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New Strategies for the Synthesis of Pyrimidine Derivatives

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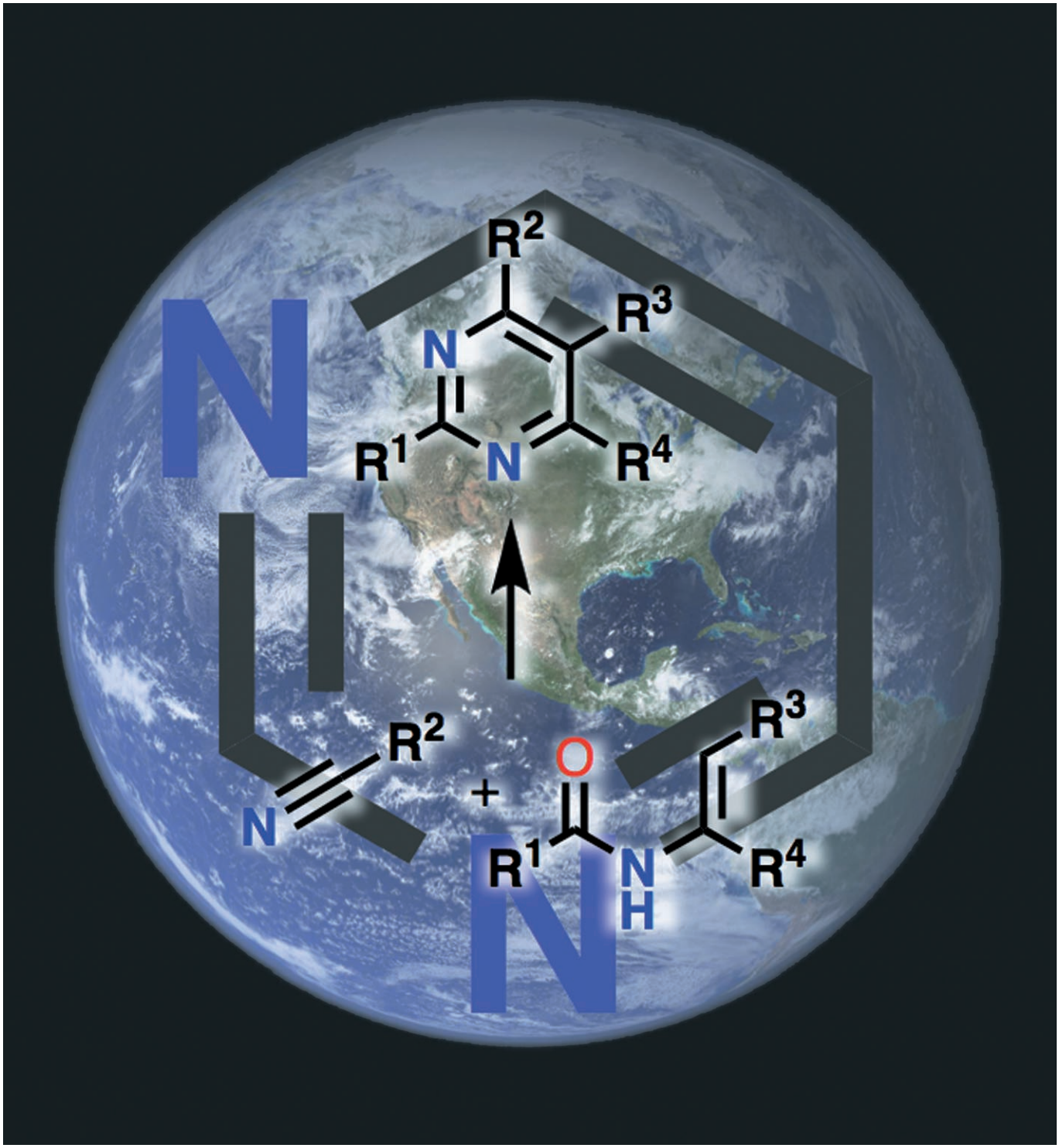


Abstract: Recent advances in pyrimidine synthesis are described. Modification of conventional strategies involving N-C-N fragment condensation with 1,3-dicarbonyl derivatives remains a common theme in current literature. Other methods, including N–C fragment condensation strategies, provide reactive intermediates capable of intramolecular cyclization and formation of pyrimidine derivatives. These recently developed methodologies offer a valuable addendum to azaheterocycle synthesis.

Keywords: amides · condensation · cyclization · heterocycles · pyrimidine

Introduction

Azaheterocycles constitute a very important class of compounds. In particular, pyrimidine derivatives include a large number of natural products, pharmaceuticals, and functional materials (Figure 1).[1] Several examples of pharmaceutically important compounds include trimethoprim (**1**),[2] sulfadiazine (**2**),[3] Gleevec (**3**, imatinib mesilate),[4] and Xeloda (**4**, capecitabine).[5] Natural and unnatural polymers also contain pyrimidine derivatives.[1,6] While development of important methodologies for the synthesis of pyrimidines enjoys a rich history, the discovery of new strategies for the convergent synthesis of pyrimidines remains a vibrant area of chemical research.

In nature, the pyrimidine ring is synthesized from glutamine, bicarbonate, and aspartate.[1b] These starting materials are converted to orotate (**6**, Figure 1), a ribonucleotide biosynthetic precursor, in four enzymatic reactions. Carbamoyl phophate synthetase II transforms glutamine, ATP, and bicarbonate to carbamoyl phosphate. Subsequent condensation of carbamoyl phosphate with aspartate is catalyzed by aspartate transcarbamoylase, affording carbamoyl aspartate. Dihydroorotase promoted dehydration followed by oxidation with dihydroorotate dehydrogenase affords the ribonucleotide precursor, orotate.[1b]

In 1818, Brugnatelli synthesized the first pyrimidine derivative, alloxan (**8**), by nitric acid oxidative degradation of uric acid (Scheme 1).[7] Another early report, by Frankland and Kolbe in 1848, described the first synthesis of a pyrimidine cyanalkine (**9**) by heating propionitrile with potassium metal (Scheme 1).[8] Gabriel and Colman first isolated pyrimidine in 1899 by decarboxylation of pyrimidine-4-carboxylic acid.[9] Since these early reports many important contributions describing a variety of synthetic strategies for preparation of pyrimidine derivatives have been published.

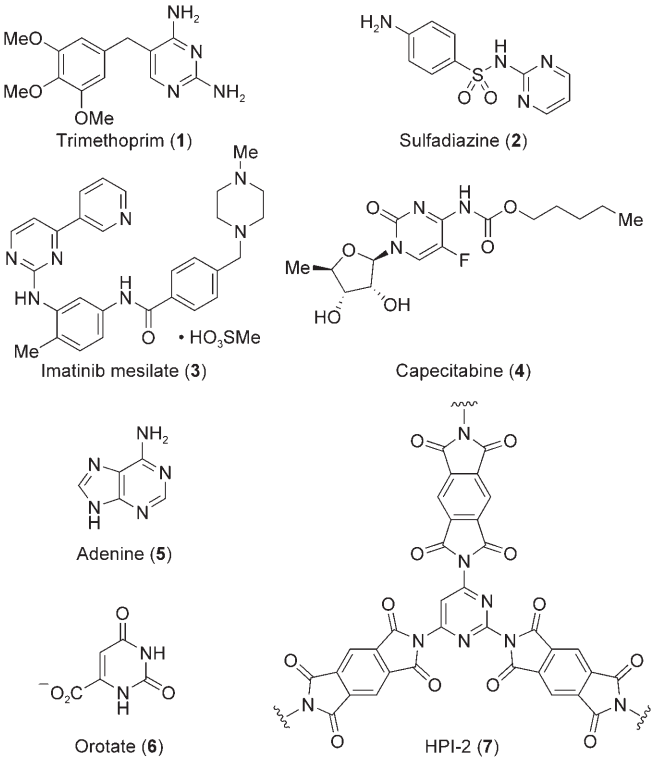
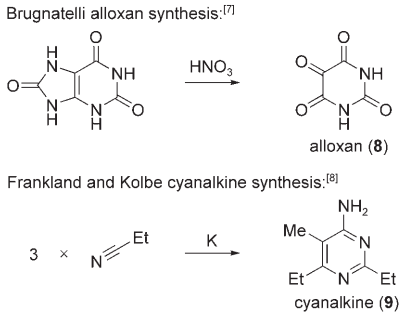
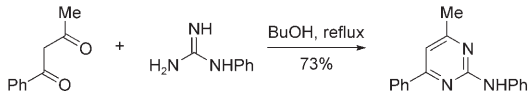


Figure 1. Representative compounds containing a pyrimidine substructure.

Many of these prevailing strategies rely on condensation of N-C-N fragments, most often amidines or guanidines, with 1,3-dicarbonyl derivatives (Scheme 2).[1,10] Another versatile approach to pyrimidine synthesis utilizes N–C frag-



Scheme 1. Early reports on the synthesis of pyrimidine derivatives.



Scheme 2. Representative synthesis of a pyrimidine by condensation of a N-C-N fragment and a diketone.[10]

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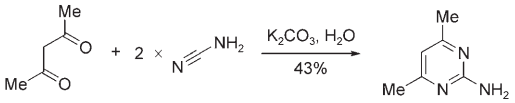
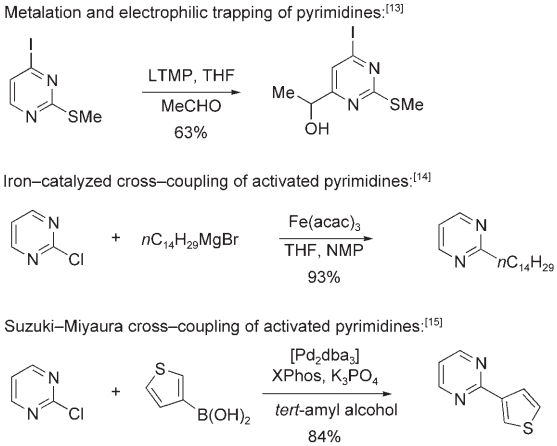
ments. Nitriles are a common N–C source and have been used to form pyrimidines in many syntheses. Cyanamide is a particularly useful nitrile derivative in the synthesis of pyrimidines as illustrated in Scheme 3.[11]



Scheme 3. Representative use of cyanamide in condensation with acetoacetone for the synthesis of a pyrimidine.[11]

With advances in cross-coupling chemistry, substituent modification on existing pyrimidine derivatives has recently gained considerable attention. Several reviews are available that describe advances in this important synthetic approach to pyrimidine derivatives.[12] Many of these procedures rely on inherent reactivity associated with the pyrimidine core (Scheme 4).[12,13] Additionally, activated heterocycle cross-coupling has become particularly important with recent advances (Scheme 4).[12,14,15] While these methods are very effective for synthesis of pyrimidines, given the availability of other reviews in this area, the focus of this article will be the synthesis of the pyrimidine ring.

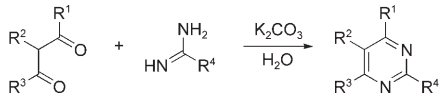


Scheme 4. Representative derivatization reactions for synthesis of pyrimidine derivatives. LTMP = lithium 2,2,6,6-tetramethylpiperidide, XPhos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl.

Recent Advances in a Versatile Synthetic Strategy: N-C-N Condensation

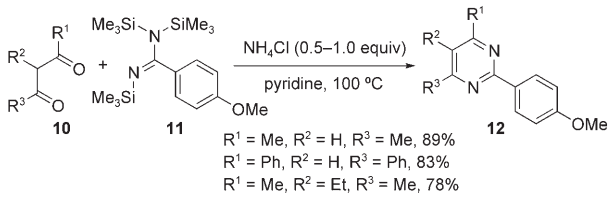
While amidine condensation with 1,3-dicarbonyl derivatives was conceptually established over a century ago as a means for accessing pyrimidines, a significant portion of the literature since that time describes advances in this application.[1,10] Whereas some of these methodologies employ the direct condensation of 1,3-dicarbonyl compounds with amidine derivatives, other reports describe multicomponent reactions to afford substituted pyrimidine derivatives.[1]

Although the literature on pyrimidine synthesis enjoys a rich array of versatile methodologies, new convergent approaches remain valuable additions to the contemporary arsenal of synthetic strategies. A recent report by Ghosh and Katzenellenbogen describes an interesting modification to the Pinner Pyrimidine Synthesis.[16] The initial dehydration is likely one of the slower steps involved in a traditional Pinner protocol for pyrimidine synthesis (Scheme 5).[17]



Scheme 5. Pinner pyrimidine synthesis.[17]

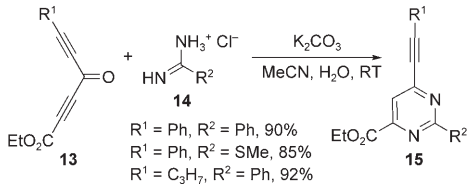
Ghosh and Katzenellenbogen were able to condense *N*,*N*,*N*′-tris-(trimethylsilyl)amidine **11**, in place of unsubstituted amidines, with 1,3-dicarbonyl compounds **10** and prepare a variety of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidine derivatives **12** (Scheme 6). The authors comment that *N*,*N*,*N*′-tris(trimethylsilyl)amidine is less basic than an amidine, allowing for milder reaction conditions and use of sensitive 1,3-dicarbonyl substrates. In addition, this procedure produces hexamethyldisiloxane in place of water upon condensation and is thought to drive the reaction forward.



Scheme 6. Modified Pinner pyrimidine synthesis using a tris(trimethylsilyl) amidine.[16]

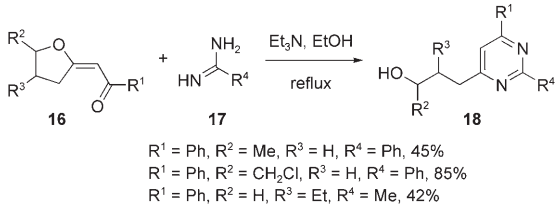
Adamo et al. have developed an interesting route to 2,4,6-trisubstituted pyrimidines **15** using amidinium chlorides **14** and diacetylenic ketoesters **13** (Scheme 7).[18] In this report, diacetylenic ketoesters **13** were prepared in two steps from aryl or alkyl propargylic aldehydes. Condensation with amidinium chloride substrates **14** afforded the trisubstituted pyrimidine derivatives **15** with alkyl, aromatic, and heteroatom substituents. The products were formed with complete control of regiochemistry and in good yields. The reaction is also chemoselective for the more electrophilic acetylene, consistent with earlier findings by Metler et al.[19]

The synthesis of 4-(3-hydroxyalkyl)pyrimidines **18** was reported by Bellur and Langer as shown in Scheme 8.[20] This methodology relied on the condensation of amidines **17** with 2-alkylidene-tetrahydrofuran derivatives **16**. These substituted tetrahydrofuran substrates were prepared from the corresponding 1,3-dicarbonyl starting materials and gave access to a variety of 2,4,6-trisubstituted pyrimidine derivatives.



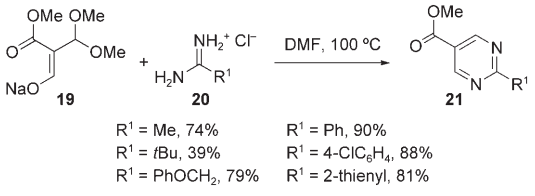
Scheme 7. Condensation of diacetylenic ketoesters **13** with amidinium chlorides **14**.[18]

Groups introduced on the pyrimidine ring included aromatic, aliphatic and heteroatom substituents. Importantly, C4- and C5-alkyl substituted 2-alkylidenetetrahydrofurans provided the corresponding substituents on the propanol segment of the pyrimidine derivatives **18**.



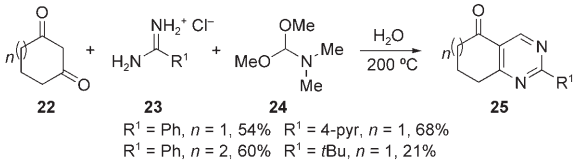
Scheme 8. Condensation of 2-alkylidenetetrahydrofurans **16** with amidines **17**.[20]

Zhichkin et al. recently published a two-step route to 2-substituted pyrimidine-5-carboxylic esters **21**.[21] In this report, a number of pyrimidine derivatives were formed by direct condensation of amidinium chlorides **20** with the sodium salt of 2-dimethoxymethyl-3-hydroxy-acrylic acid methyl ester (**19**, Scheme 9). This 1,3-dicarbonyl equivalent was prepared by condensation of methyl formate with 3,3-dimethoxypropionate. The use of **19** allowed for direct pyrimidine synthesis with aliphatic, aromatic, and heteroatom substitution at C2, providing a solution for pyrimidine derivatives lacking C4-substitution.



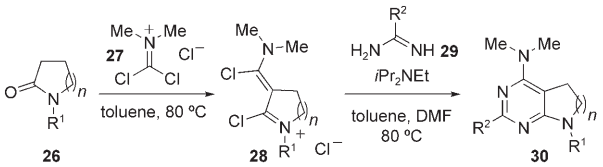
Scheme 9. Synthesis of pyrimidine-5-carboxylic acid derivatives **21**.[21]

A significant subset of dehydration approaches to pyrimidines rely on condensation of amidine derivatives with 1,3-dicarbonyl derivatives. However, these substrates often require multiple steps to prepare from readily available materials. Recently, many reports have focused on single-flask synthesis of pyrimidines that reduces starting material preparation and allow for rapid and convergent assembly of the azaheterocyclic core. One such report from Molteni et al. describes the synthesis of 2,4,5-trisubstituted pyrimidines **25** from cyclic 1,3-diketones **22**, amidinium chlorides **23**, and dimethylformamide dimethyl acetal (**24**, Scheme 10).[22] This microwave-promoted reaction proceeds via in situ enaminoketone formation by its condensation with amidinium chlorides **23**.



Scheme 10. One-pot synthesis of pyrimidine derivatives **25**.[22]

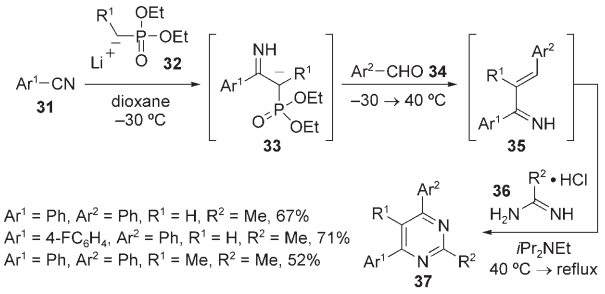
Kiselyov devised a synthesis of 2,4,5,6-tetrasubstituted pyrimidine derivatives **30** using Viehe's salt (**27**).[23] Reaction of Viehe's salt with lactams **26** provided iminium dichloride intermediates **28** that could subsequently condense with amidines **29** to provide tetrasubstituted azaheterocycles **30** (Scheme 11). Aliphatic, aromatic, and heteroaromatic substitution was permitted at C2. In addition, exchange of dimethylamine with other amine substituents was possible when pyrimidines **30** were heated to 140 °C in the presence of excess amine.



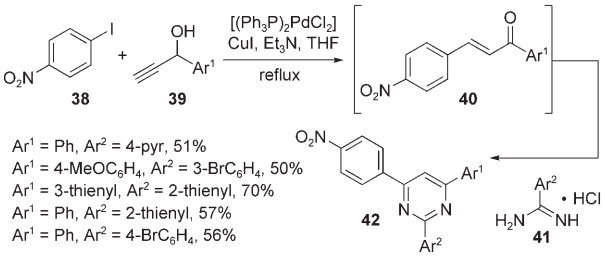
Scheme 11. Synthesis of pyrimidine derivatives **30** using Viehe's salt (**27**).[23]

Kiselyov has also provided a procedure for the synthesis of 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted pyrimidines **37**.[24] α,β-Unsaturated imines **35** were generated in situ from alkylphosphonates **32** and aryl nitriles **31** (Scheme 12). Condensation of amidinium or guanidinium chlorides **36** with imine **35** furnished a variety of polysubstituted pyrimidines. While aromatic substituents could be introduced at C4 and C6, aliphatic and heteroatom substituents could be introduced at C2 and C5.

The Müller group has demonstrated a three-component synthesis of 2,4,6-triaryl pyrimidine derivatives **42**.[25] In this protocol, electron-deficient iodobenzene (**38**) undergoes a palladium catalyzed Sonogashira cross-coupling with prop-2-yn-1-ols **39** and reduction to form enone intermediates **40**. Condensation of this intermediate with amidinium chlorides **41** and subsequent isomerization provides the corresponding pyrimidines (Scheme 13).

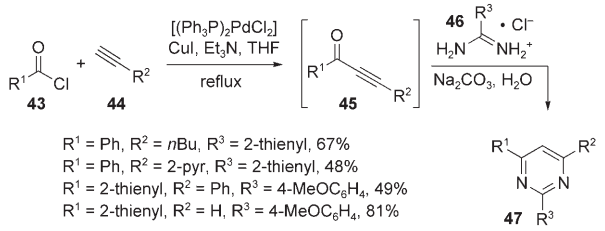


Scheme 12. Kiselyov synthesis of 4,6-diarylpyrimidines **37**.[24]

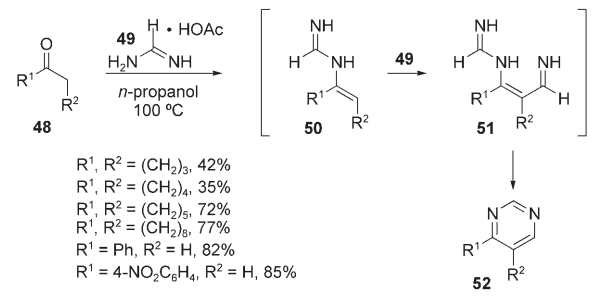


Scheme 13. One-pot, two-step synthesis of pyrimidine derivatives **42**.[25]

The Müller group also developed a cross-coupling/addition/cyclocondensation sequence for synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines **47**.[26] The procedure involves a Sonogashira cross-coupling of acid chloride **43** and alkyne **44** to afford ynone intermediate **45** (Scheme 14). The highly reactive Michael acceptor, ynone **45**, can undergo base promoted nucleophilic addition by amidinium chloride **46** followed by cyclocondensation to afford the di- and trisubstituted pyrimidines with alkyl, aromatic, and heteroatom substitution.



Scheme 14. One-pot, two-step synthesis of pyrimidine derivatives **47**.[26]



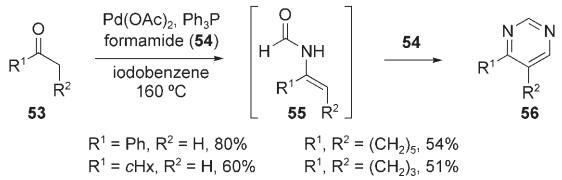
Scheme 15. Synthesis of pyrimidine derivatives **52** from ketones **48** and formamidine acetate (**49**).[27]

The Baran group has reported an interesting one-step synthesis of 4-monosubstituted and 4,5-disubstituted pyrimidines **52**.[27] Condensation of two equivalents of formamidine acetate (**49**) with cycloalkanone and acetophenone derivatives **48** provided the desired pyrimidines by heating in *n*-propanol (Scheme 15).

Alternative Strategies

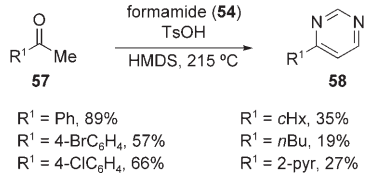
Other synthetic methodologies that do not rely on N-C-N condensation with carbonyls have been developed for the synthesis of substituted pyrimidine derivatives. These methods often require activation of carbonyl moieties followed by nucleophilic addition to the newly generated electrophilic carbon.[1] While regioselectivity is problematic in some approaches, others afford highly substituted pyrimidine products with complete positional control. Of particular interest are mild and convergent approaches that utilize readily available starting materials and mild reaction conditions.

Ingebrigsten et al. have reported a methodology for synthesis of pyrimidines **56** from ketones **53**.[28] In this procedure, condensation of two equivalents of formamide (**54**) with methyl and cyclic ketones **53** furnished a variety of mono- and disubstituted pyrimidines **56**, respectively (Scheme 16). Formation of ammonium formate was detrimental to the desired reaction, however, the inclusion of catalytic palladium(II) acetate, triphenylphosphine, and iodobenzene as additives led to its removal from the reaction mixture. Palladium is believed to accept a hydride from ammonium formate and reduce iodobenzene.



Scheme 16. Ingebrigsten et al's synthesis of pyrimidine derivatives **56**.[28]

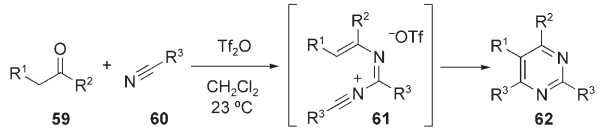
In a related report, Tyagarajan and Chakravarty reported the synthesis of various 4-monosubstituted pyrimidines **58**.[29] Microwave-assisted condensation of two equivalents of formamide (**54**) with ketone substrates **57** in the presence of *p*-toluenesulfonic acid and 1,1,1,3,3,3-hexamethyldisilizane additives was recommended (Scheme 17). The reported



Scheme 17. Microwave assisted synthesis of pyrimidine derivatives **58**.[29]

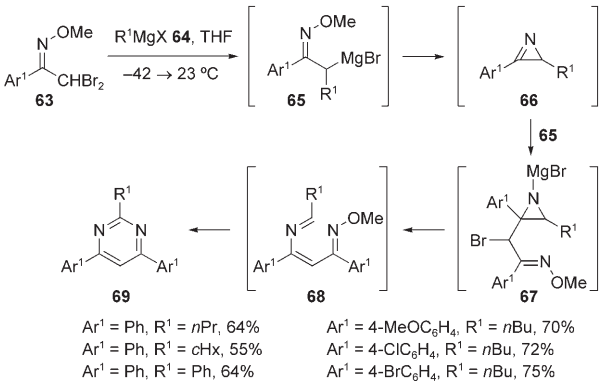
substrate scope includes aliphatic and heteroaromatic ketones.

Martínez et al. reported a pyrimidine synthesis whereby trifluoromethanesulfonic anhydride (Tf_2O) activation of ketone substrates **59** followed by nucleophilic addition of two equivalents of nitriles **60** led to 2,4,6-trisubstituted and 2,4,5,6-tetrasubstituted products **62** (Scheme 18).[30] Ketone activation was believed to afford a (trifluoromethanesulfonyloxy)carbenium ion. Nucleophilic addition of two aliphatic or aromatic nitrile equivalents forms nitrilium species **61** that underwent cyclization and loss of triflouromethanesulfonic acid. This methodology has been extended to both aliphatic and aromatic acyclic and alicyclic ketones.



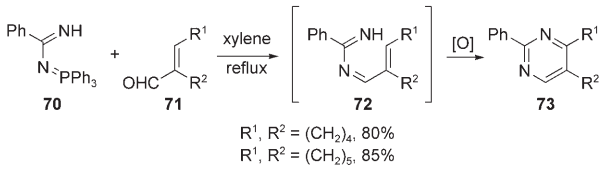
Scheme 18. Synthesis of pyrimidine **62** from ketone **59** and nitrile **60** substrates.[30]

Kakiya et al. have used α,α-dibromo oxime ethers **63** in conjunction with Grignard reagents **64** to furnish 2,4,6-trisubstituted pyrimidines **69** (Scheme 19).[31] Aryl α,α-dibromo oxime ethers can be prepared by *O*-methyl hydroxylamine hydrogen chloride condensation with α,α-dibromo ketones. Oximes **63** react with a Grignard reagent to afford intermediates **65**–**68**. Diazatriene **68** can undergo a 6π-pericyclic ring closure followed by loss of methanol to afford the desired azaheterocycles. This interesting methodology provided access to a wide variety of aryl-trisubstituted pyrimidines **69** in moderate to good yields.



Scheme 19. Alkylative annulation strategy for pyrimidine synthesis.[31]

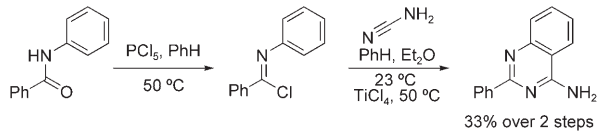
Iminophosphoranes **70**,[32] were recently used by Rossi et al. as substrates in a formal [3+3] approach to 2,5-disubstituted and 2,4,5-trisubstituted pyrimidines **73**.[33] Aza-Wittig condensation with α,β-unsaturated aldehyde **71** is believed to give diazatriene intermediate **72** (Scheme 20). Pericyclization and oxidation (likely autoxidation) afforded the pyrimidine products with complete regiochemical control.



Scheme 20. One-pot synthesis of pyrimidines **73** using iminophosphoranes **70**.[33]

Trifluoromethanesulfonic Anhydride and 2-Chloropyridine Reagent Combination for Activation of *N*-Vinyl Amides: A Convergent Pyrimidine Synthesis

We have reported a mild and convergent single-step pyrimidine synthesis based on amide activation with Tf_2O in conjunction with 2-chloropyridine (2-ClPyr).[34] Related reports describe two-step quinazoline syntheses from amides that required more forcing reaction conditions for amide derivative activation via Lewis-acid (LA) promoters (Scheme 21).[35]

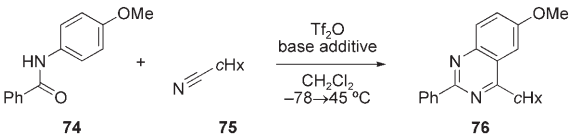


Scheme 21. Two-step, LA promoted quinazoline synthesis from benzanilide.[35a]

Our convergent strategy takes advantage of the unique reactivity associated with amide activation using the reagent combination of Tf_2O and 2-ClPyr.[36] Based on a series of mechanistic studies, we hypothesized that weakly σ-nucleophilic nitriles could add to an activated intermediate and following annulation afford the corresponding azaheterocycle. Gratifyingly, this new condensation reaction allowed the direct conversion of *p*-methoxybenzanilide (**74**) and cyclohexanecarbonitrile (**75**) to quinazoline **76**. A variety of base additives were examined and 2-ClPyr proved to be optimal (Table 1). With the exception of ethyl nicotinate, commonly used trialkylamine and alkyl-substituted pyridine bases led to lower reaction yields than halogen-substituted pyridines.

In early stages of reaction development, we recognized base non-nucleophilicity was crucial to the reaction. Charette et al. have demonstrated pyridine could add into imidoyl triflate intermediates when used for amide activation in conjunction with Tf_2O.[37] Inspired by those observations, we expected 2-chloropyridine served as a weak nucleophile capable of adding into the reactive imidoyl triflate intermediate (Scheme 22). Key NMR and React IR experiments sug-

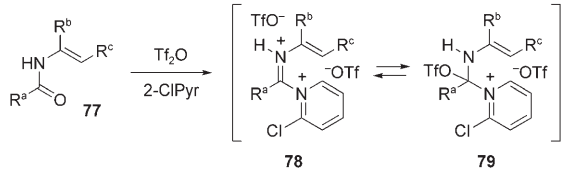
Table 1. Results with various base additives.[a]



Entry	Base equiv.	Base additive	Yield [%]
1	0	none	29
2	1.2	Et_3N	0
3	1.2	iPr_2NEt	14
4	1.2	pyridine	26
5	1.2	2,6-lutidine	28
6	1.2	2,4,6-collidine	19
7	1.2	ethyl nicotinate	59
8	1.2	3-bromopyridine	54
9	1.2	2-bromopyridine	63
10	1.0	2-chloropyridine	72
11	1.2	2-chloropyridine	90
12	3.0	2-chloropyridine	81

[a] Reaction conditions: Amide **74** (1 equiv), nitrile **75** (1.1 equiv), Tf_2O (1.1 equiv), base additive, CH_2Cl_2, −78→45 °C, 16 h.

gested that similar to pyridine, even 2-chloropyridine added into the activated amide **77** and could compete with the nitrile. Bis-cationic intermediate **78** may be in equilibrium

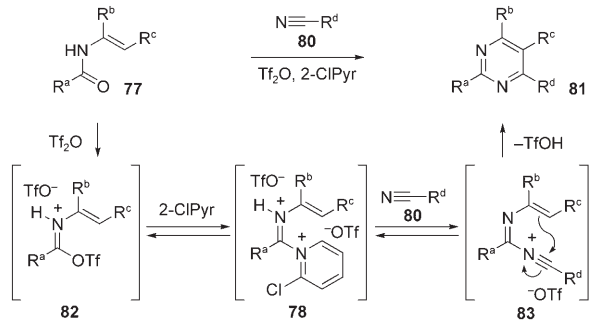


Scheme 22. Amide activation with Tf_2O in the presence of 2-ClPyr.

with triflate adduct **79** due to its expected electrophilicity. These results were consistent with the observed inverse relationship between the amount of base and reaction rate.

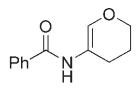
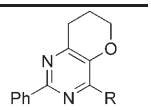
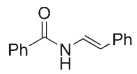
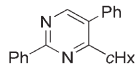
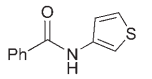
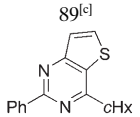
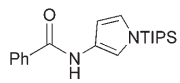
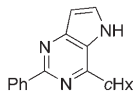
In our proposed mechanism for conversion of **77** to **81** (Scheme 23), imidoyl triflate **82** forms directly upon addition of Tf_2O. This intermediate is expected to rapidly undergo nucleophilic substitution to afford an equilibrium of intermediates **78** and **79**. Nitrile **80** addition and loss of 2-ClPyr·HOTf affords nitrilium triflate salt **83**, which undergoes annulation and subsequent expulsion of TfOH to form pyrimidine **81** (as the corresponding pyridinium triflate salt). This process occurs with complete control of substitution pattern and in one step using a wide range of readily available amide and nitrile substrates.

A broad range of highly substituted azaheterocycles were prepared using this methodology. *N*-Vinyl amides were used with several nitriles to afford the corresponding pyrimidine derivatives (Table 2, entries 1–4). A styrenyl derivative gave the desired azaheterocycle in high yield when used in conjunction with cyclohexanecarbonitrile (Table 2, entry 4). *N*-3-Thienyl and *N*-3-pyrrolo amides were also used with cyclohexanecarbonitrile to afford fused pyrimidines (Table 2, entries 5–6). Significantly, this pyrimidine synthesis was ex-



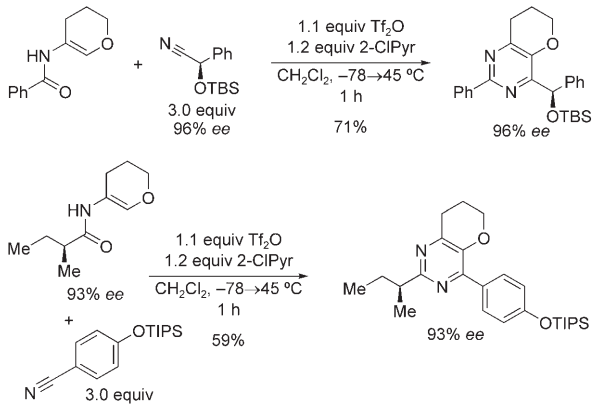
Scheme 23. Proposed mechanism for direct conversion of **77** to **81**.[34a]

Table 2. Direct synthesis of pyrimidine derivatives.

Entry	Amide	Nitrile	Conditions	Product/Yield [%][a]
				
1		R = *c*Hx	A	92
2		R = *t*Bu	A	86[b]
3		R = $(CH_2)_3C{\equiv}CH$	A	77
4			B	 89[c]
5			B	 86
6			B	 70[d]

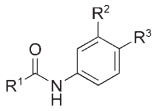
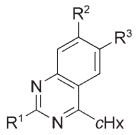
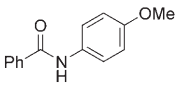
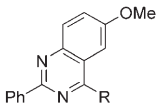
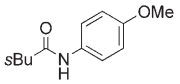
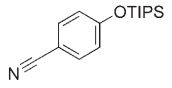
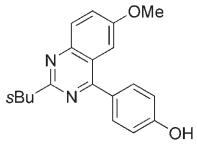
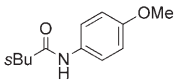
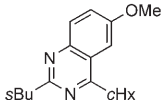
[a] Optimal reaction conditions used uniformly unless otherwise noted: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), nitrile (1.1 equiv), CH_2Cl_2, heating: A = 23 °C, 1 h; B = 45 °C, 1 h. [b] Gram-scale reaction. [c] 5 equiv of nitrile. [d] TBAF (1 equiv) used to desilylate product.

tended to epimerizable substrates. A mandelonitrile derivative was used to form the desired product without loss of optical activity (Scheme 24). Activation and cycloisomerization

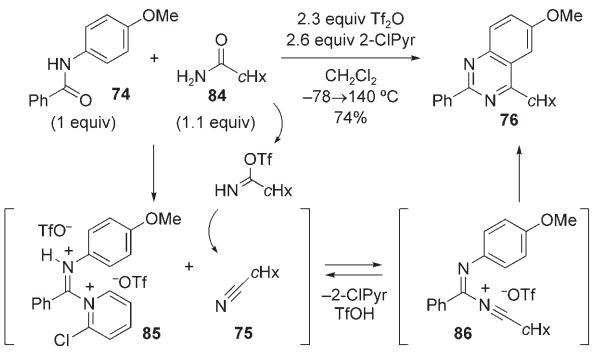


Scheme 24. Synthesis of pyrimidines using optically active substrates.

Table 3. Direct synthesis of quinazoline derivatives.

Entry	Amide	Nitrile	Conditions	Product/Yield [%][a]
				
1	R^1=Ph, R^2=H, R^3=OMe		A	89
2	R^1=Ph, R^2=H, R^3=H		A	71
3	R^1=Ph, R^2=CF_3, R^3=H		B	61
4	R^1=4-$MeOC_6H_4$, R^2=H, R^3=OMe		A	87[b]
5	R^1=4-$NO_2C_6H_4$, R^2=H, R^3=OMe		B	69
6	R^1=*t*Bu, R^2=H, R^3=OMe		B	81
7	R^1=*c*Hx, R^2=H, R^3=OMe		B	73
8	R^1=$N(CH_2CH_2)_2O$, R^2=H, R^3=H		B	80
9	R^1=cyclohex-1-enyl, R^2=H, R^3=OMe		A	88[c]
10	R^1=H, R^2=H, R^3=H		B	0
				
11		R=4-$NO_2C_6H_4$	B	86
12		R=4-$MeOC_6H_4$	B	88
13		R=4-$(CO_2Et)C_6H_4$	B	74
14		R=(*E*)-C_6H_4CH=CH	B	68
15			B	 58[d]
16			B	 85

[a] Isolated yields; all entries are an average of two experiments. Optimal reaction conditions used uniformly unless otherwise noted: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), nitrile (1.1 equiv), CH_2Cl_2; heating: A = 45 °C, 16 h; B = microwave, 140 °C, 20 min. [b] Time = 18 h. [c] 5 equiv of nitrile. [d] TBAF (2 equiv) used to desilylate product.



Scheme 25. Direct condensation of primary and secondary amides in synthesis of **76**.

of an enantiomerically enriched α-chiral amide also gave the desired pyrimidine without loss in optical activity (Scheme 24).

This method works well with *N*-aryl amides to afford quinazoline derivatives (Table 3). Aryl, aliphatic and vinyl nitriles all provided the desired quinazolines in moderate to excellent yield. Unfortunately, racemic quinazolines were generated from epimerizable α-chiral *N*-aryl amides, presumably due to the slow rate of annulation as compared to epimerization (Table 3, entries 15–16).

Primary amides have been reported to undergo a Tf_2O induced dehydration reaction in the presence of Et_3N to afford the corresponding nitrile.[38] We hypothesized that 2-ClPyr could be used as a Et_3N substitute for in situ formation of nitriles from primary amides, while selectively activating a secondary amide. Interestingly, cyclohexanecarboxamide **84** was used as a cyclohexanecarbonitrile surrogate to give quinazoline **76** in 74% yield (Scheme 25) in a single step by direct condensation.

Conclusion

Several convergent synthetic approaches to pyrimidines have been reported. While most of these involve condensation strategies involving N-C-N fragments, recently other approaches have become available. These new methodologies in conjunction with recent advances in substituent modification via cross-coupling chemistry offer complementary and valuable addendum to existing methodology for pyrimidine synthesis.

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