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Single-Step Synthesis of Pyrimidine Derivatives

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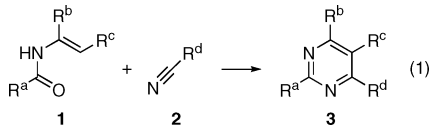
The pyrimidine substructure is ubiquitous in natural products, pharmaceuticals, and functional materials.[1] The majority of synthetic routes to this family of azaheterocycles involve strategies based on the condensation of amines and carbonyl compounds.[1,2] A complementary approach to substituted derivatives involves the use of recent advances in cross-coupling chemistry to introduce substituents on activated heterocycles.[3] Herein we report a mild, convergent, and single-step procedure for the conversion of readily available *N*-vinyl and *N*-aryl amides[4] to the corresponding substituted pyrimidines and quinazolines, respectively (eq 1).

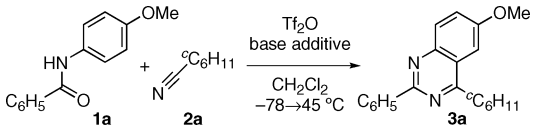
We recently reported a mild procedure for electrophilic activation of sensitive amides en route to pyridine derivatives.[5,6] We recognized the unique reactivity associated with electrophilic activation of amides using 2-chloropyridine (2-ClPyr)[7] in combination with trifluoromethanesulfonic anhydride (Tf_2O).[8] The current study concerns the trapping of highly activated amide derivatives with weakly nucleophilic nitriles to directly provide the corresponding pyrimidine derivatives (eq 1).



Benzamide **1a** and cyclohexanecarbonitrile (**2a**) were used to identify the optimum reagent combination (Table 1). The use of 2-ClPyr and Tf_2O allowed direct conversion of benzamide **1a** to the corresponding quinazoline **3a** (Table 1, entry 7).[9] Other base additives largely returned the starting amide **1a** after aqueous workup. A large excess of 2-chloropyridine was found to have an inhibitory effect (Table 1, entry 8), perhaps by competing with the addition of the weakly nucleophilic nitrile **2a** (vide infra). Under optimal conditions, the addition of Tf_2O (1.1 equiv) to a cold solution of amide **1a** (1 equiv), nitrile **2a** (1.1 equiv), and 2-ClPyr (1.2 equiv) in dichloromethane followed by warming afforded the desired quinazoline **3a** in 88−90% isolated yield.

We next explored the substrate scope with a variety of secondary amides and nitriles (Table 2). While electron rich *N*-vinyl and *N*-aryl amides proceeded to afford the corresponding pyrimidine derivatives at ambient temperatures (Table 2, condition A), less reactive substrates required heating (Table 2, conditions B and C).[10a] Electron donating and electron withdrawing substituents were tolerated in *N*-aryl benzamide derivatives (Table 2, entries 1−9). A wide range of nitriles, including electron rich and electron deficient benzonitriles in addition to saturated and unsaturated nitriles (Table 2, entries 10−16) were compatible with this chemistry. A variety of sensitive *N*-vinyl amides (Table 2, entries 14−21) served as substrates, giving the corresponding pyrimidine derivatives. Significantly, the use of epimerizable substrates (Table 2, entries 20 and 21) provided the corresponding pyrimidine derivatives *without* any loss in optical activity.[11,12] For the most reactive substrates, the introduction of the nitrile prior to the low temperature activation of the amide is essential for optimum results.[10b] In the case of highly reactive amides, excess nitrile was found to increase the yield of the desired pyrimidine product (Table 2, entry 17).[10c]

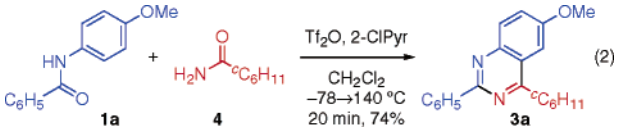
Table 1.



entry	base additive	equiv	isolated yield (%)[a]
1	none	0	29
2	Et_3N	1.2	0
3	$^iPr_2NEt$	1.2	14
4	pyridine	1.2	26
5	2,6-lutidine	1.2	28
6	2-chloropyridine	1.0	72
7	**2-chloropyridine**	**1.2**	**90**
8	2-chloropyridine	3.0	81

[a] Tf_2O (1.1 equiv), $^cC_6H_{11}CN$ (1.1 equiv), 45 °C, 16 h.

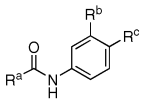
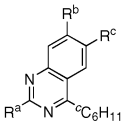
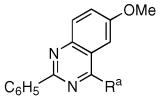
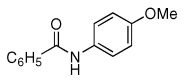
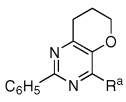
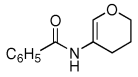
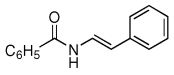
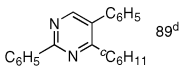
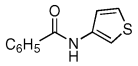
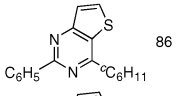
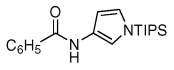
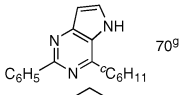
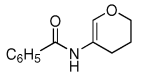
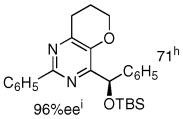
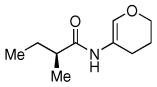
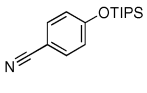
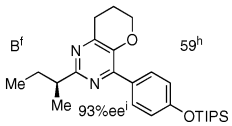
The dehydration of primary amides to the corresponding nitriles using Tf_2O and triethylamine has been reported.[13] Under optimum conditions, treatment of a solution of secondary amide **1a** (1 equiv), primary amide **4** (1.1 equiv), and 2-ClPyr (2.6 equiv) with Tf_2O (2.3 equiv) at −78 °C followed by microwave heating for 20 min, directly gave quinazoline **3a** in 74% yield (eq 2).[14] The ready availability of primary amides and their use as nitrile surrogates adds to the utility of this chemistry.



As illustrated in Scheme 1, amide activation and addition of 2-ClPyr to a protonated imidoyl triflate is envisioned to give the highly electrophilic 2-chloropyridinium adduct **5**. In contrast to pyridine, 2-ClPyr was found not to add to Tf_2O.[6,11] Monitoring of the reaction in entry 1 of Table 2 by ^{19}F NMR spectroscopy revealed the presence of trifluoromethanesulfonate (−79.6 ppm, CD_2Cl_2) throughout the reaction, without involvement of a persistent imidoyl triflate. In situ ^{13}C NMR monitoring of the amide activation using **1a**-$^{13}C{=}O$ (166.0 ppm, CD_2Cl_2) led to observation of a new broad resonance (149.8 ppm, CD_2Cl_2) prior to addition of the nitrile. React-IR monitoring during activation of amide **1a** with Tf_2O in the absence of nitrile **2a** revealed the consumption of 2-ClPyr (1580 cm^{-1}) with concomitant appearance of a new absorption band (1600 cm^{-1}). Introduction of the nitrile **2a** to this mixture led to loss of this absorption band and simultaneous release of 2-chloropyridinium trifluoromethane-sulfonate (1620 cm^{-1}) and the trifluoromethanesulfonate salt of the desired product **3a** (1575 cm^{-1}).[11] The broad

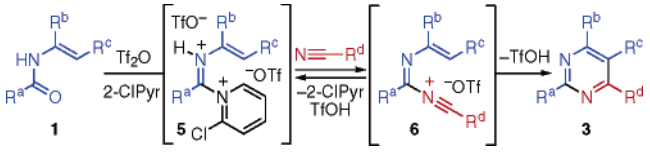
10.1021/ja066405m CCC: $33.50

Table 2. [a]

Entry	Amide	Nitrile	Conditions	Product	Yield (%)[b]
					
	R^a R^b R^c				
1	C_6H_5 H OMe		B		89
2	C_6H_5 H H		B		71
3	C_6H_5 CF_3 H		C		61
4	4-$MeOC_6H_4$ H OMe		B[c]		87
5	4-$NO_2C_6H_4$ H OMe		C		69
6	^{t}Bu H OMe		C		81
7	$^c C_6H_{11}$ H OMe		C		73
8	$N(CH_2CH_2)_2O$ H H		C		80
9	cyclohex-1-enyl H OMe		B		88[d]
					
10		R^a = 4-$NO_2C_6H_4$	C		86
11		R^a = 4-$MeOC_6H_4$	C		88
12		R^a = 4-$(CO_2Et)C_6H_4$	C		74
13		R^a = (*E*)-$C_6H_4CH{=}CH$	C		68
					
14		$R^a = {}^c C_6H_{11}$	A		92
15		$R^a = {}^t$Bu	A		94 (88)[e]
16		$R^a = (CH_2)_3C{\equiv}CH$	A		77
17			B[f]		89[d]
18			A		86
19			A		70[g]
20			B[f]		71[h]
				96%ee[i]	
21			B[f]		59[h]
				93%ee[i]	

[a] Uniform conditions 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, 16 h; C = microwave, 140 °C, 20 min. [b] Average of two experiments. [c] 18 h. [d] An amount of 5 equiv of nitrile. [e] Gram-scale reaction. [f] Time = 1 h. [g] TBAF (1 equiv) used to desilylate the product. [h] An amount of 3 equiv of nitrile. [i] ee determined by chiral HPLC analysis of a derivative.

Scheme 1



^{1}H, ^{13}C, and ^{19}F NMR resonances observed for the activated intermediate prior to addition of the nitrile suggests equilibration of **5** with the corresponding triflate adduct.[11] Reversible addition of nitrile[15] and expulsion of 2-ClPyr·HOTf to provide the nitrilium ion **6** is expected to occur en route to pyrimidine derivative **3**.[16] The inhibitory effect of more nucleophilic base additives and excess 2-ClPyr in addition to the benefit of superstoichiometric quantities of nitrile are consistent with the proposed mechanism.

We describe a single-step and convergent procedure for the synthesis of pyrimidine derivatives. This chemistry is applicable to a wide range of secondary amides and nitriles and allows for unique transformations including that in eq 2. This methodology not only alleviates the need for isolation of activated amide derivatives but also does not require the additional use of stoichiometric Lewis acids.[9] The use of this chemistry with sensitive and epimerizable substrates is noteworthy and offers a valuable addendum to methodology for azaheterocycle synthesis.

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

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(10) (a) The yield of entries 3 and 6 in Table 2 using condition B was 30 and 31%, respectively. (b) Absence of nitrile during activation of the amide substrate in entry 18 of Table 2 afforded the product in 62% yield. (c) The yield of entries 9, 17, 20, and 21 in Table 2 using 1.1 equiv of nitrile was 56, 70, 56, and 37%, respectively.

(11) See Supporting Information for details.

(12) The use of the *N*-4-methoxyphenyl variant of the amide in entry 21 of Table 2 provided the corresponding quinazoline in 58% yield but with complete racemization. Please see Supporting Information for details.

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(14) The complete formation of **2a** by treatment of **4** with Tf_2O and 2-ClPyr under the reaction conditions was confirmed independently.

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(16) The conversion of **6** to **3** may be facilitated by net addition of 2-chloropyridinium triflate to the nitrilium ion.

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