-iium-3-yl)-1,3-dimethyl-2,4,6-trioxohexahydro-pyrimidin-5-ide **33** in 41%, 55% and 57% yields respectively. It was isolated as monohydrate form while in solid state it existed as a zwitterion tautomeric form. Reaction of 2-oxoaldehyde and 1,3-dicarbonyl compound formed adduct which was reacted with nitrogen of 2-aminopyrimidine ring followed by attack of second exocyclic nitrogen nucleophile on keto carbonyl group with subsequent elimination of water to give imidazo[1,2-a]pyrimidine **33** (Scheme 15).³⁷

Multicomponent reaction between 2-aminoimidazole, aldehyde and isocyanide

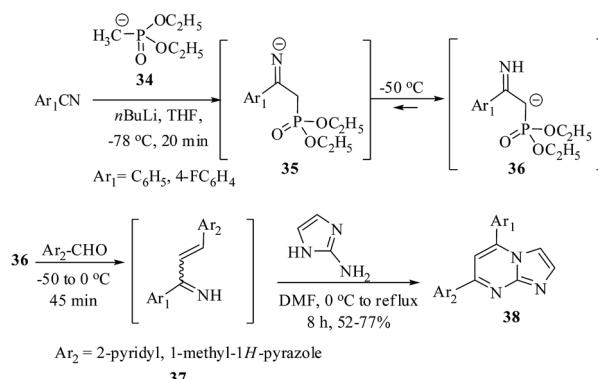
Kiselyov and coworkers reported the convenient regiospecific one pot approach for the synthesis of 5,7-diaryl imidazo[1,2-a]pyrimidines from the reaction of amine heterocycle, aldehyde and imines. Nitrile was allowed to react with methyl phosphonate **34** in the presence of *n*-butyl lithium at –78 °C in dry THF to give **35** with formation of intermediate **36** which was then



Scheme 14 MP carbonate supported synthesis of arylaminoimidazo[1,2-a]pyrimidine.



Scheme 15 Biginelli-type multicomponent reaction for synthesis of imidazo[1,2-a]pyrimidine.

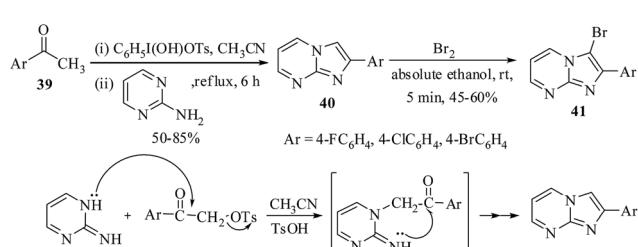


Scheme 16 Multicomponent synthesis *via* imine intermediate.

reacted with aldehyde to obtain α,β -unsaturated imine intermediate 37. Finally, compound 37 was reacted with 2-aminoimidazole to give 5,7-disubstituted imidazo[1,2-a]pyrimidine 38 in 70–77% yields (Scheme 16).³⁸

Multicomponent reaction between 2-aminopyrimidine, ketone and [hydroxy(tosyloxy)iodo]benzene (HTIB)

Aggarwal and coworkers reported [hydroxy(tosyloxy)iodo]benzene (HTIB) mediated synthesis of 2-aryl imidazo[1,2-a]pyrimidines directly from ketones. The reaction of enolizable ketone 39 with [hydroxy(tosyloxy)iodo]benzene (HTIB) in acetonitrile gave α -tosyloxy ketone followed by treatment with 2-aminopyrimidine in acetonitrile through a nucleophilic attack



Scheme 17 MCR of ketones, amidine and HTIB.

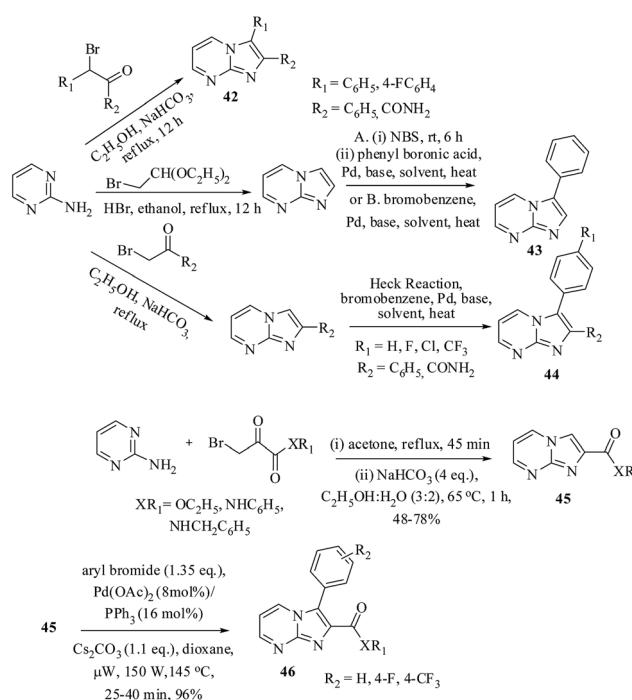
of the amino group on α -tosyloxy ketone to obtain single isomer of 2-aryl imidazo[1,2-a]pyrimidine 40 in 50–85% yields. 2-Aryl-3-bromoimidazo[1,2-a]pyrimidine 41 in 45–60% was obtained by the reaction of 40 with bromine in absolute ethanol at room temperature. Nucleophilic attack of ring nitrogen of 2-aminoimidazole on α -tosyloxy ketones gave intermediate that cyclized to form imidazo[1,2-a]pyrimidine (Scheme 17).³⁹

Condensation reactions

From alpha halo ketones

van der Eycken and coworkers in 2006 reported the efficient microwave assisted palladium catalyzed arylation of 2-substituted imidazo[1,2-a]pyrimidines. Condensation of 2-aminopyrimidine with 1,2-diaryl-2-bromoethanone in ethanol gave 2,3-diarylated imidazo[1,2-a]pyrimidine 42. Cyclization with 2-bromo-1,1-diethoxyethane gave unsubstituted imidazo[1,2-a]pyrimidine which further brominated with *N*-bromosuccinimide followed by Suzuki–Miyaura coupling with phenyl boronic acid (Pathway A) or Heck coupling (Pathway B) to obtain 3-phenyl imidazo[1,2-a]pyrimidine 43. However, cyclization with 2-bromo-1-phenylethanone gave 2-phenyl imidazo[1,2-a]pyrimidine followed by microwave assisted palladium catalyzed Heck coupling to afford 3-aryl imidazo[1,2-a]pyrimidine 44 in 82–96% yields. Imidazo[1,2-a]pyrimidine 45 bearing ethylcarboxylate/carboxamide moiety at 2-position has been synthesized from the reaction of 2-aminopyrimidine with 3-bromopyruvate and 3-bromopyruvamides. Arylation of 45 with different arylbromides gave final access to 2,3-disubstituted imidazo[1,2-a]pyrimidine 46 in 47–67% yields (Scheme 18).⁴⁰

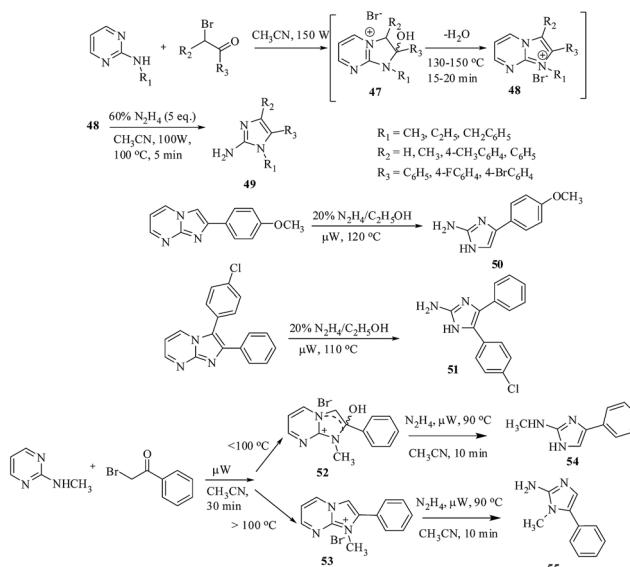
van der Eycken and coworkers in 2006 also reported the synthesis of substituted imidazo[1,2-a]pyrimidine followed by



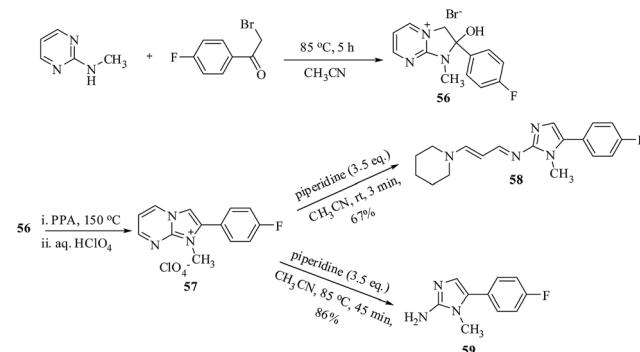
Scheme 18 Synthesis from halo carbonyls.

one pot, two step microwave assisted protocol for synthesis of 1,4; 1,5 disubstituted and 1,4,5-trisubstituted 2-aminoimidazoles. Reaction of 2-aminopyrimidine with various α -bromoketones in acetonitrile gave salt **47** which was then dissolved slowly at 130–150 °C to obtain salt **48**. Further, the reaction of **48** with hydrazine (60%) at a ceiling temperature of 100 °C for 5 min afforded substituted 2-aminoimidazole **49** in 38–96% yields.^{41,42} Later on, they developed a simple protocol for synthesis of 4(5)-mono and 4,5-disubstituted 2-aminoimidazoles from 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine and 3-(4-chlorophenyl)-2-phenylimidazo[1,2-*a*]pyrimidine. Microwave assisted synthesis of monosubstituted imidazole, 4-(4-methoxyphenyl)-1*H*-imidazol-2-amine **50** was achieved through cleavage of 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine catalyzed by hydrazine hydrate in ethanol for 25 min in 78% yield. The same protocol was then applied for the synthesis of 4,5-disubstituted imidazole. Hydrazinolysis of 3-(4-chlorophenyl)-2-phenylimidazo[1,2-*a*]pyrimidine with hydrazine hydrate under microwave irradiation at 110 °C for 10 min afforded 5-(4-chlorophenyl)-4-phenyl-1*H*-imidazol-2-amine **51** in 68% yield.⁴³ Further, the reaction of 2-aminomethyl pyrimidine with α -bromoketone under microwave irradiation at 80–100 °C for 30–60 min in acetonitrile afforded 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]pyrimidinium salt **52** in 64–77% yields, while irradiation at temperature above 100 °C for 30–60 min gave 1-substituted imidazo[1,2-*a*]pyrimidinium salt **53** in 33–84% yields. Formation of imidazoles is highly temperature dependent. Hydrazinolysis of **52** and **53** with hydrazine under microwave irradiation yielded 1-unsubstituted **54** and 1-substituted 2-aminoimidazoles **55** respectively (Scheme 19).⁴⁴

This group also reported the divergent synthesis of *N*-substituted 2-aryl imidazo[1,2-*a*]pyrimidine. Cyclocondensation of 2-aminomethylpyrimidine with α -bromoacetophenone in the presence of 4-dimethylaminopyridine (DMAP) in acetonitrile gave stable intermediate 2-hydroxy-2,3-dihydroimidazo[1,2-*a*]



Scheme 19 Microwave synthesis of 2-arylimidazo[1,2-*a*]pyrimidines and 2-aminoimidazoles.

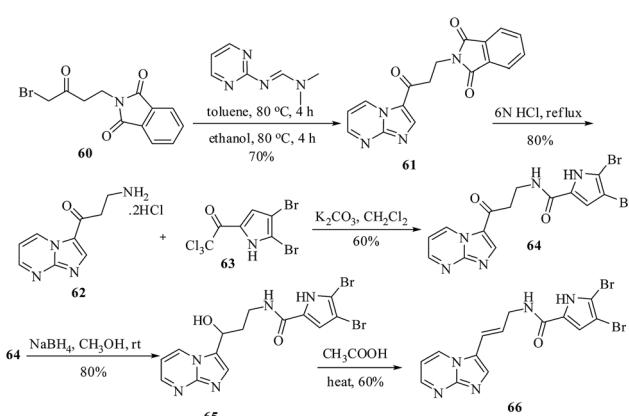


Scheme 20 Conventional synthesis of 2-arylimidazo[1,2-*a*]pyrimidine and 2-aminoimidazole.

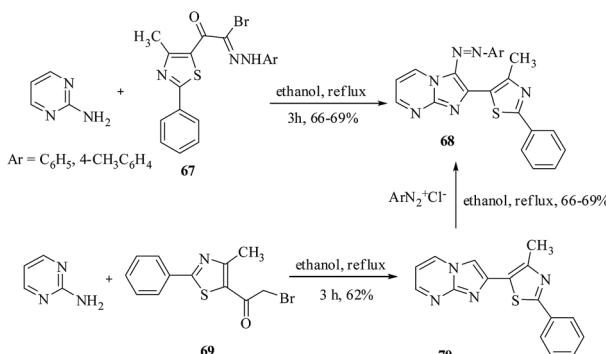
pyrimidin-4-ium bromide **56** in 88% yield followed by dehydration with polyphosphoric acid for 15 min at 150 °C to afford imidazo[1,2-*a*]pyrimidin-1-ium perchlorate salt **57** in 93% isolated yield. **57** underwent ring opening reaction with 3.5 eq. of piperidine in acetonitrile for 5 min to give azabutadiene **58** in 67% yield. However, heating in acetonitrile for 45 min at 85 °C afforded 2-aminoimidazole **59** in 86% yield (Scheme 20).⁴⁵

Reaction of phthalamide substituted bromoketone **60** with (pyrimidin-2-yl)formimidamide in toluene/ethanol at 80 °C for 4 h obtained 3-substituted imidazo[1,2-*a*]pyrimidine **61**. Acid mediated deprotection of phthalimide group afforded amine **62**. Condensation of **62** with pyrrolyl chloroketone **63** in dichloromethane gave **64** in 60% yield followed by selective reduction of keto group to benzylic alcohol with sodium borohydride to give **65** in 80% yield. Subsequent acetic acid catalyzed dehydration afforded (*E*)-4,5-dibromo-*N*-(3-(imidazo[1,2-*a*]pyrimidin-3-yl)allyl)-1*H*-pyrrole-2-carboxamide **66** in 60% yield (Scheme 21).⁴⁶

Reaction of 2-aminopyrimidine with 2-(4-methyl-2-phenyl-4,5-dihydrothiazol-5-yl)-2-oxo-*N'*-arylacetoxyhydrazone bromide **67** in refluxing ethanol for 3 h to give 4-methyl-2-phenyl-5-(3-(aryldiazeny)imidazo[1,2-*a*]pyrimidin-2-yl)thiazole **68** in 66–69% yields. However, reaction of 2-aminopyrimidine with 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone **69** in



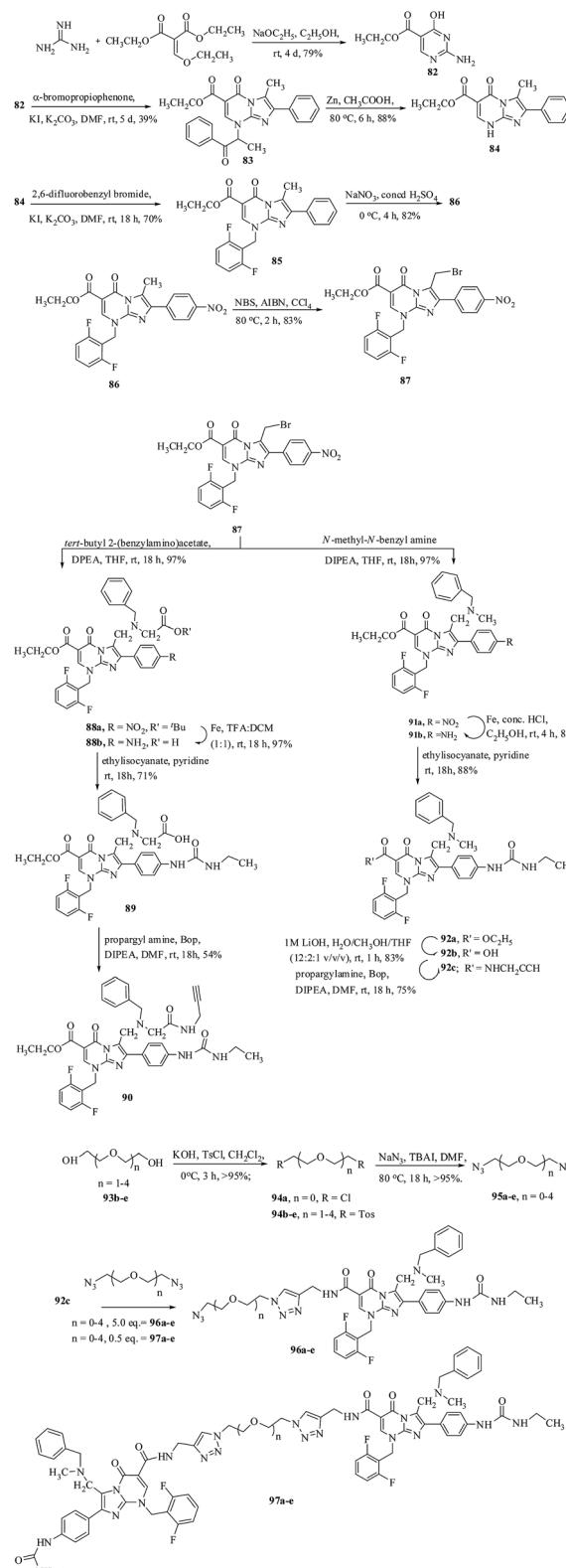
Scheme 21 Reaction of bromoketone with formimidamide.



refluxing ethanol for 3 h gave 5-(imidazo[1,2-*a*]pyrimidin-2-yl)-4-methyl-2-phenylthiazole **70** in 62% yield. Reaction of **70** with aryl diazonium chloride in ethanolic sodium acetate afforded **68** in 66–69% yields (Scheme 22).⁴⁷

Faty and coworkers in 2014 reported the synthesis of fused pyrimidine derivatives through intermediate of thioxopyrimidine carbonitriles **71** which on reaction with methyl halides gave intermediate **72**. Compound **72** underwent alkylation at N3 position with α -halocarbonyl compounds *viz.*, ethylbromoacetate, chloroacetone/chloroacetylacetone and chloroacetonitrile/monobromomalononitrile in the presence of different solvents to give compounds **73**–**75**. Compounds **73**–**75** were further reacted with hydrazine hydrate in dioxane through desulphurization followed by cyclization to afford imidazo[1,2-*a*]pyrimidin-6-carbonitriles **76**–**78** in 60–75% yields. Compound **75** was also reacted with benzylamine to afford **79** in 72% yield. Reaction of **76** to 4-chlorobenzaldehyde gave compound **80** in 60% yield while reaction with 4-methylaniline in the presence of sodium nitrite gave **81** in 68% yield (Scheme 23).⁴⁸

Condensation of guanidine with diethyl 2-(ethoxymethylene) malonate gave 2-amino-4-hydroxy pyrimidine derivative **82**. Reaction of **82** with α -bromopropiophenone gave regiosymmetric



Scheme 24 Click reaction for synthesis of bis(imidazo[1,2-*a*]pyrimidines).

mixtures of *O*- and *N*-alkylated products. But only *N*-alkylated product **83** was recrystallized in 39% yield. Zn in acetic acid was used to cleave the phenacyl group to generate phenyl-2,6-

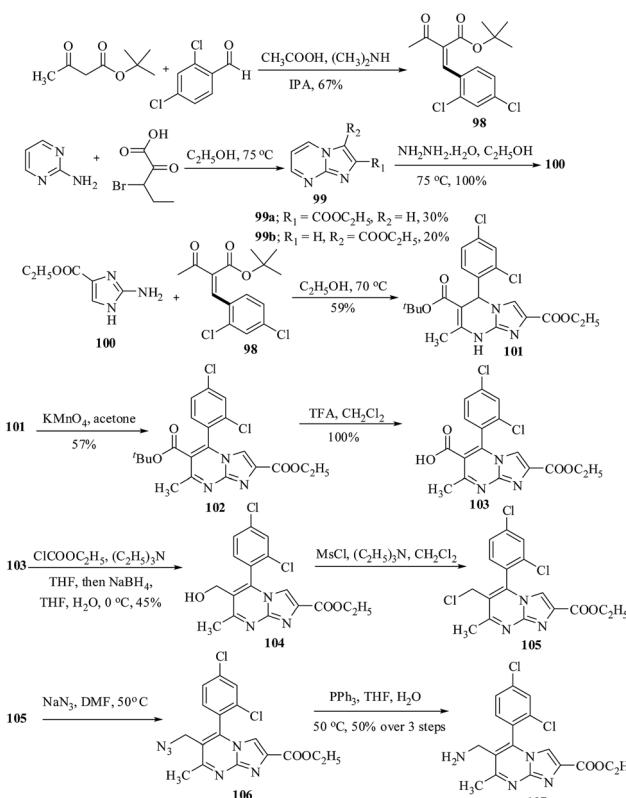
Scheme 23 Synthesis and reactivity of imidazo[1,2-*a*]pyrimidin-5-ones.

disubstituted imidazo[1,2-*a*]pyrimidinone **84** in 88% yield. Alkylation with difluorobenzyl bromide gave **85** followed by nitration with sodium nitrate in conc. sulfuric acid to obtain **86** and final bromination with NBS afforded intermediate **87**. Further, amination of **87** with *tert*-butyl-2-(benzylamino)acetate and *N*-methyl-*N*-benzyl amine in the presence of DIPEA in THF at room temperature for 18 h to obtain **88a** and **91a** respectively. Further reduction of nitro **88a** and **91a** to amine **88b** and **91b** was accomplished using iron in TFA : DCM (1 : 1) and conc. HCl respectively. Treatment of **88b** and **91b** with ethylisocyanate in the presence of pyridine afforded **89** and **92a** respectively. Saponification of ethyl ester **92a** to acid **92b** was accomplished using lithium hydroxide. Peptide condensation of **89** and **92b** with propargylamine yielded **90** and **92c** in 54% and 75% yields respectively. Ethylene glycol derivatives **93b-e** were treated with potassium hydroxide and tosyl chloride to obtain bis (*p*-toluenesulphonate)esters **94b-e** followed by reaction with sodium azide in DMF to obtain bis azide **95a-e**. Click reaction of 5.0 eq. of bis-azides **95a-e** with **92c** was performed using copper sulphate and sodium ascorbate in a mixture of tertiary butanol, acetonitrile and water to obtain monosubstituted derivatives **96a-e** in 30–47% yields., use of 0.5 eq. of bis azides **95a-e** afforded the target compounds **97a-e** in 13–36% yields (Scheme 24).⁴⁹

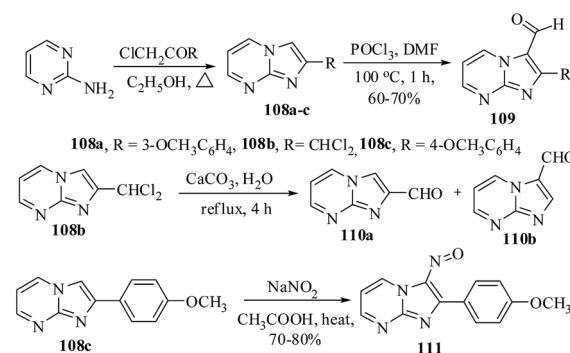
Meng and coworkers in 2010 synthesized 2,5,6,7-tetrasubstituted imidazo[1,2-*a*]pyrimidines. Knoevenagel condensation of *t*-butylacetacetate with 2,4-dichlorobenzaldehyde in the presence of dimethylamine in catalytic amount of acetic acid in isopropyl alcohol gave 1 : 1 *E/Z* mixture of **98** in 67% yield. Condensation of 2-aminopyrimidine with ethylbromopyruvate in ethanol at 75 °C obtained a mixture of imidazo[1,2-*a*]pyrimidine **99a** and **99b** followed by hydrazine hydrate mediated cleavage to yield imidazole **100**. Condensation of acrylate **98** with imidazole **100** in ethanol at 70 °C gave dihydroimidazo[1,2-*a*]pyrimidine **101** followed by oxidation with potassium permanganate provided diester derivative **102**. Acid mediated hydrolysis of *t*-butyl group in **102** obtained acid derivative **103** in 100% yield. Reaction of **103** with ethyl chloroformate in triethylamine and then treated with sodium borohydride in THF/H₂O yielded hydroxymethyl derivative **104** in 45% yield. Mesylation was done with mesyl chloride in dichloromethane to attain **105**. Compound **105** was further reacted with sodium azide in DMF to form azide derivative **106** which reacted with triphenyl phosphine to give final access to aminomethyl imidazo[1,2-*a*]pyrimidine **107** in 50% yield (Scheme 25).⁵⁰

Condensation of 2-aminopyrimidine with chlorinated precursors in boiling ethanol gave 2-substituted imidazo[1,2-*a*]pyrimidine **108a-c** followed by Vilsmeier-Haack reaction to obtain 3-formyl-2-substituted imidazo[1,2-*a*]pyrimidine **109**. Out of these, 2-dichloromethane imidazo[1,2-*a*]pyrimidine **108b** was converted to 2- and 3-formyl imidazo[1,2-*a*]pyrimidines **110a** and **110b** respectively on reaction with aqueous solution of calcium carbonate through partial Dimroth rearrangement of aldehyde. Nitration of 2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine **108c** with sodium nitrite in acetic acid afforded 3-nitroso imidazo[1,2-*a*]pyrimidine **111** (Scheme 26).⁵¹

Chen and coworkers reported the condensation of 2-aminopyrimidine with 2-bromo-2'-methoxyacetophenone to give

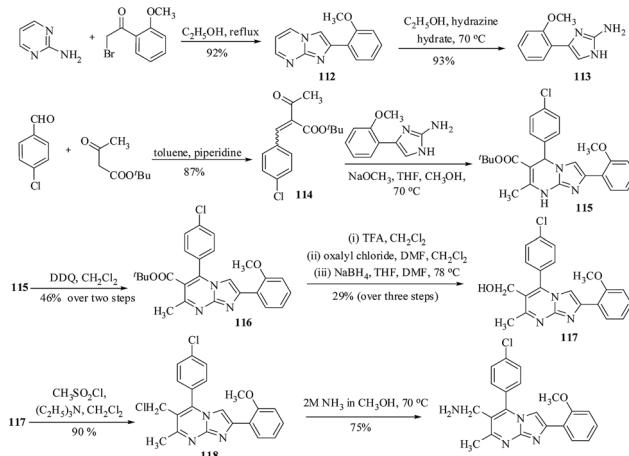


Scheme 25 Synthesis of 2,5,6,7-tetrasubstituted imidazo[1,2-*a*]pyrimidines.



Scheme 26 Condensation of 2-aminopyrimidine with ketones.

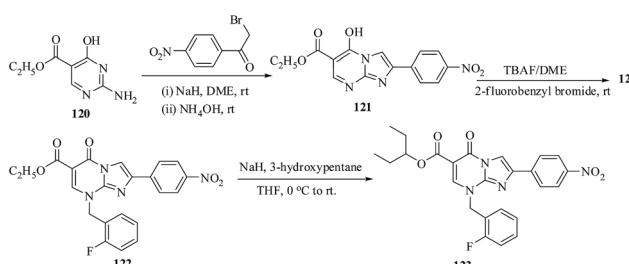
112 in 92% yield followed by hydrazine hydrate mediated cleavage to get **113** in 93% yield. On the other hand, the Knoevenagel condensation reaction of *p*-chlorobenzaldehyde with *tert*-butyl acetacetate gave enone **114** in 87% yield. Subsequent reaction with 4-(2-methoxyphenyl)-1*H*-imidazol-2-amine using sodium methoxide gave **115** followed by DDQ mediated oxidation to deliver **116** in 46% yield over two steps. Three step sequence reaction of **116** with TFA (cleave *t*-butyl ester linkage), oxalyl chloride (for acid chloride formation) and NaBH₄ (for reduction) gave alcohol **117** in 29% yield over three steps. Conversion of alcohol **117** to chloride **118** in 90% yield was achieved by methane sulphonyl chloride in dichloromethane, following the reaction with 2 M NH₃ in methanol at



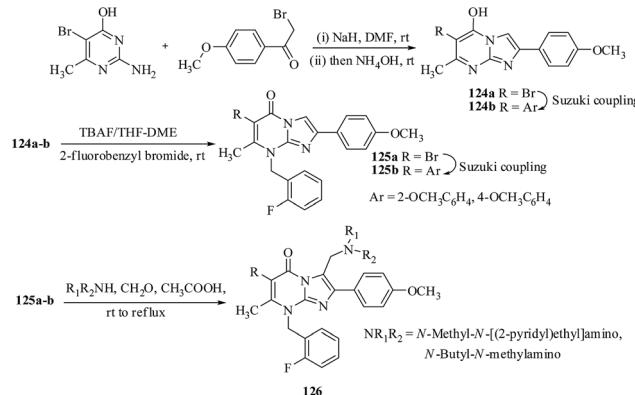
Scheme 27 Reaction of 2-aminopyrimidine with 2-bromo-2'-methoxyacetophenone.

elevated temperature to provide amine **119** in 75% yield (Scheme 27).⁵² Reaction of ethyl 2-amino-4-hydroxypyrimidine-5-carboxylate **120** with α -bromoacetophenone in the presence of NaH in dimethoxyethane (DME) followed by treatment with ammonium hydroxide to obtain ethyl 5-hydroxy-2-(4-nitrophenyl)imidazo[1,2-*a*]pyrimidine-6-carboxylate **121**. *N*-Alkylation of **121** with 2-fluorobenzyl bromide in tetrabutylammonium fluoride (TBAF) in DME afforded ethyl 8-(2-fluorobenzyl)-2-(4-nitrophenyl)-5-oxo-5,8-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylate **122**. Transesterification of **122** with 3-hydroxypentane in the presence of NaH at 0 °C to room temperature achieved pentan-3-yl-8-(2-fluorobenzyl)-2-(4-nitrophenyl)-5-oxo-5,8-dihydroimidazo[1,2-*a*]pyrimidine-6-carboxylate **123** (Scheme 28).⁵³ Reaction of 2-amino-5-bromo-6-methylpyrimid-4-one with α -bromo-4'-methoxy acetophenone in the presence of NaH in DMF and then treatment with ammonium hydroxide gave imidazo[1,2-*a*]pyrimidinol **124a**, **b**. Alkylation of **124a**, **b** with 2-fluorobenzyl bromide in TBAF in DME at room temperature afforded *N*-alkylated product **125a**, **b**. Palladium catalyzed Suzuki–Miyaura coupling of **124a** and **125a** with aryl boronic acids afforded **124b** and **125b** respectively. Mannich reaction with secondary amines in the presence of formaldehyde in acetic acid gave final access to imidazo[1,2-*a*]pyrimidin-5-one **126** (Scheme 29).⁵⁴

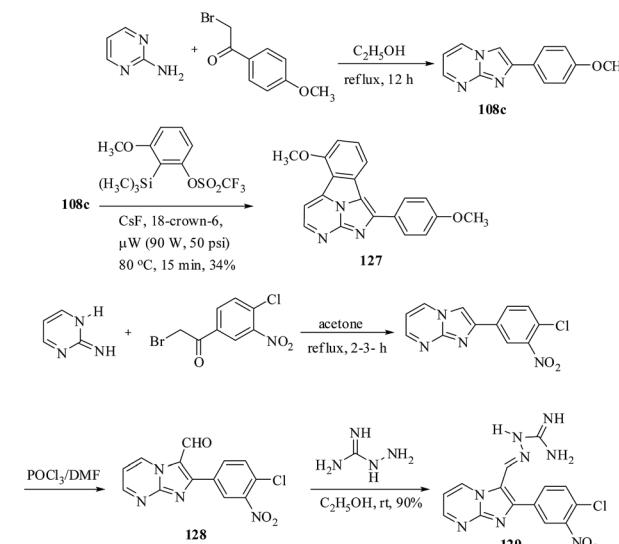
Reaction of 2-aminopyrimidine with α -bromo acetophenone in refluxing ethanol gave 2-aryl-imidazo[1,2-*a*]pyrimidine **108c**



Scheme 28 Reaction of 2-aminopyrimidine with α -bromoacetophenone.



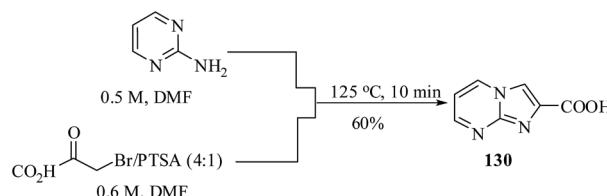
Scheme 29 Reaction of 2-aminopyrimidine with α -bromo-4'-methoxyacetophenone.



Scheme 30 Synthesis from α -bromoacetophenone and its reaction with benzene.

in 86% yield. Aginagalde *et al.* reported the tandem microwave mediated [8 + 2] cycloaddition and [2 + 6 + 2] dehydrogenation reaction of 2-aryl-imidazo[1,2-*a*]pyrimidine with benzene precursor 3-methoxy-2-(trimethylsilyl)phenyl triflate in the presence of 18-crown-6 and cesium fluoride to give cycloadduct **127** in 34% yield.⁵⁵ However, reaction of 2-imino pyrimidine with 2-bromo-1-(4-chloro-3-nitrophenyl)ethanone in refluxing acetone gave 2-substituted imidazo[1,2-*a*]pyrimidine followed by Vilsmeier–Haack reaction to obtain 3-formyl derivative **128** which underwent Schiff base formation with the amino group of aminoguanidine afforded access to 2,3-disubstituted imidazo[1,2-*a*]pyrimidine **129** (Scheme 30).⁵⁶

Cosford and coworkers in 2010 developed the first continuous flow synthesis of imidazo[1,2-*a*]pyrimidine achieved through condensation of 2-aminopyrimidine with 1.2 eq. of bromopyruvic acid (0.5 M) catalyzed by *p*-toluenesulphonic acid (PTSA) in DMF at 125 °C for 10 min to afford imidazo[1,2-*a*]pyrimidine-2-carboxylic acid **130** in 60% yield (Scheme 31).⁵⁷



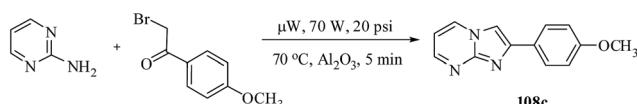
Scheme 31 Continuous flow synthesis of imidazo[1,2-a]pyrimidine from PTSA.

Microwave assisted reaction of 2-aminopyrimidine with α -bromoketone in the presence of neutral Al_2O_3 at 150 °C and 20 psi for 5 min afforded 2-aryl substituted imidazo[1,2-a]pyrimidine **108c** in 75% yield (Scheme 32).⁵⁸

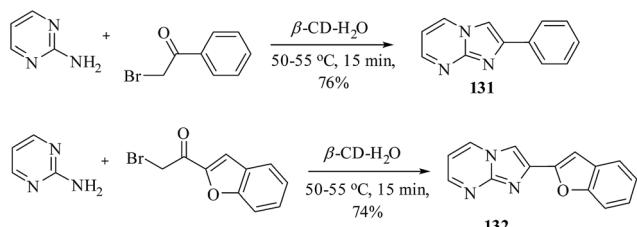
Sahu and coworkers in 2008 reported the aqueous phase synthesis of 2-aminopyrimidine with 2-bromo-1-phenylethanone and 1-(benzofuran-2-yl)-2-bromoethanone in the presence of β -cyclodextrin (β -CD) at 50–55 °C afforded 2-arylated imidazo[1,2-a]pyrimidines **131** and **132** in 76% and 74% yields respectively (Scheme 33).⁵⁹

Condensation of 2-aminopyrimidine with benzyl 2-bromo-3-oxobutanoate in the presence of sodium bicarbonate in 1,2-dimethoxyethane afforded 2,3-disubstituted imidazo[1,2-a]pyrimidine **133** (Scheme 34).⁶⁰

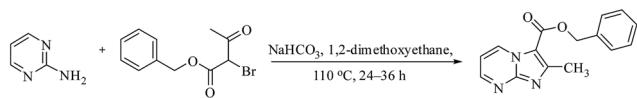
Condensation of 2-amino-4,6-dimethoxypyrimidine with 4-nitrobromoacetophenone in ethanol gave 5,7-dimethoxy-2-(4-nitrophenyl)imidazo[1,2-a]pyrimidine **134** in 82% yield followed by reduction with stannous chloride in DMF to yield **135** in 77% yield. Reaction of **135** with methyl iodide in chloroform



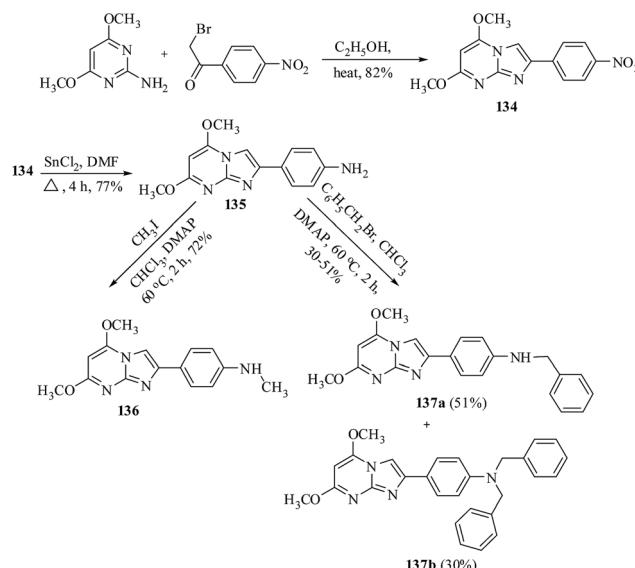
Scheme 32 Microwave synthesis of 2-arylimidazo[1,2-a]pyrimidine from Al_2O_3 .



Scheme 33 Condensation reaction in the presence of cyclodextrin.



Scheme 34 Condensation reaction for synthesis of 3-substituted imidazo[1,2-a]pyrimidine.

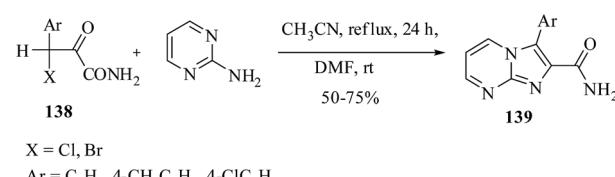


Scheme 35 Reaction with 4-nitrobromoacetophenone.

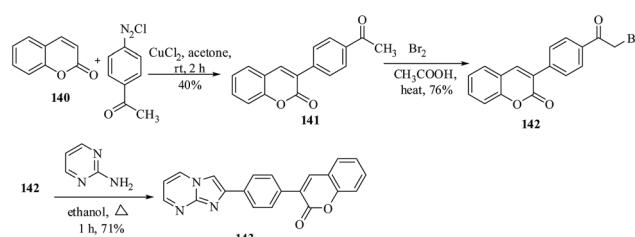
and 4-dimethylaminopyridine (DMAP) afforded imidazo[1,2-a]pyrimidine **136** in 72% yield. But, when compound **135** was treated with benzylbromide in the same reaction conditions gave imidazo[1,2-a]pyrimidine **137a** and **137b** in 51% and 30% yields respectively (Scheme 35).⁶¹

Robert and coworkers reported the reaction of N-based nucleophile 2-aminopyrimidine with 3-halopyruvamides **138** in refluxing acetonitrile to yield 2,3-disubstituted imidazo[1,2-a]pyrimidine **139** in 56–71% yields (Scheme 36).⁶²

Coumarin **140** was treated with 4-acetylphenyl diazonium chloride in the presence of CuCl_2 to give **141** in 40% yield, which underwent bromination in acetic acid to get 3-[4-(2-bromoacetyl)phenyl]-2H-chromen-2-one **142** in 76% yield. Compound **142** was then reacted with 2-aminopyrimidine to afford 3-(4-imidazo[1,2-a]pyrimidin-2-ylphenyl)-2H-chromen-2-one **143** in 71% yield (Scheme 37).⁶³



Scheme 36 Synthesis of imidazo[1,2-a]pyrimidine-2-amide.

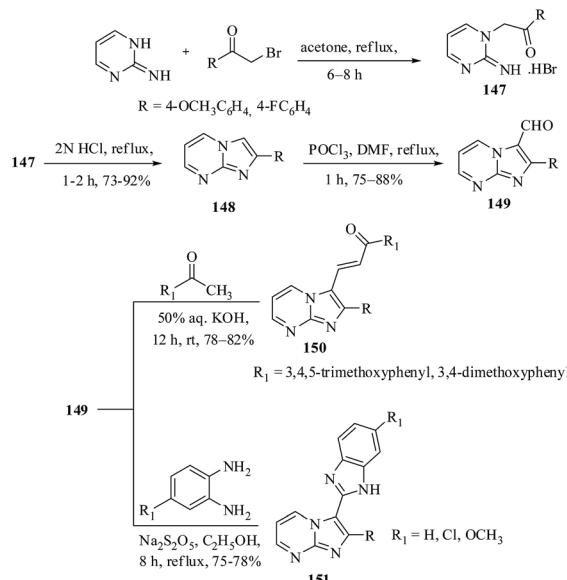


Scheme 37 Cyclocondensation reaction with coumarin.

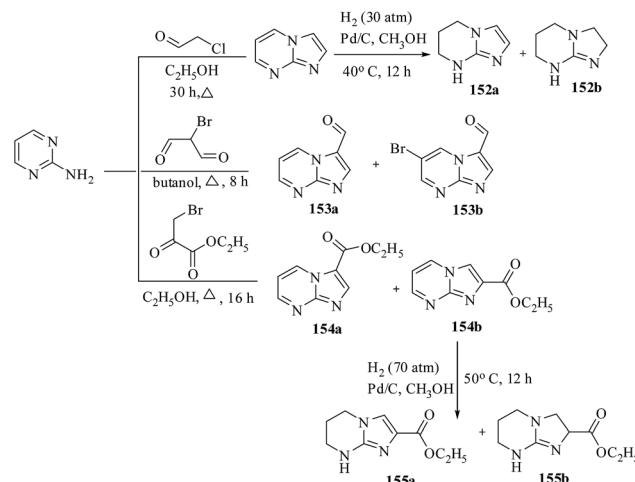
Shaaban in 2013 developed a novel microwave assisted alkylation of 2-hydroxyacetophenone **144a** and 4-hydroxyacetophenone **144b** with dibromoalkanes in the presence of potassium hydroxide in ethanol followed by regioselective bromination with NBS/*p*-TsOH/CH₃CN mixture thermally as well as under microwave to afford mixture of *ortho* **145a** and *para* bis(ω-bromoacetophenones) **145b** with better reactivity and selectivity. Subsequent reactions of **145a** and **145b** with 2-aminopyrimidine afforded bis(imidazo[1,2-*a*]pyrimidine) derivative **146** with 53–68% (thermally) and 70–86% yields (microwave) (Scheme 38).⁶⁴

Reaction of 2-iminopyrimidine with various bromoketones in acetone at reflux temperature gave intermediate **147** which get cyclized in the presence of 2 N HCl to give **148**. Vilsmeier-Haack reaction of **148** with POCl₃ in DMF afforded 3-formyl imidazo[1,2-*a*]pyrimidine **149** in 75–88% yields. Claisen-Schmidt condensation of **149** with 3,4,5-trimethoxyacetophenone or 3,4-dimethoxyacetophenone in the presence of 50% aq. KOH gave access to imidazo[1,2-*a*]pyrimidine-chalcone hybrid **150** in 78–82% yields.^{65a} However, oxidative cyclization of **149** with substituted *o*-phenylene diamines in presence of sodium metabisulphite afforded imidazo[1,2-*a*]pyrimidine-benzimidazole hybrid **151** in 75–78% yields (Scheme 39).^{65b}

Unsubstituted imidazo[1,2-*a*]pyrimidine has been synthesized in 84% yield by the reaction of 2-aminopyrimidine with 50% aq. chloroacetaldehyde which was then underwent Pd/C mediated reduction to obtain tetrahydro **152a** and hexahydro **152b** imidazo[1,2-*a*]pyrimidine in 64% and 1% yields respectively. However, reaction of 2-aminopyrimidine with 2-bromo-malonic dialdehyde gave mixtures of **153a** and **153b** in 60% and 2.5% yields respectively. While condensation of 2-amino-pyrimidine with ethyl bromopyruvate gave mixtures of 3-substituted (not separated) **154a** and **154b** (30% yield) imidazo[1,2-*a*]pyrimidine followed by Pd/C mediated reduction to access mixture of tetrahydro imidazo[1,2-*a*]



Scheme 39 Synthesis of imidazo[1,2-*a*]pyrimidine-chalcone/benzimidazole hybrids.

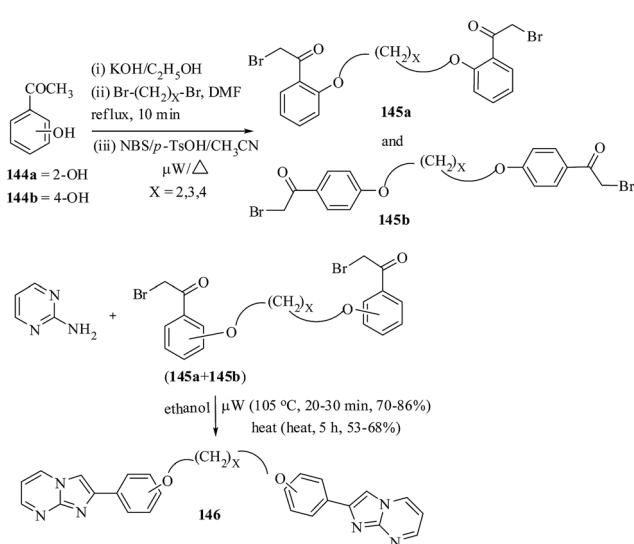


Scheme 40 Synthesis from 2-aminopyrimidine.

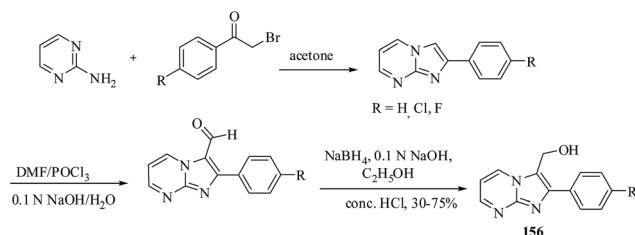
pyrimidin-2-carboxylate **155a** and **155b** in 90% yield (Scheme 40).⁶⁶

Condensation reaction of 2-aminopyrimidine with various substituted bromoacetophenones gave 2-substituted imidazo[1,2-*a*]pyrimidine followed by Vilsmeier-Haack reaction with POCl₃ in DMF to give 3-formyl substituted imidazo[1,2-*a*]pyrimidine. Subsequent reduction of formyl derivative with NaBH₄ in alkaline ethanol afforded final access to 3-hydroxymethyl imidazo[1,2-*a*]pyrimidine **156** in 30–75% yields (Scheme 41).¹⁹

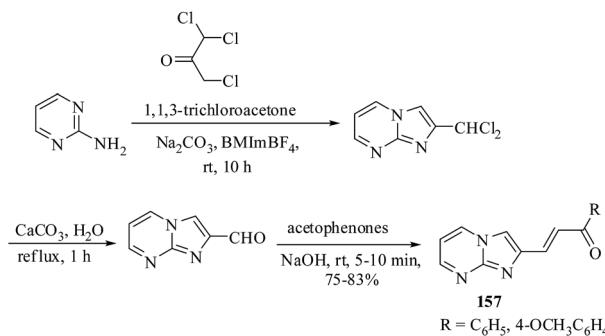
2-Aminopyrimidine underwent cyclocondensation reaction with 1,1,3-trichloroacetone using green recyclable ionic liquid, *n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄) as a solvent at room temperature to give 2-(dichloromethyl)imidazo[1,2-*a*]pyrimidine followed by reaction with calcium carbonate



Scheme 38 Synthesis of bis(imidazo[1,2-*a*]pyrimidine) derivatives.



Scheme 41 Reaction of 2-aminopyrimidine with acetophenones.



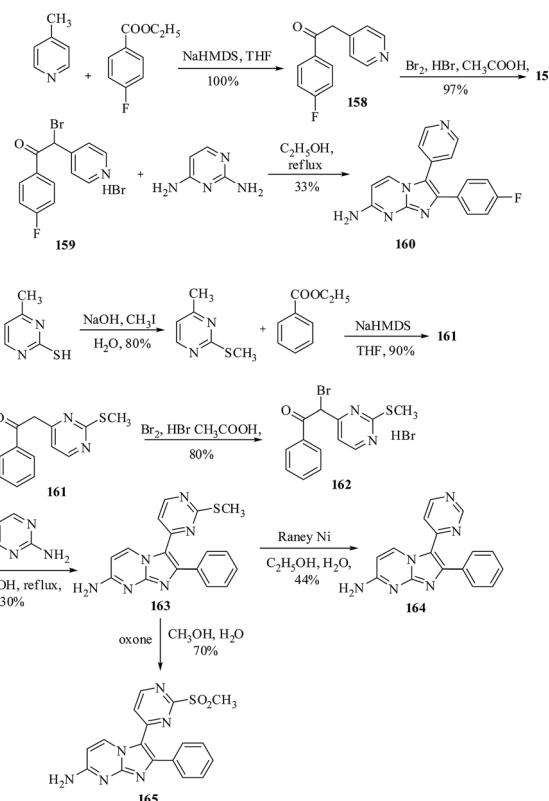
Scheme 42 Synthesis from 1,1,3-trichloroacetone.

in water to give imidazo[1,2-*a*]pyrimidine-2-carbaldehyde. Subsequent solvent free Claisen–Schmidt condensation reaction with different acetophenones using NaOH as a solid catalyst afforded 2-substituted imidazo[1,2-*a*]pyrimidine 157 in 75–83% yields (Scheme 42).⁶⁷

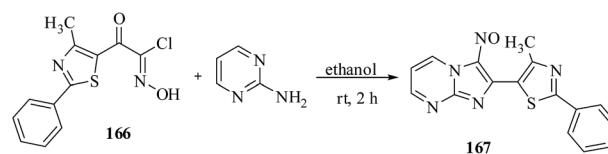
4-Picoline was reacted with ethyl-4-fluorobenzoate in the presence of sodium hexamethyl disilazane (NaHMDS) to obtain ketone 158 followed by bromination with Br₂/HBr in methanol to give α -bromoketone 159. Condensation of 159 with 2,4-diaminopyrimidine afforded regioselective 2-(4-fluorophenyl)-3-(pyridin-4-yl)imidazo[1,2-*a*]pyrimidin-7-amine 160 in 33% yield. Alkylation of 2-mercaptop-4-methyl pyrimidine with iodomethane gave 4-methyl-2-(thiomethyl)pyrimidine in 80% yield which was further treated with ethyl benzoate in the presence of NaHMDS in THF to obtain 161 in 90% yield followed by bromination with Br₂/HBr-acetic acid to obtain α -bromoketone 162 in 80% yield. Cyclization of 162 with 2,4-diaminopyrimidine in ethanol provided 3-(2-(methylthio)pyrimidin-4-yl)-2-phenylimidazo[1,2-*a*]pyrimidin-7-amine 163 in 30% yield. Removal of thiomethyl group of 163 with RANEY®-Ni in aq. ethanol gave unsubstituted pyrimidine 164 in 44% yield. Oxidation of thiomethyl 163 with oxone in aq. methanol afforded methylsulphone pyrimidine 165 in 70% yield (Scheme 43).⁶⁸

Condensation of (*Z*)-*N*-hydroxy-2-(4-methyl-2-phenylthiazol-5-yl)-2-oxoacetimidoyl chloride 166 with 2-aminopyrimidine in ethanol afforded 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*a*]pyrimidine 167 in 90% yield (Scheme 44).⁶⁹

Berteina-Raboin *et al.* in 2003 reported the solid phase synthesis of imidazo[1,2-*a*]pyrimidine through the reaction of the solid support resin coated 168 and 169 through palladium catalyzed coupling followed by bromination with *N*-bromo-succinimide to yield α -bromoketone derivatives 170 and 171



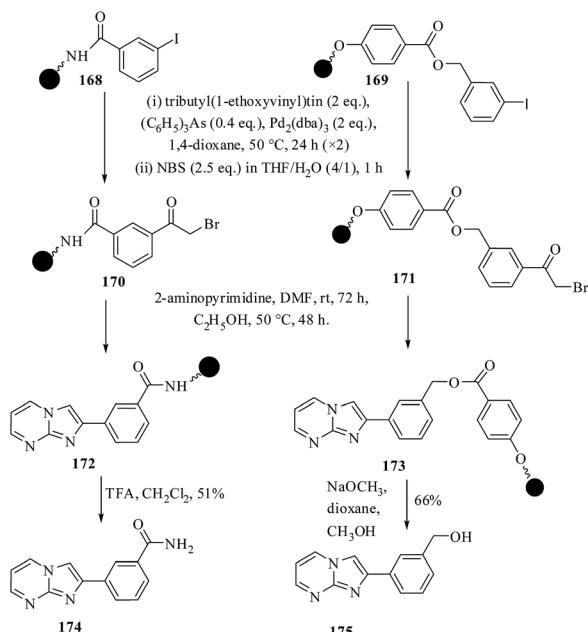
Scheme 43 Synthesis from 2,6-diaminopyrimidine.

Scheme 44 Synthesis of 2-thiazole substituted imidazo[1,2-*a*]pyrimidine.

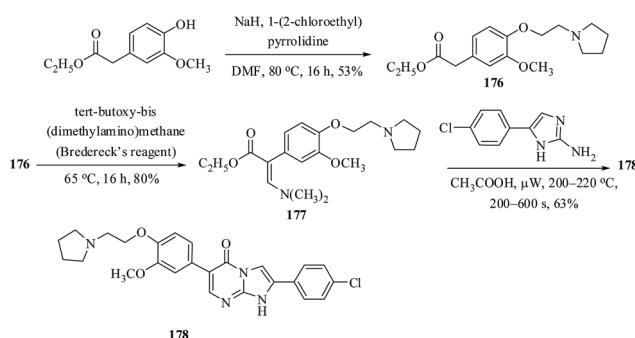
respectively. Further treatment of resin bound α -bromoketones 170 and 171 with 2-aminopyrimidine in DMF/ethanol gave solid support bounded imidazo[1,2-*a*]pyrimidine 172 and 173 respectively. Cleavage of resin 172 with trifluoroacetic acid and 173 with sodium methoxide in dioxane and methanol afforded imidazo[1,2-*a*]pyrimidine 174 and 175 in 51% and 66% yields respectively (Scheme 45).⁷⁰

From α,β -unsaturated ketones

Treatment of ethylhomovalinate with 1-(2-chloroethyl)pyrrolidine in the presence of NaH in DMF gave ethyl 2-(3-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)acetate 176. Reaction with Bredereck's reagent (*tert*-butoxy-bis-(dimethylamino)methane) at 65 °C, obtained 3-dimethylamino-2-aryl-propenoate derivative 177. Microwave assisted reaction of 177 with 5-(4-chlorophenyl)-1*H*-imidazol-2-amine afforded 2-(4-chlorophenyl)-6-(2-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl) imidazo[1,2-*a*]pyrimidin-5(1*H*)-one 178 in 63% yield (Scheme 46).⁷¹

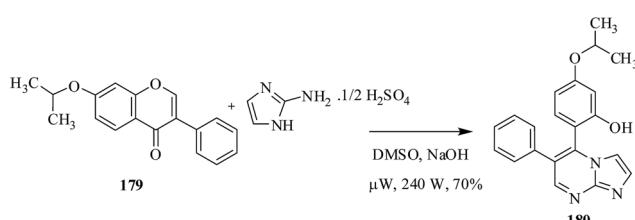


Scheme 45 Solid phase synthesis of 2-substituted imidazo[1,2-a]pyrimidines.

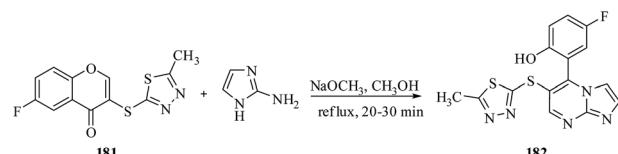


Scheme 46 Synthesis of 2,6-disubstituted imidazo[1,2-a]pyrimidin-5-one.

Zhang and coworkers reported an efficient, simple and one pot procedure for microwave assisted synthesis of 5,6-diphenylimidazo[1,2-a]pyrimidines. Microwave assisted cyclocondensation of isoflavone 179 with 2-aminoimidazole in the presence of sodium hydroxide in DMSO afforded 180 in 70% yield (Scheme 47).⁷² Later, they reported the synthesis of thiadiazole substituted imidazo[1,2-a]pyrimidine. Reaction of 6-



Scheme 47 Condensation reaction of 2-aminoimidazole with isoflavone.

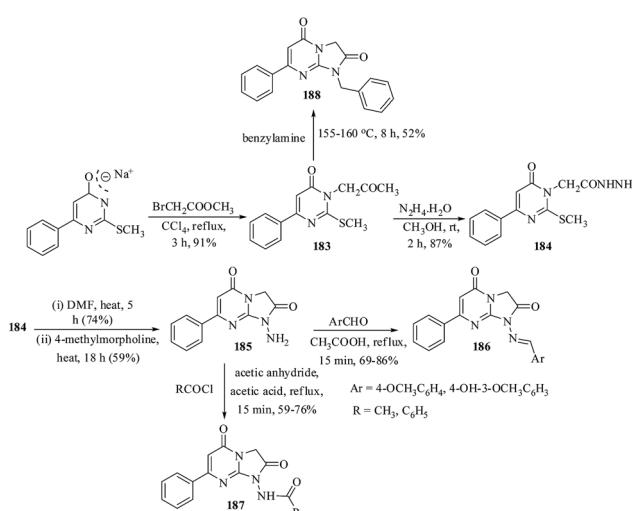


Scheme 48 Reaction of 2-aminoimidazole with isoflavone.

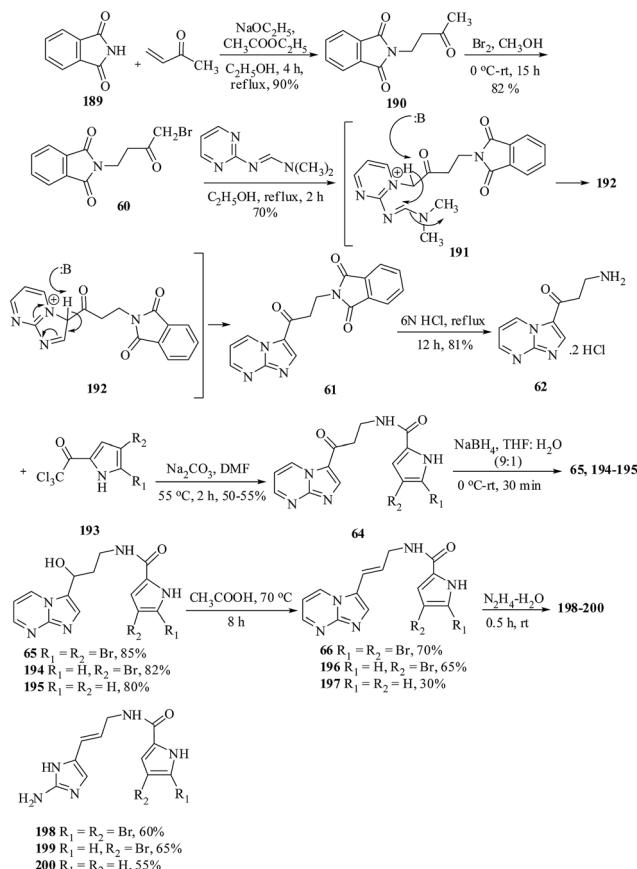
fluoro-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)-4*H*-chromen-4-one 181 with 2-amino imidazole in the presence of sodium methoxide (1 : 3) afforded 182 in 47% (boiling methanol as solvent) and 84% yields (DMSO as solvent at 110 °C) (Scheme 48).⁷³

Alkylation of 2-methylsulphanyl-6-phenyl-3*H*-pyrimidin-4-one with methyl bromoacetate in CCl_4 gave ester derivative 183 followed by reaction with hydrazide hydrate to obtain hydrazide 184. Heating of hydrazide 184 in DMF for 5 h gave imidazo[1,2-a]pyrimidin-2,5-dione 185 in 74% yield. However, cyclization with 4-methyl morpholine as solvent and catalyst for 18 h gave 185 in 25% yield. Subsequent treatment of 185 with aromatic aldehydes and acyl chlorides afforded respective hydrazone imidazo[1,2-a]pyrimidine 186 in 69–86% yields and acylated imidazo[1,2-a]pyrimidine 187 in 59–76% yields. Similarly, the reaction of ester 183 with benzyl amine gave 1-benzyl-7-phenylimidazo[1,2-a]pyrimidine-2,5(1*H*,3*H*)-dione 188 (Scheme 49).⁷⁴

With the continuation of previous work, Rasapalli and coworkers reported the total synthesis of oroidin, hymenindin and clathrodin *via* synthesis of intermediate imidazo[1,2-a]pyrimidine. The reaction of phthalimide 189 with methyl vinyl ketone gave ketone 190 which was brominated with bromine in methanol to afford 60 in 82% yield. Due to instability of 60, it was converted into its hydrate form of atmospheric exposure and used as such for next step immediately followed by reaction with *N,N*-dimethyl-*N*-2-pyrimidinyl-(*E*)-methanimidamide to afford 61 in 70% yield chemospecifically. Deprotection of a phthalamide group of 61 under hydrazinolysis condition was very troublesome due to a competing attack of imidazo[1,2-a]



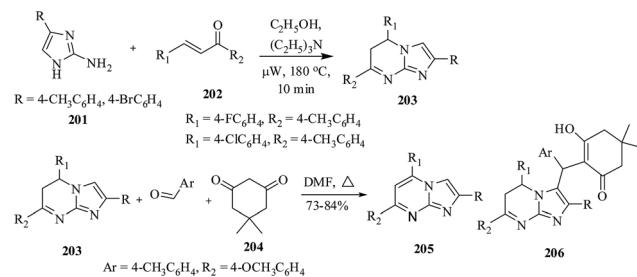
Scheme 49 Synthesis and reactivity of imidazo[1,2-a]pyrimidin-2,5-dione.



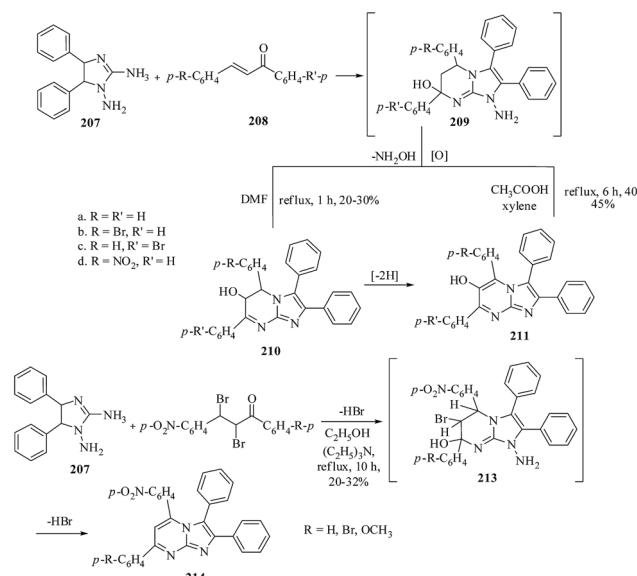
pyrimidine. But this attempt was made successful on refluxing with HCl to give amine **62** in hydrochloride form in 81% yield. Acylation of amine·HCl **62** with pyrrolyl trichloromethyl ketone **193** with excess base gave **64** in 50–55% yield with subsequent NaBH₄ mediated reduction of carbonyl group to give benzylic alcohols **65**, **194**, **195** in 80–85% yields followed by dehydration with acetic acid to give unsaturated compounds **66**, **196**, **197** in 30–75% yields. Subsequent reaction with hydrazine hydrate gave access to oroidin **198**, hymenidin **199** and clathrodin **200** in 60%, 65% and 55% yields respectively (Scheme 50).⁷⁵

Microwave assisted reaction of 2-amino-4-aryl imidazole **201** with substituted chalcone **202** gave imidazo[1,2-*a*]pyrimidine **203** in 80–88% yields. Multicomponent reaction of **203** with different aldehyde and dimedone **204** under conventional as well as microwave irradiation afforded final access to imidazo[1,2-*a*]pyrimidine **205** in 73–84% yields. However, Knoevenagel–Michael adduct **206** have not been detected (Scheme 51).⁷⁶

Cyclization of 1,2-diamino-4,5-diphenylimidazole **207** with 1,3-diarylpropenones **208** gave intermediate **209** with subsequent elimination of N-amino group followed by oxidation of dihydropyrimidine ring through oxygen of the air in DMF at C–H bond of bicyclic system to afford 5,7-diaryl-6-hydroxy-2,3-diphenyl-5,6-dihydroimidazo[1,2-*a*]pyrimidine **210** in 20–30% yields. Cyclization in the presence of acetic acid in xylene afforded 6-hydroxy-2,3,5,7-tetraphenylimidazo[1,2-*a*]pyrimidine **211** in 40–45% yields. However, synthesis of **214** without



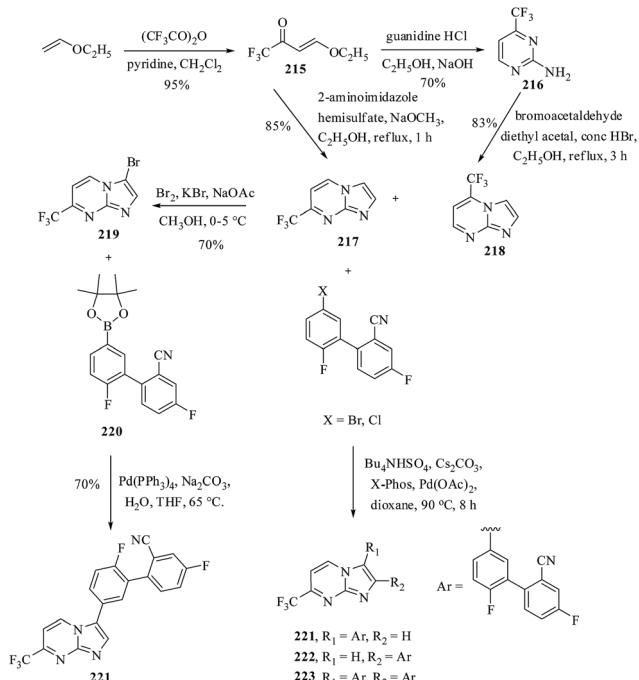
Scheme 51 Synthesis of 2,5,7-trisubstituted imidazo[1,2-*a*]pyrimidines.



Scheme 52 Condensation reaction of diaryl propenones with diphenyl imidazoles.

hydroxyl group was achieved through reaction of diamine **207** with dibromoketone **212** in presence of triethylamine in ethanol through formation of intermediate **213** (Scheme 52).⁷⁷

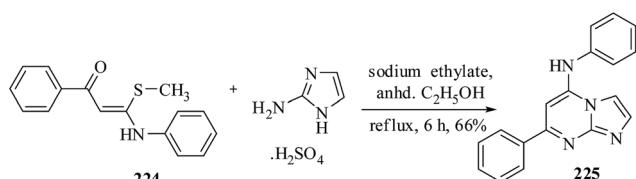
Cameron and coworkers in 2006 reported an efficient and expeditious synthesis of trifluoro substituted imidazo[1,2-*a*]pyrimidines. Treatment of ethylvinyl ether with trifluoroacetic anhydride gave unstable (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one **215** in 95% yield. Immediate condensation of unstable **215** with 2-aminoimidazole hemisulfate obtained regioselective 7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidine **217** in 85% yield. Reaction of **215** with guanidine·HCl in ethanol afforded 4-trifluoromethyl-2-aminopyrimidine **216** in 70% yield followed by condensation with bromoacetaldehyde diethyl acetal in ethanol to obtain **218** in 83% yield. 3-Bromo-7-trifluoromethyl imidazo[1,2-*a*]pyrimidine **219** was obtained on bromination of 7-trifluoromethyl imidazo[1,2-*a*]pyrimidine **217** with bromine in presence of potassium bromide and sodium acetate in methanol in 70% yield. Palladium catalyzed Suzuki–Miyaura coupling of **219** with biaryl boronate **220** ester gave **221** in 70% yield. However, palladium catalyzed coupling of **217** with biaryl chloride afforded biaryl substituted imidazo[1,2-*a*]pyrimidine **221–223** in excellent yields (Scheme 53).⁷⁸



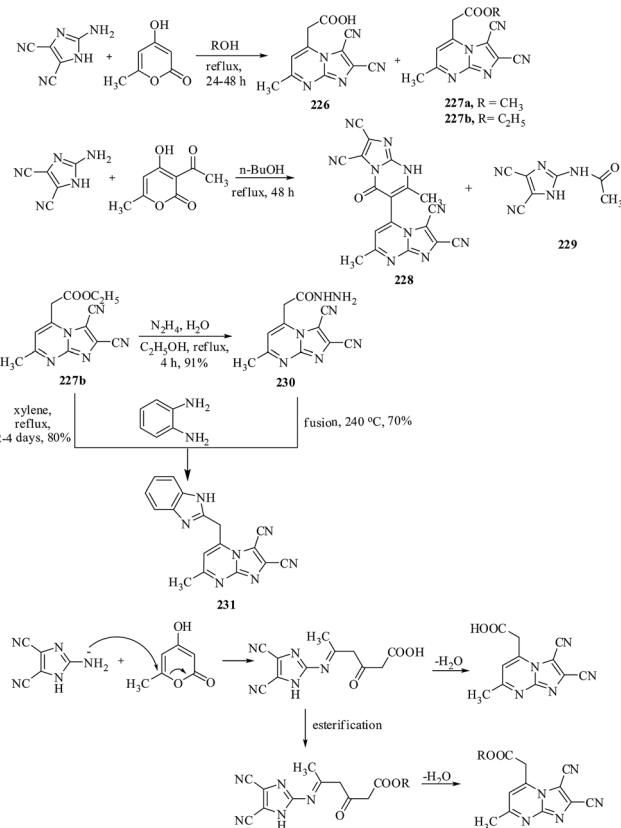
Scheme 53 Synthesis of trifluoromethyl substituted imidazo[1,2-a]pyrimidines.

Heterocyclization reaction of 3-methylthio-1-phenyl-3-phenylaminopropenone 224 with 2-aminoimidazole sulfate and sodium ethylate in anhydrous ethanol afforded *N*,*7*-diphenylimidazo[1,2-*a*]pyrimidine-5-amine 225 in 66% yield (Scheme 54).⁷⁹

Essassi and coworkers in 2008 reported the synthesis of 2,3-dicyano derivatives of imidazo[1,2-*a*]pyrimidine. Treatment of dicyano aminoimidazole with pyran-2-one in different alcohols *viz.* methanol and ethanol for 24–48 h gave acid derivative 226 in 17% and 23% yields respectively, and ester derivative 227a, b in 75% and 70% yields respectively. Condensation of 2 eq. of 2-amino-1*H*-imidazole-4,5-dicarbonitrile with 3-acetyl-4-hydroxy-6-methylpyran-2-one in refluxing *n*-butanol afforded bis(imidazopyrimidine) 228 in 70% yield and 2-acetamido-4,5-dicyanoimidazole 229 in 10% yield. Hydrazide 230 was formed in 91% yield on reaction of 227b with hydrazine hydrate in refluxing ethanol. Final condensation reaction of ester 227b and hydrazide 230 with *o*-phenylenediamine in refluxing xylene and fusion afforded [benzimidazol-2-yl]methylimidazo[1,2-*a*]pyrimidine 231 in 80% and 70% yields respectively (Scheme 55).⁸⁰

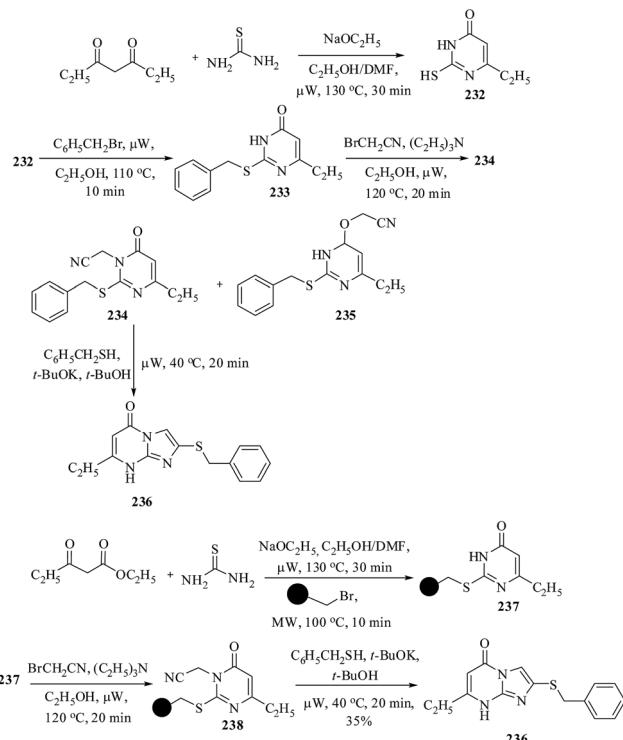


Scheme 54 Synthesis of *N*,*7*-diphenylimidazo[1,2-*a*]pyrimidine-5-amine.



Scheme 55 Synthesis of benzimidazolyl imidazo[1,2-*a*]pyrimidine.

Lam and coworkers in 2010 developed a microwave assisted synthesis of 2-(benzylthio)imidazo[1,2-*a*]pyrimidin-5-ones. Condensation of ethyl 3-oxopentanoate with thiourea in the presence of sodium ethoxide in ethanol under conventional condition for 24 h as well as microwave irradiation at 130 °C for 30 min gave 6-ethyl-2-mercaptopurimidin-4(3*H*)-one 232 in 75% and 83% yields respectively. Treatment with benzyl bromide in ethanol under microwave irradiation for 10 min at 100 °C, 110 °C and 120 °C afforded *S*-benzylated product 233 in 90%, 96% and 90% yields respectively. Attempted for alkylation at N-3 position with chloroacetonitrile proved to be unsuccessful. However, reaction with bromoacetonitrile under conventional condition and microwave irradiation provided *N*-alkylated 234 in 60% and 74% and *O*-alkylated product 235 in 39% and 25% yields respectively. Complete conversions to 234 and 235 have been achieved under microwave irradiation at 120 °C within 20 min. Subsequent treatment of 234 with benzyl thiol in the presence of potassium *t*-butoxide and *t*-butanol at 40 °C for 18 h and under microwave irradiation at 40 °C for 20 min afforded 6-ethyl-2-mercaptopurimidin-4(3*H*)-one 236 in 41% and 61% yields respectively. Following the solution phase synthesis, microwave assisted solid phase synthesis of 236 has also been developed. One pot reaction of ethyl-3-oxopentanoate with thiourea gave 232 followed by microwave assisted treatment with bromomethyl resin at 100 °C for 10 min to afford resin 237 followed by treatment with bromoacetonitrile to give resin 238. Compound 238 was then reacted with benzyl thiol and



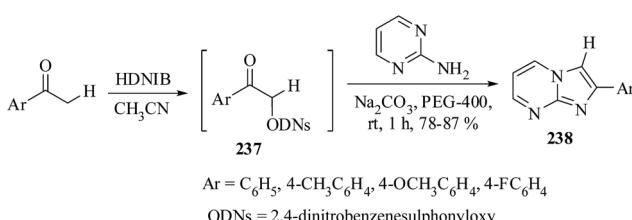
Scheme 56 Microwave and solid phase synthesis of 2-benzylthioimidazo[1,2-a]pyrimidine.

t-butoxide under microwave irradiation at 40°C to afford cyclized product followed by cleavage of solid support residue to provide compound 236 in 35% yield (Scheme 56).⁸¹

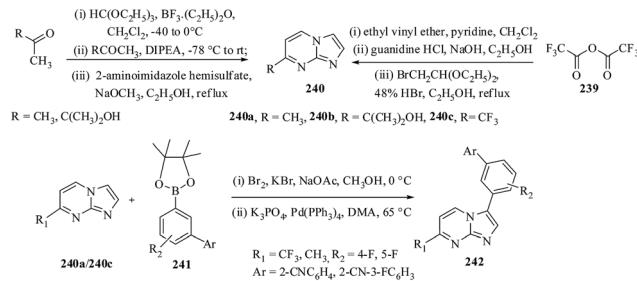
From saturated ketones

Chen and coworkers developed hypervalent iodine(III)sulphonate mediated synthesis of 2-arylated imidazo[1,2-a]pyrimidine. Reaction of aromatic ketones with [hydroxyl(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) in acetonitrile gave intermediate [(2,4-dinitrobenzene)sulfonyl]oxyketone 237. Cyclocondensation of 237 with 2-aminopyrimidine in PEG-400 afforded 2-aryl imidazo[1,2-a]pyrimidine 238 in 78–87% yields (Scheme 57).⁸²

Treatment of ketone with triethylorthoformate and diethoxy carbonium fluoroborate in dichloromethane at -40°C to 0°C followed by treatment of ketoacetals with 2-amino imidazole hemisulphate in the presence of sodium methoxide in ethanol to obtain 7-substituted imidazo[1,2-a]pyrimidine 240a–c. On



Scheme 57 Hypervalent iodine(III)sulphonate mediated synthesis.



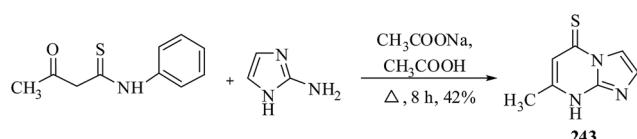
Scheme 58 Synthesis of 7-substituted imidazo[1,2-a]pyrimidines.

the other hand, the reaction of trifluoroacetic anhydride 239 with ethylvinyl ether in pyridine, then guanidine and sodium hydroxide in ethanol followed by treatment with 2-bromo-1,1-diethoxyethane to afford 7-trifluoromethyl imidazo[1,2-a]pyrimidine 240c. Bromination of 7-trifluoromethyl/methyl imidazo[1,2-a]pyrimidine 240a/240c with subsequent Suzuki-Miyaura coupling with boronate ester 241 afforded 3-aryl-7-alkyl imidazo[1,2-a]pyrimidine 242 in 82% yield (Scheme 58).⁸³

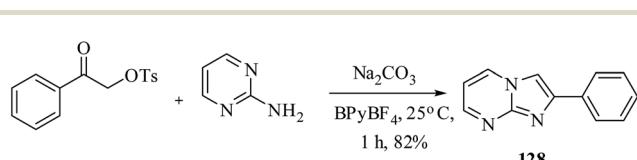
Condensation of 3-oxo-*N*-phenylbutanethioamide with 2-aminoimidazole in the presence of sodium acetate in acetic acid was non-selective and gave 7-methylimidazo[1,2-a]pyrimidine-5(8*H*)-thione 243 in 42% yield (Scheme 59).⁸⁴

Cyclocondensation of α -tosyloxyacetophenone with 2-aminoimidazole catalyzed by ionic liquid BPYBF₄ (*n*-butylpyridinium tetrafluoroborate) at 25°C for 1 h afforded 2-phenyl imidazo[1,2-a]pyrimidine 128 in 82% yield. However, refluxing in a classical solvent like ethanol, reaction time of 6 h was required (Scheme 60).⁸⁵

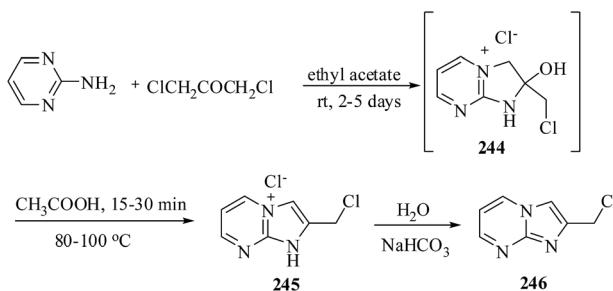
Kornilov and coworkers developed novel, simple and efficient method for the synthesis of 2-chloromethyl substituted imidazo[1,2-a]pyrimidine. Reaction of 2-aminopyrimidine with 1,3-dichloroacetone in ethylacetate gave 2-(chloromethyl)-2-hydroxy-1*H*,2*H*,3*H*-imidazo[1,2-a]pyrimidinium chloride 244 followed by treatment with acetic acid at 80 – 100°C to obtain 2-(chloromethyl)-1*H*-imidazo[1,2-a]pyrimidinium chloride 245. Subsequent treatment of 245 with sodium bicarbonate in water afforded 2-(chloromethyl)imidazo[1,2-a]pyrimidine 246 (Scheme 61).⁸⁶



Scheme 59 Synthesis of imidazo[1,2-a]pyrimidine-5(8*H*)-thione.



Scheme 60 Condensation with α -tosylketone.



Scheme 61 Synthesis of 2-chloromethylimidazo[1,2-a]pyrimidine.

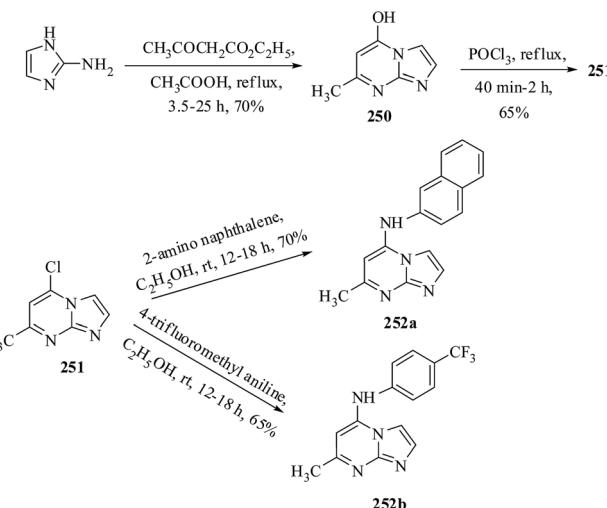
From ethylacetooacetate

Zhou and coworkers in 2008 reported the reaction of guanidine carbonate with ethyl acetooacetate in the presence of sodium methoxide to give 2-amino-4-hydroxy-6-methyl-pyrimidine which then cyclized with 2-bromo-4'-substituted-acetophenone in DMF at refluxed condition to afford 2,5,7-trisubstituted imidazo[1,2-a]pyrimidine 247. Compound 247 underwent Vilsmeier-Haack reaction with POCl_3 in DMF to generate 3-formyl substituted imidazo[1,2-a]pyrimidine 248. Subsequently, 248 was condensed 4-substituted aniline in presence of PTSA and chloroform to give final access to imine derivative of imidazo[1,2-a]pyrimidine 249 (Scheme 62).⁸⁷

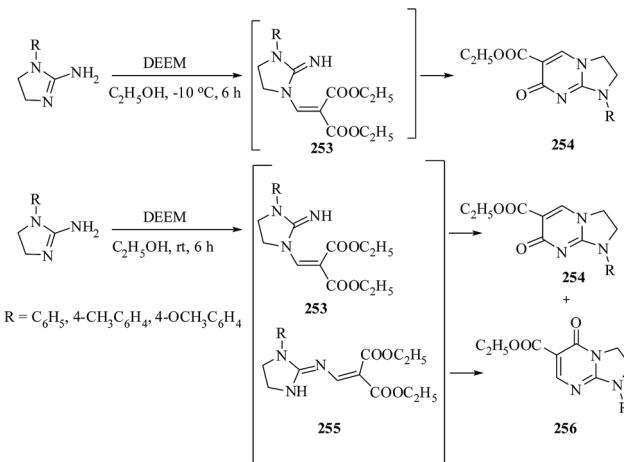
Condensation of 2-aminoimidazole hemisulphate with ethylacetooacetate in refluxing acetic acid gave 5-hydroxy-7-methyl-imidazo[1,2-a]pyrimidine 250 in 70% yield followed by chlorination with phosphorus oxychloride at 5-position to obtain 5-chloro-7-methylimidazo[1,2-a]pyrimidine 251 in 65% yield. Nucleophilic substitution reaction of 251 with 2-amino naphthalene and 4-trifluoromethyl aniline afforded 7-methyl-N-(naphthalen-2-yl)imidazo[1,2-a]pyrimidin-5-amine 252a and 7-methyl-N-(4-(trifluoromethyl)phenyl)imidazo[1,2-a]pyrimidin-5-amine 252b in 70% and 65% yields respectively (Scheme 63).⁸⁸

From dialkylmalonates

Matosiuk and coworkers in 2003 reported a temperature dependent pseudo-Michael reaction of 1-aryl-2-imidazolines with diethyl ethoxy methylene malonate. Cyclization of 1-aryl-2-aminoimidazolines with diethyl ethoxy methylene malonate



Scheme 63 Condensation of 2-aminoimidazole with ethylacetooacetate.

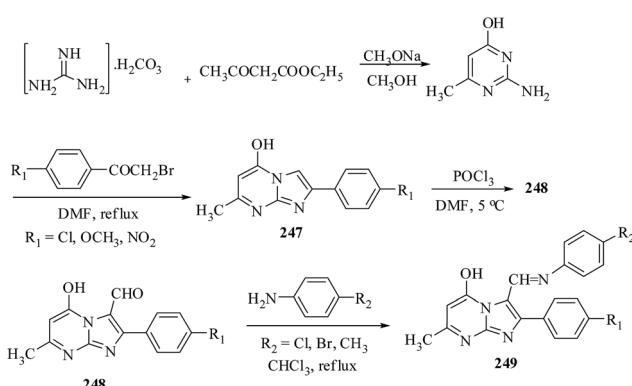


Scheme 64 Pseudo-Michael reaction of imidazoline with DEEM.

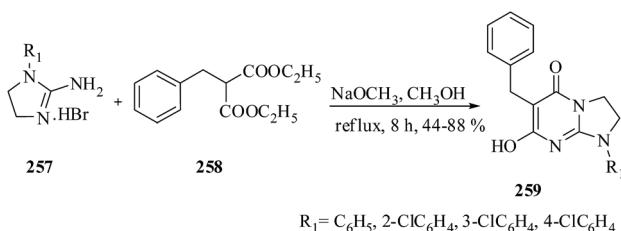
(DEEM) in ethanol at $-10\text{ }^\circ\text{C}$ gave intermediate 253 that was immediate cyclized to afford 1-aryl-7(1*H*)-oxo-2,3-dihydroimidazo[1,2-a]pyrimidine-6-carboxylates 254. However, condensation with DEEM at room temperature for 6 h afforded mixture of isomers 7-oxoimidazo[1,2-a]pyrimidine 254 and 5-oxoimidazo[1,2-a]pyrimidine 256 (Scheme 64).⁸⁹

Rzadkowska and coworkers reported the one pot cyclocondensation of 1-aryl-4,5-dihydro-1*H*-imidazol-2-amine 257 with diethyl 2-benzylmalonate 258 in sodium methoxide in methanol to afford 6-benzyl-7-hydroxy-1-aryl-2,3-dihydroimidazo[1,2-a]pyrimidin-5(1*H*)-one 259 in 44–88% yields (Scheme 65).⁹⁰

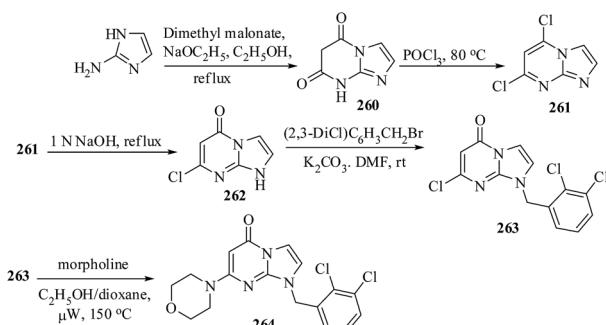
Condensation of 2-aminoimidazole with dimethylmalonate in sodium ethoxide in refluxing ethanol gave imidazo[1,2-a]pyrimidine-dione 260. Chlorination with POCl_3 at $80\text{ }^\circ\text{C}$ gave dichloride imidazo[1,2-a]pyrimidine 261. Further hydrolysis with NaOH at $100\text{ }^\circ\text{C}$ yielded 262. Alkylation of 262 at N-position with 2,3-dichlorobenzyl bromide in the presence of potassium



Scheme 62 Condensation of guanidine carbonate with ethylacetooacetate.



Scheme 65 Condensation of imidazoline with diethyl 2-benzylmalonate.



Scheme 66 Condensation of imidazoline with dimethyl malonate.

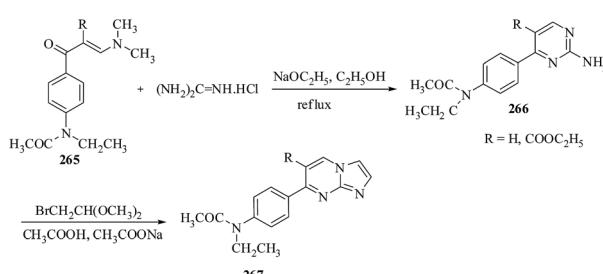
carbonate and DMF afforded *N*-substituted imidazo[1,2-*a*]pyrimidin-5-one 263. Microwave assisted nucleophilic displacement of chlorine with secondary amine, morpholine provided 1-(2,3-dichlorobenzyl)-7-morpholinoimidazo[1,2-*a*]pyrimidin-5(1*H*)-one 264 as a final product (Scheme 66).⁹¹

From enamones

Condensation of enamones 265 with guanidine·HCl in the presence of sodium ethoxide in ethanol gave intermediate 2-amino-4-[4-(*N*-acetyl-*N*-ethyl)aminophenyl]pyrimidines 266. Subsequent cyclization with bromoacetaldehyde dimethyl acetal in the presence of sodium ethoxide in acetic acid afforded 7-substituted imidazo[1,2-*a*]pyrimidine 267 in 32–38% yields (Scheme 67).⁹²

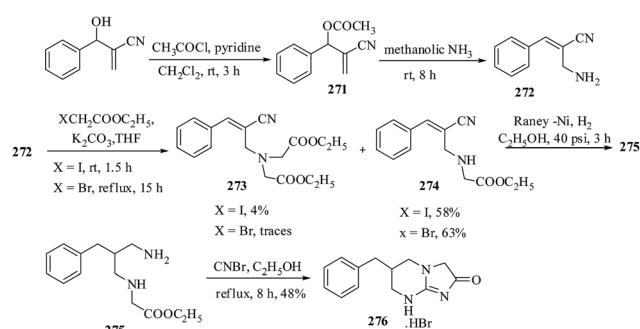
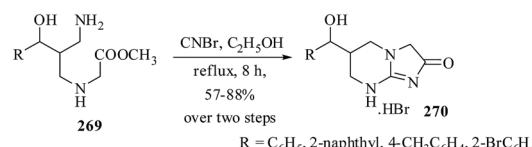
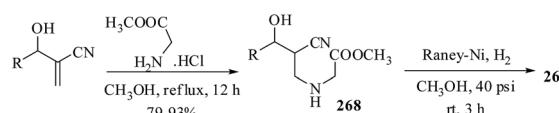
From Baylis–Hillman adduct of acrylonitrile

Batra and coworkers in 2003 and 2004 developed an expeditious synthesis of 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyrimidin-2-ones from Baylis–Hillman adducts of acrylonitrile. Treatment of

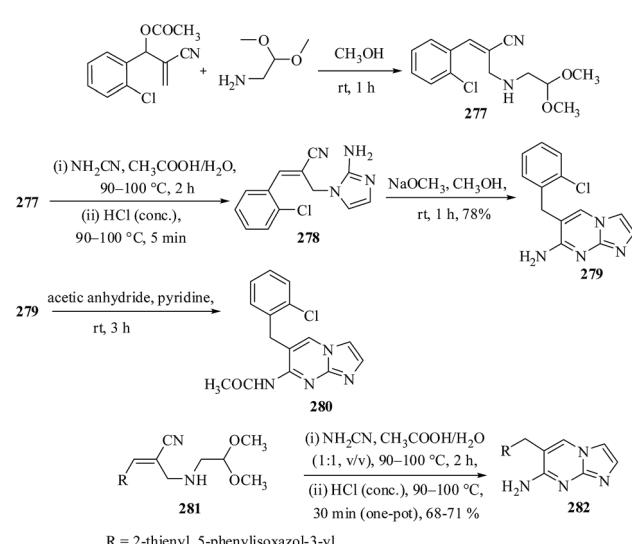


Scheme 67 Condensation of enaminone with guanidine·HCl.

acrylonitrile derivative with glycine ester in refluxing methanol gave diastereomeric mixture (1 : 1) of 268 in 83–95% yields followed by hydrogenation with RANEY®-Ni afforded diamine 269. Being unstable, compound 269 was immediately treated with cyanogen bromide in refluxing ethanol afforded tetrahydroimidazo[1,2-*a*]pyrimidin-2-one as hydrobromide salt 270 in 57–89% yields. Treatment of 2-(hydroxy(phenyl)methyl)acrylonitrile with acetyl chloride in pyridine gave 2-cyano-1-phenylallyl acetate 271 followed by reaction with methanolic ammonia at room temperature to give 272. Subsequent treatment with ethyliodoacetate in the presence of potassium carbonate in THF yielded mixtures of 273 and 274 in 4% and 58% yields respectively. However, reaction with



Scheme 68 Synthesis of tetrahydroimidazo[1,2-*a*]pyrimidine 2-one.



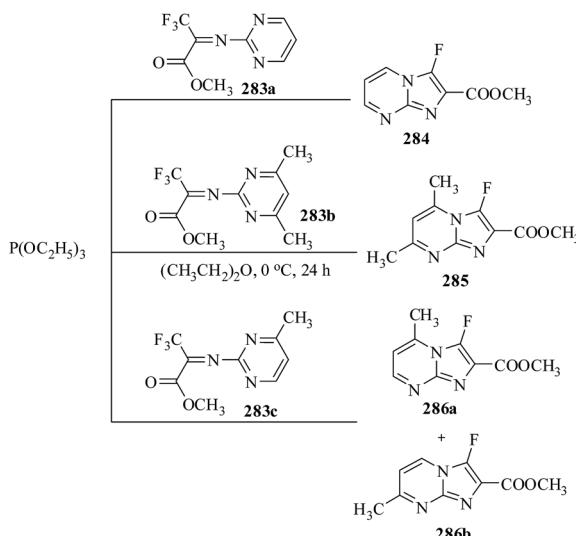
Scheme 69 Synthesis from Baylis–Hillman acetate.

ethylbromoacetate gave **274** in 63% yield with the formation of **273** in traces. Hydrogenation of **274** with RANEY®-Ni gave diamino derivative **275** which being unstable and immediately reacted with cyanogen bromide to obtained **276** in 48% yield (Scheme 68).⁹³ Later, they reported the facile and efficient one pot synthesis of imidazo[1,2-*a*]pyrimidin-7-yl-amines. Reaction with Baylis–Hillman acetate, 1-(2-chlorophenyl)-2-methylallyl acetate with 3 eq. of 2,2 dimethoxyethylamine in methanol gave allylamine derivative **277** in 95% yield followed by treatment with cyanamide in an aq. acetic acid at 90–100 °C for 2 h to give **278** in 69% yield. **278** was then allowed to react with sodium methoxide in methanol yielded cyclized product 6-(2-chlorobenzyl)imidazo[1,2-*a*]pyrimidin-7-amine **279** in 78% yield. To confirm the presence of free amino group in **279**, it was treated with acetic anhydride in pyridine to afford acetylated derivative **280**. However allylamine derivative **281** reacted with cyanamide in an aq. acetic acid and then treatment with HCl directly provided **282** in 68–71% yields (Scheme 69).⁹⁴

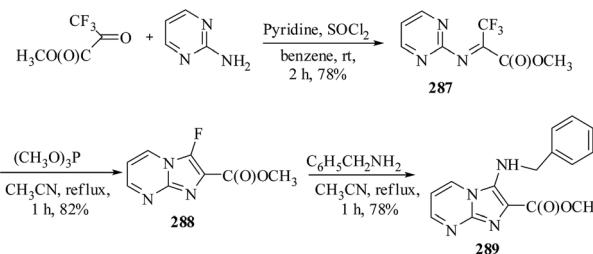
From trifluoropyruvates

Gakh and coworkers developed an efficient synthetic method for the synthesis of fluorine containing imidazo[1,2-*a*]pyrimidine through heterocyclization of triethylphosphite with *N*-(heteroarylmino)trifluoropyruvates. Treatment of triethylphosphite with iminocarboxylate **283a–c** in diethylether at 0 °C afforded methyl 3-fluoroimidazo[1,2-*a*]pyrimidine-2-carboxylate **284**, methyl 3-fluoro-5,7-dimethylimidazo[1,2-*a*]pyrimidine-2-carboxylate **285**, methyl 3-fluoro-5-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate **286a** and methyl 3-fluoro-7-methylimidazo[1,2-*a*]pyrimidine-2-carboxylate **286b** in 83%, 81% and 72% (2 : 1) yields respectively (Scheme 70).⁹⁵

Sokolov and coworkers developed an efficient synthetic approach for *N*-benzyl methyl-3-aminoimidazo[1,2-*a*]pyrimidine-2-carboxylate **289**. Reaction of 2-amino pyrimidine with methyl trifluoropyruvate in the presence of thionyl



Scheme 70 Condensation of triethylphosphite with trifluoropyruvates.



Scheme 71 Condensation with methyl trifluoropyruvate.

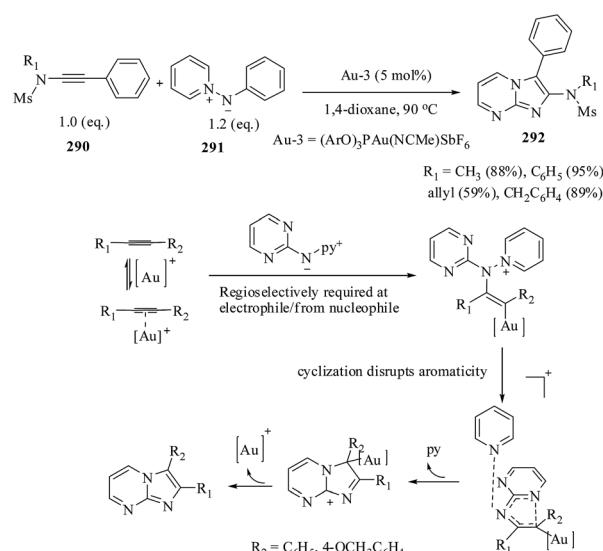
chloride and pyridine in benzene to obtain *N*-(pyrimdin-2-yl) imines of methyl trifluoropyruvate **287**. Cyclization of **287** with trimethyl phosphite in refluxing acetonitrile gave methyl 3-fluoroimidazo[1,2-*a*]pyrimidine-2-carboxylate **288**. Replacement of fluorine atom of **288** with benzylamine led to the formation of *N*-benzyl methyl-3-aminoimidazo[1,2-*a*]pyrimidine-2-carboxylate **289** in 78% yield (Scheme 71).⁹⁶

1,3-Dipolar cycloaddition

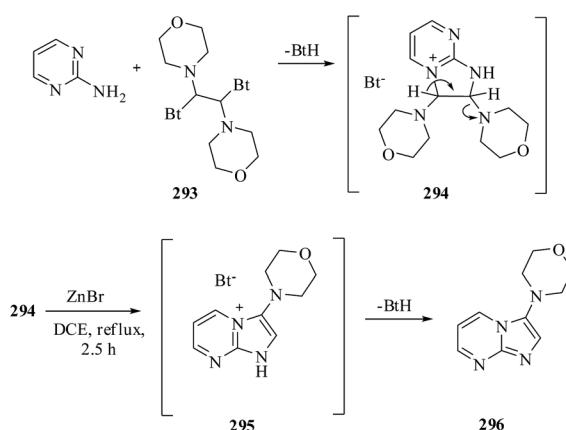
Davies and coworkers reported the regioselective synthesis of fused pyrimidines **292** in 59–95% yields, being approached through [3 + 2] dipolar cycloaddition reactions of nucleophilic nitrenoid pyridinium-*N*-(heteroaryl)-aminide **291** as a synthetic equivalent of 1,3-*N,N*-dipole with electron rich triple bond **290** under gold catalysts (0.2 M) in dioxane at 90 °C for 24 h (Scheme 72).⁹⁷

From dialkyl aminoalkanes

An efficient and simple approach for one pot regiospecific synthesis of imidazo[1,2-*a*]pyrimidines has been reported by Katritzky and coworkers through reaction of 2-amino pyrimidine with 1,2-bis(benzotriazolyl)-1,2-(dialkylamino) ethanes **293** to obtain intermediate **294** which was cyclized in the presence of zinc bromide (increase the leaving ability of



Scheme 72 Dipolar cycloaddition reaction.



Scheme 73 Regiospecific synthesis of 3-morpholinoimidazo[1,2-a]pyrimidines.

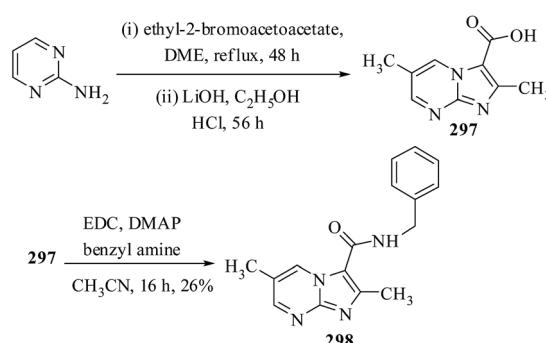
benzotriazolyl group) in refluxing dichloroethane to afford 3-morpholino imidazo[1,2-a]pyrimidine **296** in 35% yield (Scheme 73).⁹⁸

From α -haloester

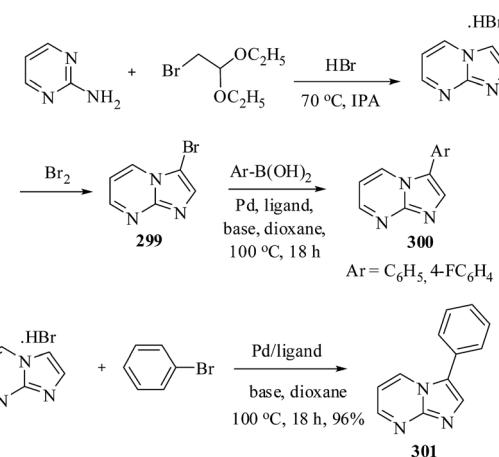
Miller and coworkers reported the synthesis of 3-substituted imidazo[1,2-a]pyrimidines through reaction of 2-amino pyrimidine with ethyl-2-bromoacetoacetate and subsequent saponification with LiOH in ethanol followed by acidification to give acid derivative **297** which was coupled with benzyl amine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) to afford **298** in 26% yield (Scheme 74).⁹⁹

From haloalkanes

Li *et al.* reported the palladium catalyzed regioselective arylation at 3-position using aryl halides proceeding through reaction of 2-aminopyrimidine with 2-bromo-1,1-diethoxyethane to give unsubstituted imidazo[1,2-a]pyrimidine·HBr followed by bromination at 3-position to give **299** which on subsequent Suzuki–Miyaura coupling with various aryl boronic acids afforded **300**. As the bromination occurred regioselectively at 3-position, that conferred the potential high regioselectivity for



Scheme 74 Synthesis of 3-amide substituted imidazo[1,2-a]pyrimidines.

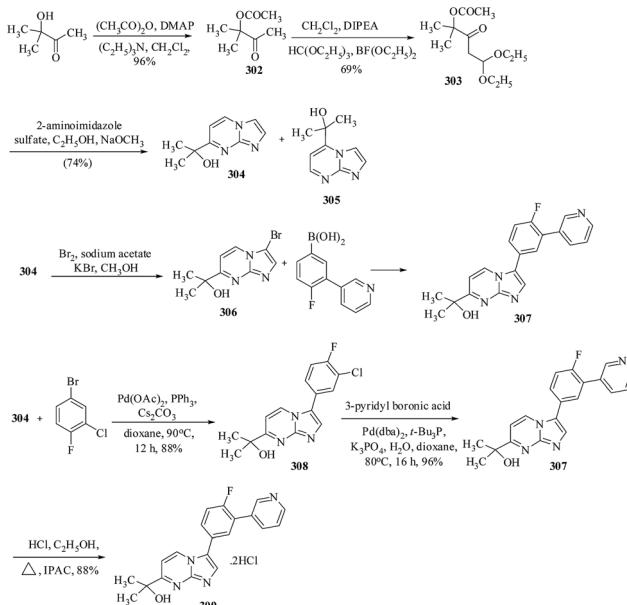


Scheme 75 Reaction of 2-aminopyrimidine with 2-bromo-1,1-diethoxyethane.

arylation. Keeping in view, imidazo[1,2-a]pyrimidine·HBr was also arylated with bromobenzene using Pd(OAc)₂ (2 mol%), PPh₃ (4 mol%) and Cs₂CO₃ (2 eq.) in dioxane at 100 °C to provide 3-phenyl imidazo[1,2-a]pyrimidine **301** in 96% yield (Scheme 75).¹⁰⁰

From ketoacetals

Jensen and coworkers in 2005 reported regioselectively the synthesis of imidazo[1,2-a]pyrimidine through palladium catalyst in high yield. Reaction of 3-hydroxy-3-methyl-2-butanone with acetic anhydride in presence of 4-dimethylaminopyridine (DMAP) gave the acetate derivative **302** in 96% yield. Formation of β -keto acetal **303** was achieved through reaction of **302** with triethylorthoformate in the presence of boron trifluoride etherate and DIPEA at –65 °C. Subsequent condensation with 2-aminoimidazole sulphate with sodium methoxide obtained the imidazo[1,2-a]pyrimidine core. Regioselective formation of imidazo[1,2-a]pyrimidine was highly pH dependent. Increase in pH resulted in the formation of 7-substituted regiosomer **304** while lower pH favoured the formation of 5-substituted isomer **305**. However, use of excess sodium methoxide resulted in the formation of both regiosomers **304** and **305** in 96 : 4 ratio. Bromination of **304** with bromine in presence of sodium acetate and potassium bromide in methanol gave 3-bromo substituted imidazo[1,2-a]pyrimidine **306** followed by Suzuki–Miyaura coupling with aryl boronic acid to obtain 3-aryl imidazo[1,2-a]

Scheme 76 Condensation reaction with β -ketoacetal.

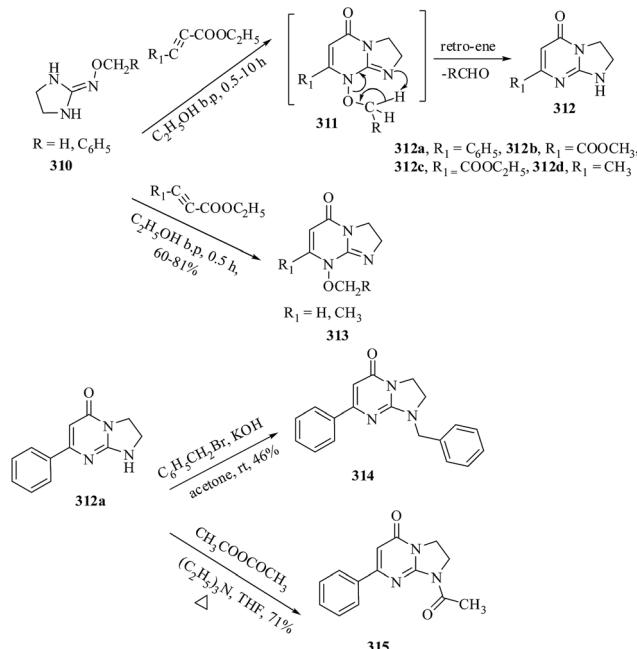
pyrimidine 307. Aryl substituent was directly installed on coupling 304 with 4-bromo-2-chloro-1-fluorobenzene to obtain 308 in 88% yield. Suzuki–Miyaura coupling with 3-pyridyl boronic acid was achieved under troublesome conditions to afford 307 followed by subsequent reaction in HCl in ethanol to obtain bis hydrochloride salt of 309 (Scheme 76).¹⁰¹

From alkynes

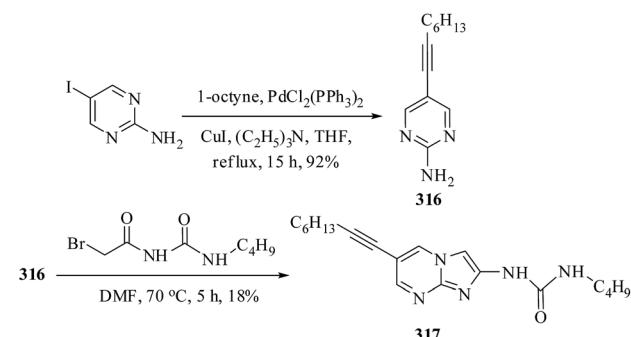
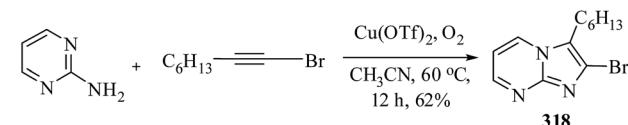
Reaction of 2-alkoxyiminoimidazolidine 310 with acetylene dicarboxylates and ethylphenylpropiolate in boiling ethanol gave intermediate 8-alkoxy imidazo[1,2-*a*]pyrimidin-5-ones 311 which underwent multihetero retro-ene fragmentation to afford imidazo[1,2-*a*]pyrimidin-5-ones 312a–d with a loss of aldehyde group. On the other hand, reaction of 310 with ethylpropiolate gave 8-alkoxy imidazo[1,2-*a*]pyrimidin-5-one 313 in 60–81% yields. Alkylation of 312a with benzyl bromide and acetylation with acetic anhydride afforded 314 and 315 in 46% and 71% yields respectively (Scheme 77).¹⁰²

Sonogashira coupling of 2-amino-5-iodo-pyrimidine with 1-octyne catalyzed by palladium and CuI in THF to obtain 5-(oct-1-ynyl)pyrimidin-2-amine 316 in 92% yield. Coupling followed by cyclization of 316 with 2-bromo-N-(butylcarbamoyl)acetamide in DMF afforded 1-butyl-3-(6-(oct-1-ynyl)imidazo[1,2-*a*]pyrimidin-2-yl)urea 317 in 18% yield (Scheme 78).¹⁰³

Jiang and coworkers in 2013 reported an efficient one pot copper catalyzed synthesis of 3-hexylimidazo[1,2-*a*]pyrimidine 318 in 92% yield through reaction of 2-aminopyrimidine with bromoalkyne in the presence of molecular oxygen (Scheme 79).¹⁰⁴ Bakherad and coworkers in 2011 reported the palladium catalyzed copper free Sonogashira coupling for synthesis of imidazo[1,2-*a*]pyrimidines. Reaction of 2-aminopyrimidine with propargyl bromide in refluxing acetonitrile gave 1-(prop-2-ynyl)pyrimidin-2(1*H*)-imine 319 in 80% yield. Sonogashira coupling of 319 with various aryl iodides under Pd/C catalyst in

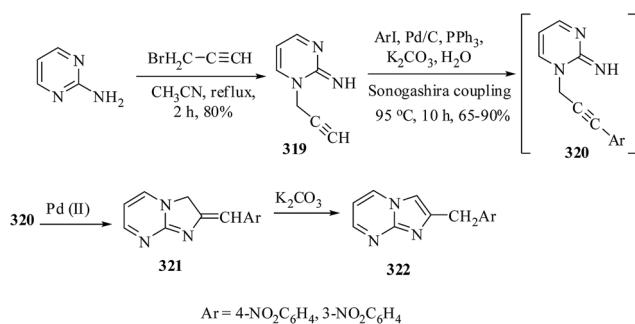


Scheme 77 Reaction of alkoxyiminoimidazolidine with acetylene dicarboxylates.

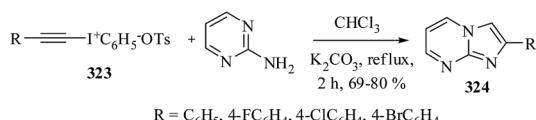
Scheme 78 Synthesis of 6-alkyne substituted imidazo[1,2-*a*]pyrimidine.Scheme 79 Synthesis of 3-hexyl-2-bromo-imidazo[1,2-*a*]pyrimidine.

the presence of triphenyl phosphine in water at 95 °C to obtain intermediate 320 which underwent cyclization with Pd(II) to form 2-(arylidene)-2,3-dihydroimidazo[1,2-*a*]pyrimidine 321. Compound 321 was then treated with potassium carbonate under argon atmosphere to achieve 2-arylsubstituted imidazo[1,2-*a*]pyrimidine 322 in 65–90% yields (Scheme 80).¹⁰⁵

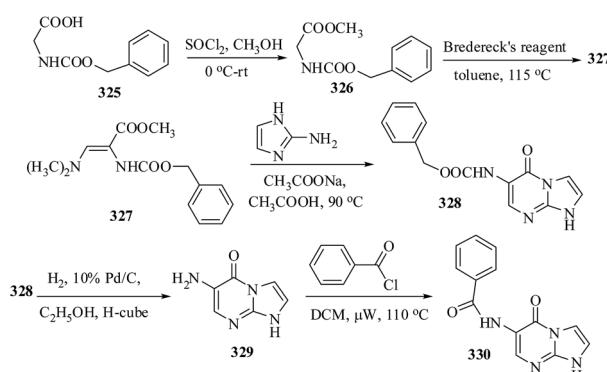
Cyclization of alkynyl(aryl)iodonium salts 323 with 2-aminopyrimidine in potassium carbonate in chloroform obtained 2-substituted imidazo[1,2-*a*]pyrimidine 324 in 69–80% yields. It involves the electrophilic attack of β -carbon of alkynyl (aryl)



Scheme 80 Reaction with bromoalkyne and Pd catalyzed cyclization.



Scheme 81 Condensation reaction of alkynyl(aryl)iodonium salts.



Scheme 82 Cyclization of acid amide with 2-aminoimidazole.

iodonium salts on exocyclic nitrogen with the elimination of iodobenzene followed by aromatization (Scheme 81).¹⁰⁶

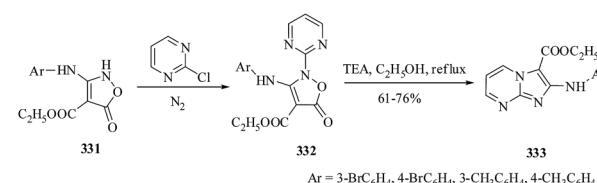
From acid amides

Treatment of 2-(benzyloxycarbonylamino)acetic acid 325 with thionyl chloride in methanol gave 326. Compound 326 was then reacted with Bredereck's reagent in toluene to give 327.

Subsequent reaction with 2-amino imidazole in sodium methoxide and acetic acid gave benzyl 5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidin-6-ylcarbamate 328 followed by reduction with Pd/C in the presence of hydrogen to obtain 6-aminoimidazo[1,2-a]pyrimidin-5(1H)-one 329. Reaction with benzoyl chloride afforded final access to benzamide derivative of imidazo[1,2-a]pyrimidine 330 (Scheme 82).¹⁰⁷

Intramolecular cyclization

Treatment of ethyl 5-oxo-3-arylamino-2,5-dihydroisoxazole-4-carboxylates 331 with 2-chloropyrimidine under nitrogen atmosphere gave corresponding isoxazolones 332 with 2-



Scheme 83 Synthesis of 2-aminoaryl imidazo[1,2-a]pyrimidin-3-carboxylate.

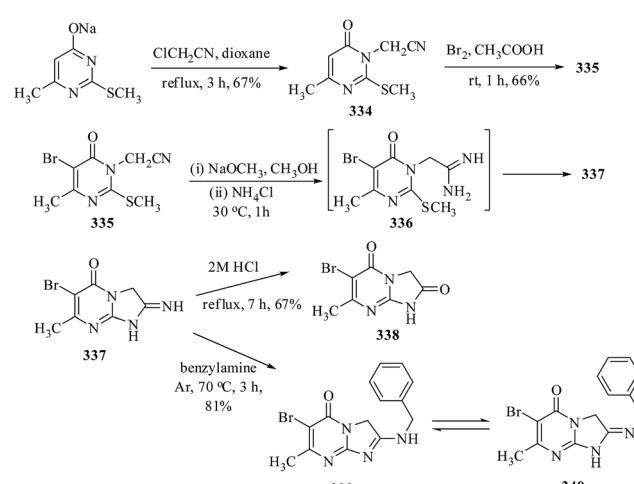
substituted pyrimidine ring. Intramolecular cyclization through rearrangement of isoxazolones 332 with triethyl amine (TEA) in refluxing ethanol afforded 333 in 61–76% yields (Scheme 83).¹⁰⁸

Reaction of sodium salt of pyrimidine with chloroacetonitrile in dioxane obtained 3-nitrile derivative of pyrimidine 334. Bromination at 5-position of 334 with bromine in acetic acid gave 335. Further, compound 335 was reacted with sodium methoxide in methanol followed by treatment with ammonium chloride to give intermediate 336 which underwent cyclization *in situ* to afford 6-bromo-2-imino-7-methyl-2,3-dihydroimidazo[1,2-a]pyrimidin-5(1H)-one 337 in 66% yield. Refluxing with 2 M HCl for 7 h and heating with benzyl amine at 70 °C for 3 h gave final access to 6-bromo-7-methylimidazo[1,2-a]pyrimidine-2,5(1H,3H)-dione 338 in 67% yield and 2-(benzylamino)-6-bromo-7-methylimidazo[1,2-a]pyrimidin-5(3H)-one 339 in 81% yield respectively and later tautomerize to 340 (Scheme 84).¹⁰⁹

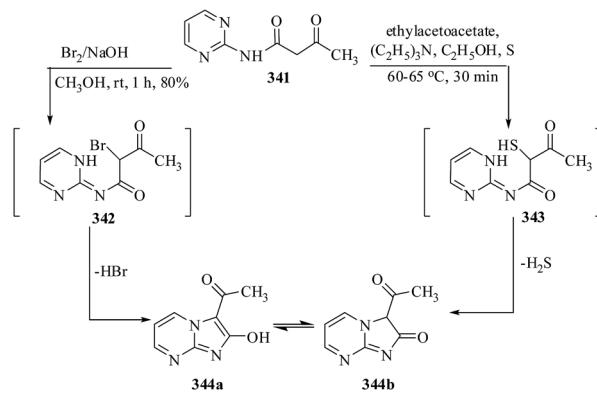
Treatment of butanamide 341 with Br₂ in NaOH and sulphur at room temperature gave intermediates 342 and 343 respectively. Initial bromination of methylene group was followed by elimination of hydrogen bromide and hydrogen sulphide to access 2-hydroxy imidazo[1,2-a]pyrimidine 344a which tautomerizes to its keto form 344b (Scheme 85).¹¹⁰

Tandem reactions

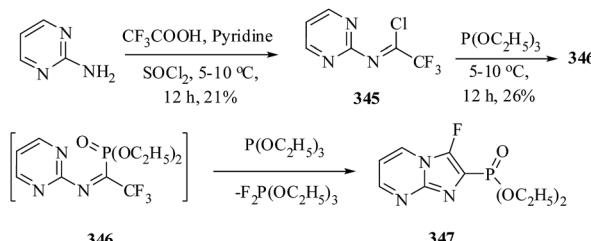
Aksinenko and coworkers reported the tandem reaction of (pyrimidin-2-yl)imidoyl chloride with triethyl phosphite to synthesize 2-(dialkoxypyrophoryl) imidazo[1,2-a]pyrimidines. 2-Aminopyrimidine was reacted with trifluoroacetic acid (TFA)



Scheme 84 Synthesis of dihydroimidazo[1,2-a]pyrimidin-5-one.



Scheme 85 Intramolecular cyclization to imidazo[1,2-a]pyrimidine.



Scheme 86 Reaction of pyrimidin-2-yl imidoyl chloride with triethyl phosphite.

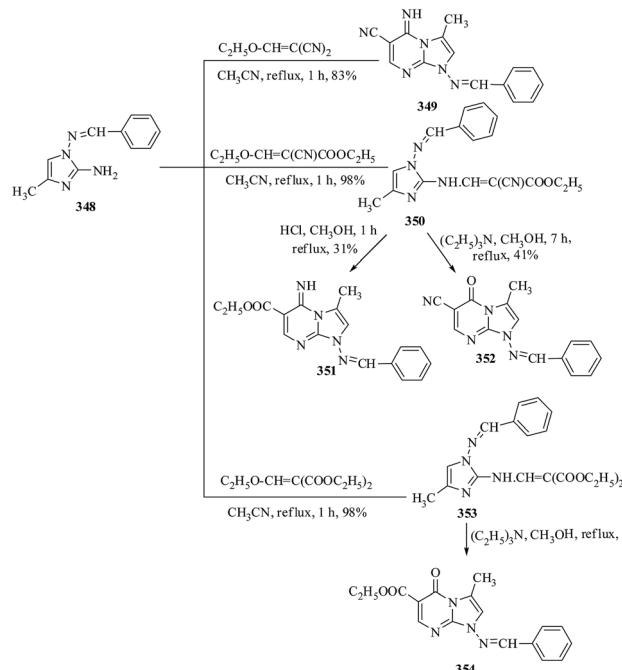
and thionyl chloride in pyridine to give imidoyl chloride **345**. Exothermic reaction of **345** with one molecule of triethyl phosphite gave intermediate **346** which immediately underwent cyclization on reaction with a second molecule of triethyl phosphite to afford diethyl (3-fluoroimidazo[1,2-a]pyrimidin-2-yl)phosphonate **347** in 26% yield (Scheme 86).¹¹¹

Annulation reactions

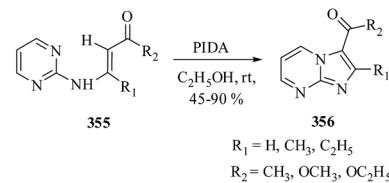
Treatment of (*Z*)-N1-benzylidene-4-methyl-1*H*-imidazole-1,2-diamine **348** with ethoxymethylene malononitrile in refluxing acetonitrile gave 1-benzylideneamino-6-cyano-5-imino-3-methyl-1*H*-imidazo[1,2-a]-pyrimidine **349** in 83% yield. However, treatment with ethyl 2-cyano-3-ethoxyacrylate gave intermediate ethyl (1-benzylideneamino-4-methylimidazol-2-yl)aminomethylenecyanoacetate **350** in 98% yield followed by cyclization with HCl in methanol for 1 h and triethylamine in methanol for 7 h to access ethyl 1-benzylideneamino-5-imino-3-methyl-1*H*-imidazo-[1,2-a]pyrimidine-6-carboxylate **351** and 1-benzylideneamino-6-cyano-3-methyl-5-oxo-1*H*-imidazo[1,2-a]pyrimidine **352** in 31% and 41% yields respectively. Reaction of **348** with diethyl 2-(ethoxymethylene)malonate gave intermediate **353** followed by cyclization with triethylamine in methanol for 3 h to obtain ethyl 1-(benzylideneamino)-3-methyl-5-oxo-1,5-dihydroimidazo[1,2-a]pyrimidine-6-carboxylate **354** (Scheme 87).¹¹²

Intramolecular C–H bond cycloamination reaction

An efficient protocol for the metal free synthesis of imidazo[1,2-a]pyrimidines from pyrimidyl enamines through hypervalent



Scheme 87 Synthesis of imidazo[1,2-a]pyrimidin-5-one-6-carboxylate.

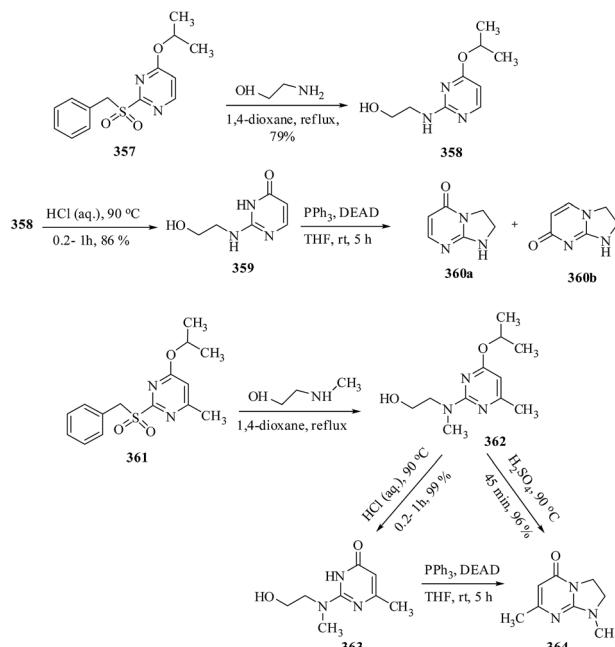


Scheme 88 Synthesis of imidazo[1,2-a]pyrimidines from pyrimidyl enamines.

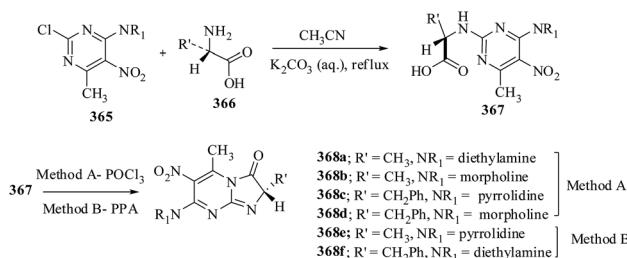
iodine mediated intramolecular C–H bond cycloamination reaction has been developed by Xu and co-workers. 3-(Pyrimidin-2-ylamino)-acrylate **355** was reacted with phenyl-iodine diacetate (PIDA) as oxidant in ethanol to give **356** in 45–90% yields (Scheme 88).¹¹³

Intramolecular C–N bond cycloamination reaction

Villalgorro and coworkers in 2006 developed a straightforward approach for synthesis of imidazo[1,2-a]pyrimidinones through intramolecular cyclization of pyrimidines/pyrimidinones with amino alcohol which underwent ring closure through Mitsunobu reaction. Reaction of pyrimidinyl sulphone **357** with 2-aminoethanol in dioxane afforded pyrimidine **358** in 79% yield. Compound **358** underwent acidic hydrolysis with conc. HCl to give pyrimidinones **359** with 86% yield. Subsequent treatment of **359** with triphenylphosphine in the presence of DEAD in dry THF afforded mixture of regioisomers **360a** and **360b** (12 : 88). However, the reaction of sulphonyl having methyl at 2-position **361** with 2-(methylamino)ethanol gave **362** followed by acidic hydrolysis to give **363**. Reaction with triphenylphosphine in the presence of DEAD gave final access to only



Scheme 89 Reaction of pyrimidinyl sulphone with aminoalcohols.



Scheme 90 Chiral synthesis of imidazo[1,2-a]pyrimidin-3-ones.

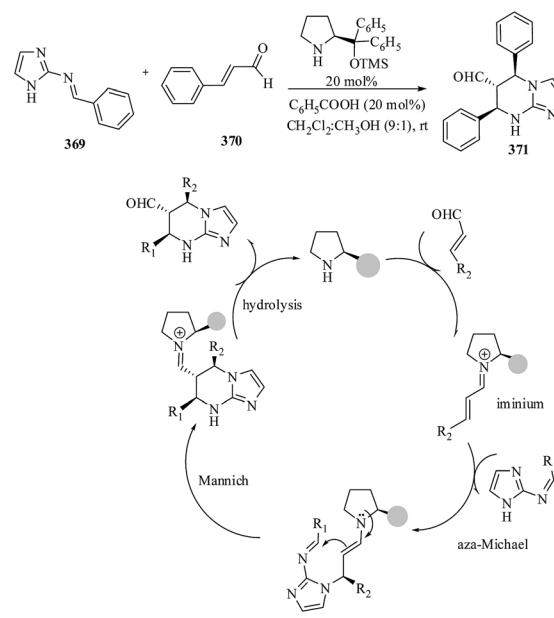
1,7-dimethyl-2,3-dihydroimidazo[1,2-a]pyrimidin-5(1*H*)-one **364** in 96% yield. Compound **364** could also be directly synthesized through the reaction of pyrimidine **362** with sulphuric acid at 90 °C in 99% yield (Scheme 89).¹¹⁴

Optically active imidazo[1,2-a]pyrimidines

Bakavoli and coworkers reported the synthesis of optically active imidazo[1,2-a]pyrimidin-3-ones. Treatment of pyrimidine derivative **365** with L-(α -amino acids) **366** in the presence of potassium carbonate in refluxing acetonitrile afforded N-heteroarylamino acid **367**. Chlorination of **367** with POCl₃ (method A) with subsequent cyclization at moderate temperature afforded chiral imidazo[1,2-a]pyrimidin-3(2*H*)-one **368a-d** in 45–57% yields. However, cyclization with polyphosphoric acid (PPA) at 70–75 °C (method B) afforded chiral **368e,f** in 45–52% yields (Scheme 90).¹¹⁵

Aza-Michael–Mannich reaction

Li and coworkers in 2011 reported a highly efficient synthesis of three chiral centered tetrahydroimidazopyrimidine **371** through

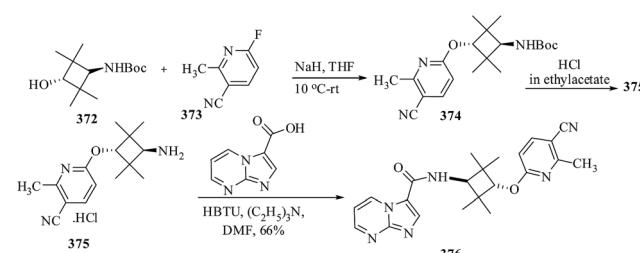


Scheme 91 Aza-Michael–Mannich reaction.

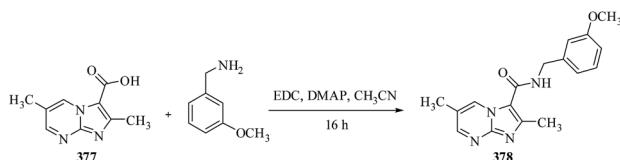
organocatalytic domino aza-Michael–Mannich reaction of benzylidene-1*H*-imidazol-2-amine **369** with cinnamaldehyde **370** catalyzed by 20 mol% of 2-(diphenyl(trimethylsilyloxy)methyl)pyrrolidine and benzoic acid in a mixture of DCM : CH₃OH (9 : 1). The reaction provided high stereoselectivity (>97% ee and >20 : 1 dr) and good percentage of yield (Scheme 91).¹¹⁶

Reactivity of imidazo[1,2-a]pyrimidines

Guo and coworkers in 2011 reported the nucleophilic displacement reaction of 6-fluoro-2-methylnicotinonitrile **373** with Boc-protected cyclobutyl amino alcohol **372** in THF gave Boc protected intermediate **374** followed by acidic removal of protecting group to give amine **375**. Subsequently, **375**·HCl was reacted with imidazo[1,2-a]pyrimidine-3-carboxylic acid in presence of O-benzotriazole-*N,N,N',N'*-tetramethyl-uronium-hexafluorophosphate (HBTU) in DMF to provide *N*[(1*r*,3*r*)-3-(5-cyano-6-methylpyridin-2-yloxy)-2,2,4,4-tetramethylcyclobutyl]imidazo[1,2-a]pyrimidine-3-carboxamide **376** in 66% yield (Scheme 92).^{117,118}



Scheme 92 Reaction of cyclobutyl amine with imidazo[1,2-a]pyrimidine-3-carboxylic acid.

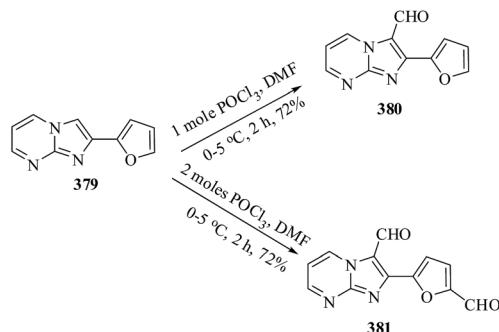


Scheme 93 Amide synthesis of imidazo[1,2-a]pyrimidines.

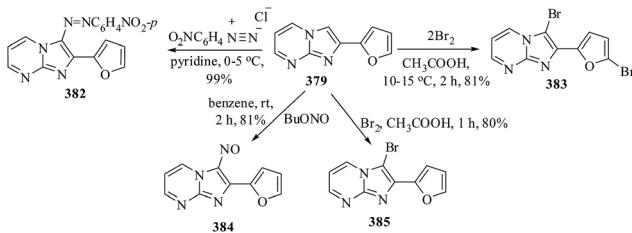
Miller and coworkers reported the synthesis of substituted 3-amide imidazo[1,2-a]pyrimidine. Treatment of imidazo[1,2-a]pyrimidine-3-carboxylic acid 377 with (3-methoxyphenyl)methanamine with coupling reagent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of 4-dimethylaminopyridine (DMAP) in acetonitrile afforded *N*-(3-methoxybenzyl)-2,6-dimethylimidazo[1,2-a]pyrimidine-3-carbamide 378 (Scheme 93).¹¹⁹

2-(2'-Furyl)-imidazo[1,2-a]pyrimidine 379 underwent Vilsmeier–Haack reaction with 1 mole of POCl_3 in DMF to give 3-formyl-2-(2'-furyl)imidazo[1,2-a]pyrimidine 380 in 72% yield. However, reaction of 379 with 2 moles of POCl_3 in DMF afforded diformylation at 5' of furan ring and 3-position of imidazo[1,2-a]pyrimidine 381 in 72% yield (Scheme 94).¹²⁰

Electrophilic substitution reaction of 379 with *p*-nitrophenyl diazonium chloride and *n*-butyl nitrite provided respective 3-(*p*-nitrophenylazo) derivative 382 in 99% yield and 3-nitroso substituted imidazo[1,2-a]pyrimidine 384 in 81% yield. However, reaction of 379 with 1 mole of Br_2 gave only 3-substituted product 383 in 81% yield, but with 2 moles of bromine afforded 3 and 5'-disubstituted imidazo[1,2-a]pyrimidine 385 in 80% yield (Scheme 95).¹²¹



Scheme 94 Vilsmeye–Haack reaction.



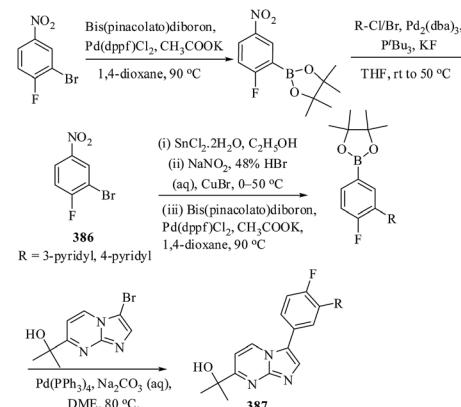
Scheme 95 Electrophilic substitution reaction of 2-(2'-furyl)-imidazo[1,2-a]pyrimidine.

2-Bromo-1-fluoro-4-nitrobenzene was converted to boronate ester using Suzuki–Miyaura cross coupling reaction. Further, it was coupled with various aryl chlorides or aryl bromides using Fu protocol to obtain 386. A reduction of 386 with stannous chloride followed by reaction with sodium nitrite and CuBr to give *in situ* intermediate bromide derivative through Sandmeyer reaction which on subsequent Suzuki–Miyaura coupling gave boronate ester. Final Suzuki–Miyaura coupling of boronate ester with 3-bromo imidazo[1,2-a]pyrimidine afforded 387 (Scheme 96).¹²²

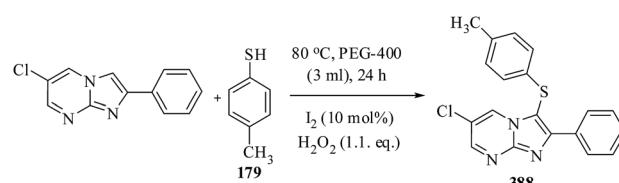
Hiebel and coworkers developed a simple and efficient method for the synthesis of 2,3-disubstituted imidazo[1,2-a]pyrimidine 388 through iodine mediated sulphenylation of 2-phenyl-6-chloroimidazo[1,2-a]pyrimidine with 4-methylbenzenethiol in the presence of oxidizing agent hydrogen peroxide in polyethylene glycol (PEG-400). Sulphenylation makes use of nontoxic reaction medium and without use of transition metal catalyst with an advantage of regenerating the iodine through hydrogen peroxide (Scheme 97).¹²³

Zhou and coworkers developed an efficient and environmentally friendly method for the synthesis of 2,3-disubstituted imidazo[1,2-a]pyrimidines through CuI catalysis of C–H chalcogenylation of azaheterocycles with diphenyldisulphide. Reaction of diphenyl disulphide 389 with 2-substituted imidazo[1,2-a]pyrimidine catalyzed by CuI in DMSO at 110 °C afforded 3-sulphenylimidazo[1,2-a]pyrimidine 390 in 70% yield (Scheme 98).¹²⁴

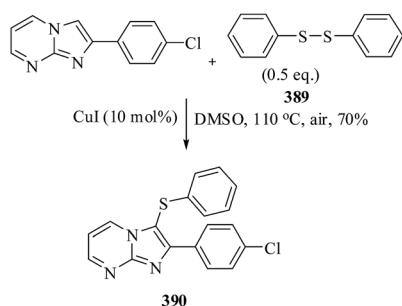
3-Bromo-2-bromomethyl imidazo[1,2-a]pyrimidine 393 in 56% yield was obtained by the reaction of either imidazo[1,2-a]pyrimidinium salt 391 or dehydrated imidazo[1,2-a]pyrimidinium salt 392 using hydrogen peroxide (Scheme 99).¹²⁵



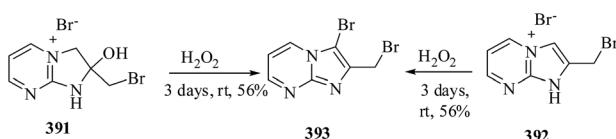
Scheme 96 Suzuki–Miyaura coupling at 3-position of imidazo[1,2-a]pyrimidine.



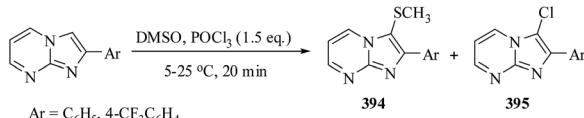
Scheme 97 Sulphenylation at 3-position of imidazo[1,2-a]pyrimidine.



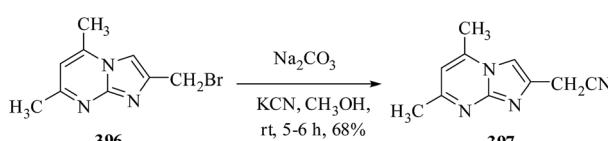
Scheme 98 C-H chalcogenylation of imidazo[1,2-a]pyrimidine.



Scheme 99 Reaction with hydrogen peroxide.



Scheme 100 Synthesis of 3-thiomethyl imidazo[1,2-a]pyrimidine.



Scheme 101 Synthesis of 2-cyanomethyl imidazo[1,2-a]pyrimidine.

Roychowdhury and coworkers developed a practical and metal free approach for methylthiolation of imidazo[1,2-*a*]pyrimidines. 2-Aryl imidazo[1,2-*a*]pyrimidines on reaction with dimethylsulphoxide and phosphorus oxychloride at 5–25 °C for 25 minutes afforded 2-aryl-3-thiomethyl imidazo[1,2-*a*]pyrimidine **394** in 73–82% yields with traces of formation of 2-aryl-3-chloro imidazo[1,2-*a*]pyrimidine **395** (Scheme 100).¹²⁶

Bromomethyl substituted imidazo[1,2-*a*]pyrimidine **396** was also reacted with potassium cyanide in methanol to afford 2-cyanomethyl derivative of imidazo[1,2-*a*]pyrimidine **397** in 68% yield (Scheme 101).¹²⁷

Summary and outlook

Imidazo[1,2-*a*]pyrimidine has been found to be an important scaffold owing to its applications in organic as well as medicinal chemistry. Various synthetic techniques and methodologies have been developed to access this skeleton *viz.* multicomponent reaction, condensation reaction, intramolecular cyclizations, aza-Michael–Mannich reaction *etc.* Though methods of

one pot synthesis and condensation of two moieties are introduced, the traditional reaction conditions are usually used. This review has also covered the reactivity of imidazo[1,2-*a*]pyrimidines of past decade and signifies how this versatile scaffold can be accessed by use of easily available substrates and precursors without the need of any prefunctionality. The ring nitrogen atoms and various aromatic groups attached to the ring carbon atoms will likely be focus of future development and taking full advantage of their special properties. With this wealth of synthetic chemical and application knowledge exhibited by compounds containing the imidazo[1,2-*a*]pyrimidines scaffold, we can expect many further developments of this template in drug discovery, novel materials exploration, agromedicine development, or even new applications in some other fields. In addition, the continuing interest of future research will certainly focus more on developing the modifications based on the imidazole and pyrimidine scaffolds and pharmacophores to build a low molecular weight medicine with high efficacy and low side effects. Moreover, imidazo[1,2-*a*]pyrimidines demonstrate less performance in applications on materials. Therefore, continuing research is required on the conformation and ordered supramolecular structures of this simplest heterocycle in optics and electromagnetism will let us access a new research aspect of imidazo[1,2-*a*]pyrimidines. Nevertheless, even for the fruitful imidazo[1,2-*a*]pyrimidines derivatives, we obtained further exploration on favorable chemosynthesis methods and conditions of imidazo[1,2-*a*]pyrimidines are necessary and will certainly contribute to the chemistry of heterocyclic compounds in the development of new drugs and functional materials for practical applications.

Acknowledgements

KP is thankful to CSIR, New Delhi (02(0034)/11/EMR-II) for providing funds. RG thanks CSIR for SRF (09/677(0020)/2013.EMR-I).

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