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Synthesis of Densely Substituted Pyrimidine Derivatives

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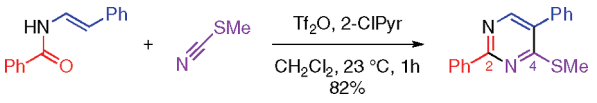
Received August 6, 2009



The direct condensation of cyanic acid derivatives with *N*-vinyl/aryl amides affords the corresponding C4-heteroatom substituted pyrimidines. The use of cyanic bromide and thiocyanatomethane in this chemistry provides versatile azaheterocycles poised for further derivatization. The synthesis of a variety of previously inaccessible C2- and C4-pyrimidine derivatives using this methodology is described.

Pyrimidine derivatives are important azaheterocycles that have inspired the development of new methodologies for their chemical synthesis for over a century.[1] In addition to reports concerning variation of established protocols, new methods[2] are also described that rely on the union of amine- and carbonyl-containing fragments to assemble the important pyrimidine substructures of interest. Additionally, the advancement of transition metal-catalyzed methodologies for cross-coupling of activated azaheterocycles offers complementary access to substituted azaheterocycles.[3] We reported the development of a methodology[4] for the convergent synthesis of pyrimidine and pyridine derivatives in a single step from the corresponding *N*-vinyl/aryl[5] amides. This methodology relies on electrophilic amide activation,[6] using the reagent combination of trifluoromethanesulfonic anhydride[7] (Tf_2O) and 2-chloropyridine[8] (2-ClPyr). Herein we report the use of cyanic acid derivatives as nucleophiles for rapid synthesis of versatile C4-heteroatom substituted pyrimidines. Furthermore, we discuss the utility of this chemistry in the synthesis of a variety of pyrimidine derivatives that are not directly accessible due to functional group incompatibility with the condensation reaction conditions.

Scheme 1 illustrates a plausible mechanism for the union of an *N*-vinyl/aryl amide **1** with nitrile **2** by interception of an activated intermediate[9] followed by cyclization of the nitrilium ion **5** to give the corresponding substituted pyrimidine **6**. Among the various nucleophiles we have explored for this chemistry, nitriles proved to be most sensitive to conditions for amide activation; their addition being inhibited even by excess 2-ClPyr additive. The prevalence of C4-heteroatom-substituted pyrimidine derivatives in fine chemicals and pharmaceuticals coupled with our observations that more electron rich σ- and π-nucleophiles served as excellent condensation partners prompted our investigation of cyanic acid derivatives in the context of our pyrimidine synthesis methodology.[4]

The use of a variety of cyanic acid derivatives in the direct synthesis of C4-heteroatom-substituted pyrimidine derivatives is shown in Table 1. Synthesis of the 4-morpholinopyrimidine **6a** is illustrative: introduction of Tf_2O to a solution of *N*-vinyl amide **1a**, morpholine-4-carbonitrile (**2a**), and 2-ClPyr in dichloromethane at −78 °C followed by warming to 23 °C gave the desired azaheterocycle **6a** in 87% yield. Both *N*-vinyl and *N*-aryl amides serve as effective coupling partners with various cyanic acid derivatives to give the corresponding azaheterocycles. We recommend either simple warming to 23 °C after electrophilic activation or heating at 140 °C in a microwave reactor to accelerate the rate of cyclization. The union of morpholine-4-carbonitrile (**2a**)

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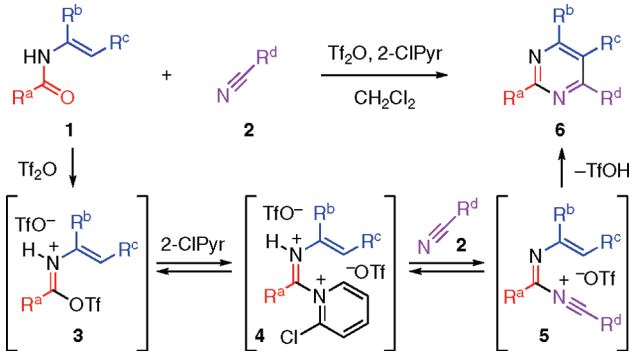
Published on Web 10/07/2009 DOI: 10.1021/jo9017149

SCHEME 1



with amides **1a**, **1b**, and **1c** gave the corresponding pyrimidines **6a** and **6b**, and quinazoline **6c**, respectively, within an hour at 23 °C (condition A). The use of the less nucleophilic 1,3-dioxoisoindoline-2-carbonitrile (**2b**) necessitated the use of more forcing cyclization conditions (condition B) to deliver the desired azaheterocycles. Interestingly, while cyanatobenzene (**2c**) afforded the targeted pyrimidine **6f** and quinazoline **6g** in moderate yield (Table 1), the use of thiocyanatobenzene failed to provide the corresponding 4-thiophenyl-substituted azaheterocycles in synthetically useful yields.[10] On the basis of our interest in the synthesis of 4-thio-derivatives as versatile precursors to other compounds of interest[11] we were delighted to see the formation of the desired products **6h**−**k** (Table 1) in good yield using thiocyanatomethane (**2d**) as the nucleophile in this chemistry. Importantly, even cyanic bromide (**2e**) can be used as a starting material in this azaheterocycle synthesis illustrated by 4-bromoquinazolines **6*l*** and **6m** (Table 1).[12] The direct synthesis of azaheterocycles **6h**−**m** is noteworthy as they offer exciting options for introduction of a wide range of other substituents at C4.[13]

The conversion of 4-methylthioquinazoline **6h** and 4-bromoquinazoline **6m** to azaheterocycles **6s**−**v** (Scheme 2) is illustrative of the versatility of the products accessed by using thiocyanatomethane (**2d**) and cyanic bromide (**2e**), respectively, as the nucleophilic component in this chemistry. Reduction of **6h** with Raney nickel[14] provided the C4-H quinazoline **6s** in 59% yield. Alternatively, the free radical-based reduction[15] of C4-Br **6m** proceeded cleanly to give product **6s** in 99% yield. It is important to note that the use of trimethylsilyl cyanide in our condensative synthesis of pyrimidines did not proceed under optimal conditions.[16] Furthermore, the oxidative activation of the 4-methylthiopyrimidines sets the stage for addition of various nucleophiles.[17] For example, oxidation

(10) Treatment of amide **1b** with thiocyanatobenzene provided the corresponding quinazoline in <15% yield under various reaction conditions.

(11) Jang, M.-Y.; De Jonghe, S.; Gao, L.-J.; Rozenski, J.; Herdewijn, P. *Eur. J. Org. Chem.* **2006**, *18*, 4257.

(12) Treatment of amide **1a** with cyanic bromide did give the corresponding 4-bromopyrimidine albeit in low yields (37−56%).

(13) We have considered mechanisms other than direct nucleophilic addition of **2e** to an electrophilic intermediate; however, in the absence of any contrary data, a plausible mechanism based on our prior studies is used here.

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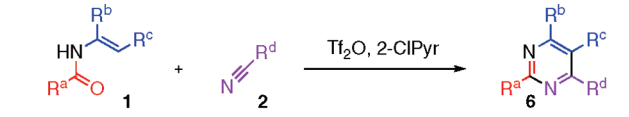
TABLE 1. Synthesis of Pyrimidines and Quinazolines[a]

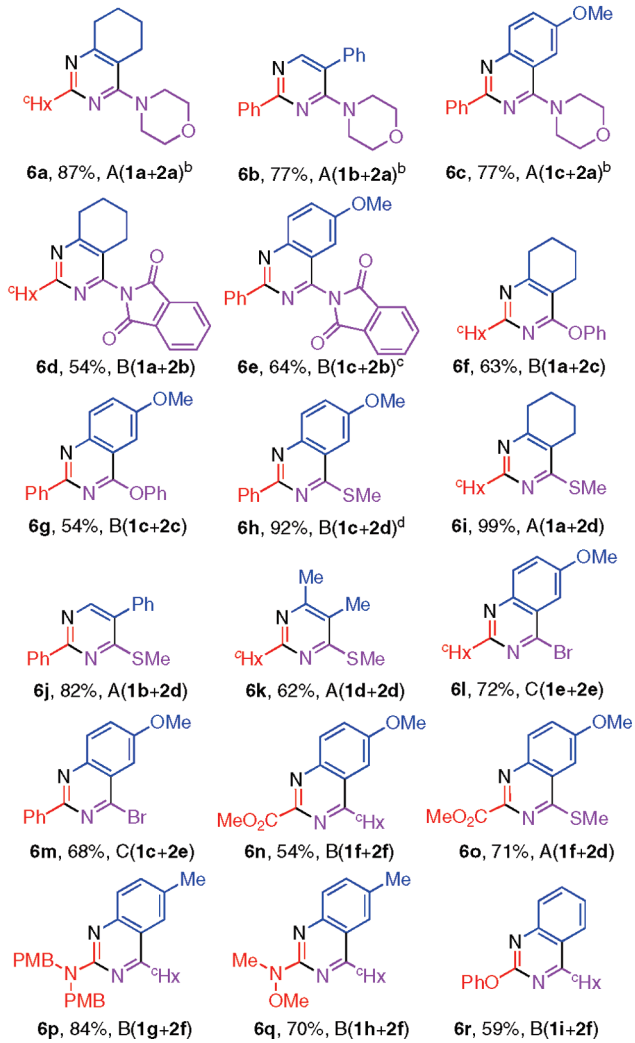


Amide:

1a, R^a=^{c}Hx, R^b, R^c=$(CH_2)_4$
1b, R^a=Ph, R^b=H, R^c=Ph
1c, R^a=Ph, $R^b CCHR^c$=4-MeOPh
1d, R^a=^{c}Hx, R^b=Me, R^c=Me
1e, R^a=^{c}Hx, $R^b CCHR^c$=4-MeOPh
1f, R^a=CO_2Me, $R^b CCHR^c$=4-MeOPh
1g, R^a=N(PMB)$_2$, $R^b CCHR^c$=4-MePh
1h, R^a=N(Me)OMe, $R^b CCHR^c$=4-MePh
1i, R^a=OPh, $R^b CCHR^c$=Ph

Nucleophile:

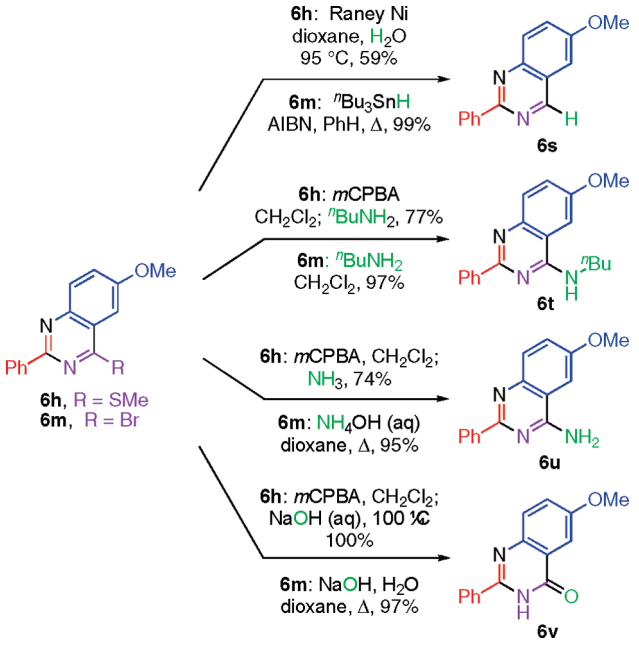
2a, R^d=N$(CH_2CH_2)_2$O
2b, R^d=NPhth
2c, R^d=OPh
2d, R^d=SMe
2e, R^d=Br
2f, R^d=^{c}Hx



[a]All yields are the average of two experiments. [c]Hx = cyclohexyl. PMB = *p*-methoxybenzyl. Uniform reaction conditions unless otherwise noted: Tf_2O (1.1 equiv), 2-ClPyr (1.2 equiv), nucleophile (2.0 equiv), CH_2Cl_2. Heating: A, 23 °C, 1 h; B, microwave, 140 °C, 5 min; C, 1,2-dichloroethane, reflux, 2 h, nucleophile (4.0 equiv; large excess required to compensate for loss of nucleophile due to sublimation). [b]Nucleophile (1.1 equiv). [c]Heat in the microwave for 10 min. [d]Experiment on 6-gram scale was heated to 45 °C (oil bath) for 6 h, giving 81% yield of **6h**.

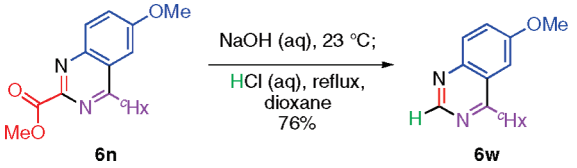
of 4-methylthioquinazoline **6h** with *m*-chloroperbenzoic acid (*m*CPBA) followed by treatment with butylamine, ammonia, or aqueous sodium hydroxide gave the corresponding 4-butylaminoquinazoline **6t**, 4-aminoquinazoline **6u**, and the

SCHEME 2



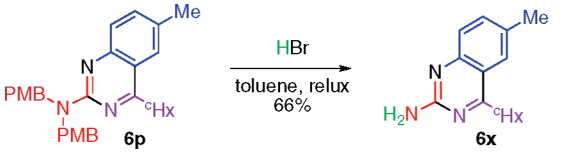
quinazoline-4(3*H*)-one **6v**, respectively. Importantly, the 4-bromoquinazoline **6m** obviated the need for oxidative activation and allowed direct conversion to the desired products **6t**−**v** with superior overall efficiency (Scheme 2). It should be noted that products **6t**−**v** could not be accessed directly by condensation of amide **1c** with the respective cyanamide or cyanate nucleophiles.[18]

We have also been interested in expansion of our chemistry to address the need for synthesis of pyrimidines with maximum flexibility for the C2-substituent. In prior studies we have demonstrated the use of various benzoic, heteroaromatic, alkanoic, and alk-2-enoic amide derivatives in our condensative synthesis of azaheterocycles.[4] These substrates offer the corresponding 2-alkyl, aryl, heteroaryl, and vinyl azaheterocycles. However, we have noted[4b] that formamides are not substrates for this azaheterocycle synthesis methodology due to competing formation of isonitriles during the activation of the substrates.[7,19] The rapid decarboxylation of pyrimidine-2-carboxylic acids[20] prompted exploration of oxamates as substrates for our azaheterocycle synthesis. Simple acylation of amines with use of the commercially available methyl 2-chloro-2-oxoacetate provides the necessary substrates for the condensative union with various nucleophiles. As an illustration, the coupling of amide **1f** with cyclohexylnitrile (**2f**) and thiocyanatomethane (**2d**) provided the corresponding quinazolines **6n** and **6o**, respectively (Table 1). The simple decarboxylation of quinazoline-2-carboxylate **6n** to the corresponding quinazoline **6w** is shown in eq 1. The use of readily available oxamates in our azaheterocycle synthesis followed by decarboxylation affords access to products that are not viable by using formamides as discussed above. Notably, (2*H*)-quinazolines are important kinase inhibitors and are of value in the development of anticancer drugs.[21]



(1)

The synthesis of 2-aminoazaheterocycles is of interest due to their prevalence in a variety of pharmacological drug targets.[22] Typically, their synthesis involves condensation of guanidine derivatives with appropriate coupling partners. We had previously noted that trisubstituted ureas function effectively under activation conditions for both pyridine and pyrimidine synthesis using our methodology.[4] However, less substituted ureas simply undergo dehydration under the activation conditions.[23] In this regard the use of *p*-methoxybenzyl amine derived ureas as substrates provides a solution for rapid access to the desired 2-aminoazaheterocycles by simple unraveling of the C2-amino group post azaheterocycle synthesis. For example, the direct condensation of methoxybenzylurea derivative **1g** with cyclohexanecarbonitrile (**2f**) gave the desired methoxybenzylquinazoline **6p** in 84% yield (Table 1). Treatment of the quinazoline **6p** with hydrogen bromide in toluene at reflux results in the desired 2-aminoquinazoline **6x** as shown in eq 2.



(2)

Similarly, use of the methoxy-3-(4-methoxyphenyl)-1-methylurea **1h** and the phenyl carbamate **1i** in this methodology affords the corresponding 2-dimethylhydroxyaminoquinazoline **6q** and 2-phenoxy **6r**, respectively (Table 1). It should be noted that carbamothioates did not provide 2-thiopyrimidines in synthetically useful yields.[24]

In summary, the direct condensation of cyanic acid derivatives with *N*-vinyl/aryl amides affords the corresponding C4-heteroatom-substituted pyrimidines. In particular, the use of cyanic bromide and thiocyanatomethane in this chemistry yields versatile azaheterocycles ready for further C4 derivatization. Additionally, we describe the use of oxamates

(18) Cyanamide, bis(trimethylsilyl)carbodiimide, and potassium cyanate do not serve as competent nucleophiles under our condensative pyrimidine synthesis reaction conditions; for example, amide **1c** and cyanamide did not afford **6u**.

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(24) A variety of 2-thiopyrimidine derivatives were synthesized in low yield (<20%) primarily due to the incomplete activation of the carbamothioates.

and benzylated ureas to access C2-H and C2-amino azaheterocycles, compounds previously inaccessible with this methodology. This chemistry provides densely substituted and functionalized pyrimidine derivatives and extends the scope of this condensative strategy for azaheterocycle synthesis.

Experimental Section

6-Methoxy-4-(methylthio)-2-phenylquinazoline (6h, Table 1). Trifluoromethanesulfonic anhydride (4.79 mL, 29.0 mmol, 1.10 equiv) was added via syringe over 2 min to a well-stirred mixture of amide **1c** (6.00 g, 26.4 mmol, 1 equiv) and 2-chloropyridine (3.00 mL, 31.7 mmol, 1.20 equiv) in dichloromethane (88 mL) at −78 °C. After 10 min, the reaction mixture was placed in an ice−water bath and warmed to 0 °C. After 4 min, nucleophile **2d** (2.12 g, 29.0 mmol, 1.10 equiv) was added via syringe over 1 min. The resulting solution was allowed to warm to 23 °C for 5 min before the reaction mixture was heated to 45 °C in an oil bath. After 6 h, the reaction vessel was allowed to cool to 23 °C and then triethylamine (8.08 mL) was introduced to neutralize the trifluoromethanesulfonate salts. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (eluent: 10% EtOAc in hexanes; SiO_2: 11 × 6.5 cm) on neutralized silica gel to give quinazoline derivative **6h** as a white solid (6.05 g, 81%). Mp 104−105 °C; TLC (20% EtOAc in hexanes) R_f 0.49 (UV); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ 8.61−8.57 (m, 2H), 7.91 (d, 1H, J = 9.1 Hz), 7.52−7.43 (m, 4H), 7.25−7.23 (m, 1H), 3.93 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ 169.1, 157.8, 157.2, 144.5, 138.4, 130.5, 130.2, 128.5, 128.3, 125.9, 123.2, 101.6, 55.7, 12.8; FTIR (neat) (cm^{-1}) 3059, 1564, 1536, 1493, 1231, 1214; HRMS (ESI) calcd for $C_{16}H_{15}N_2OS$ $[M + H]^+$ 283.0900, found 283.0898.

4-Bromo-6-methoxy-2-phenylquinazoline (6m, Table 1). Trifluoromethanesulfonic anhydride (450 μL, 2.67 mmol, 1.10 equiv) was added dropwise to a mixture of amide **1c** (552 mg, 2.43 mmol, 1 equiv) and 2-chloropyridine (275 μL, 2.91 mmol, 1.20 equiv) in 1,2-dichloroethane (4.0 mL) at −78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, a solution of cyanic bromide (**2e**, 1.07 g, 10.1 mmol, 4.17 equiv) in 1,2-dichloroethane (4.1 mL) was added via cannula. After 5 min, the reaction mixture was heated to reflux. After 1 h, the reaction mixture was allowed to cool to 23 °C, the volatiles were removed under reduced pressure, and the residue was purified by flash column chromatography (eluent: 10% EtOAc and 1% Et_3N in hexanes; SiO_2: 18 × 3 cm) on neutralized silica gel to afford the desired quinazoline derivative **6m** as a white solid (633 mg, 83%). Mp 141−142 °C; TLC (10% EtOAc in hexanes) R_f 0.30 (UV); ^{1}H NMR (500 MHz, DMSO-d_6, 20 °C) δ 8.49 (app. dt, 2H, J = 7.5 Hz, 2.0 Hz), 7.92 (d, 1H, J = 9.0 Hz), 7.52 (dd, 1H, J = 9.0, 3.0 Hz), 7.49−7.44 (m, 3H), 7.36 (d, 1H, J = 2.5 Hz), 3.96 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 20 °C) δ 159.3, 158.4, 155.4, 147.5, 136.8, 130.9, 130.6, 128.8, 128.5, 127.8, 125.8, 105.3, 56.0; FTIR (nujol) (cm^{-1}) 2855, 2828, 1619, 1553, 1482, 1391; HRMS (ESI) calcd for $C_{15}H_{12}BrN_2O$ $[M + H]^+$ 315.0128, found 315.0136.

Acknowledgment. M.M. is an Alfred P. Sloan Research Fellow, a Beckman Young Investigator, and a Camille Dreyfus Teacher−Scholar. We acknowledge financial support from NSF (547905), Amgen, and DuPont.

Supporting Information Available: Experimental procedures and spectroscopic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.