Direct Synthesis of Substituted Pyrimidines and Quinazolines

Matthew D. Hill, Mohammad Movassaghi*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
Fax +1(617)2521504; E-mail: movassag@mit.edu

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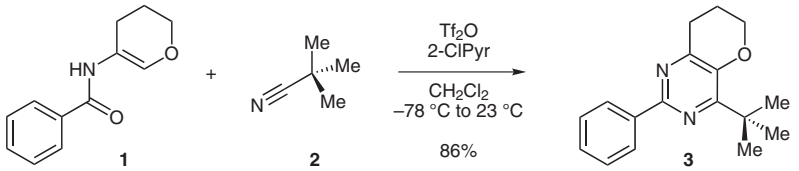
Abstract: A variety of *N*-vinyl and *N*-aryl amides were converted in one step into the corresponding pyrimidine and quinazoline derivatives, respectively. Amide activation with trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine followed by nitrile addition to the activated amide derivative and annulation provides the desired azaheterocycles.

Key words: amide, nitrile, pyrimidine, quinazoline, annulation



Scheme 1

Introduction

Due to the presence of pyrimidines and quinazolines in many pharmaceuticals, natural products, and fine materials, important contributions have been reported concerning synthetic methodology for their preparation.[1] Condensation reactions between amines and carbonyl derivatives or intermolecular cycloaddition approaches are common to many of these synthetic methodologies.[1,2] Cross-coupling chemistry has recently enabled the introduction of substituents on existing activated azaheterocycles.[3] We describe here a convergent and single-step procedure for the synthesis of a variety of pyrimidine and quinazoline derivatives from *N*-vinyl and *N*-aryl amides, respectively.[4]

Both *N*-vinyl and *N*-aryl amides are readily available and attractive starting materials for azaheterocycle synthesis.[5] Based on observations made while pursuing a two-step synthesis of pyridine derivatives,[6] we envisioned amide activation, subsequent nitrile σ-nucleophilic addition, followed by annulation of the corresponding nitrilium ion to give access to a wide variety of pyrimidine derivatives.[7] Nitriles, including optically active derivatives, are commercially available, can be accessed by dehydration of amides,[8] or prepared by hydrocyanation of carbonyl derivatives and serve as versatile starting materials for azaheterocycle synthesis.

We found the reagent combination of trifluoromethanesulfonic anhydride (Tf_2O)[9,10] and 2-chloropyridine (2-ClPyr)[11] to be optimal for direct condensation of amides and nitriles en route to pyrimidine derivatives. The single-step conversion of amide **1** and nitrile **2** to pyrimidine **3** is illustrative of this methodology (Scheme 1). Various base additives were examined but were less effective than 2-ClPyr, as shown in optimization studies conducted using amide **4** and nitrile **5** (Table 1). Superstoichiometric 2-ClPyr was found to have an inhibitory effect on conversion of **4** and **5** into the quinazoline **6** (Table 1, entry 12). Under optimal reaction conditions, data from in situ ^1H, ^{13}C, and ^{19}F NMR, and IR monitoring studies suggest that activation of an amide substrate (**7** in Scheme 2) with Tf_2O and 2-ClPyr leads to a mixture of intermediate **8** and triflate adduct **9**.[4] Subsequent σ-nucleophilic addition of nitrile **10** is expected to give nitrilium ion **11** followed by rapid annulation with concomitant loss of 2-ClPyr·HOTf to afford the pyrimidine **12** (Scheme 2).

Scope and Limitations

A variety of quinazoline and pyrimidine derivatives were prepared from readily available amide and nitrile substrates using this chemistry (Table 2). While cyclization of electron-rich *N*-aryl amides and nitriles typically proceeded with mild heating (45 °C), increasing the reaction temperature to 140 °C in a microwave reactor lowered reaction times and often increased isolated yields (Table 2, entries 3, 5–8, 10–14). The electron-deficient *N*-aryl substrate, shown in entry 3 of Table 2, required reaction temperatures of 140 °C to obtain complete conversion to the product. The use of a formamide substrate failed to give the desired pyrimidine due to competing isocyanide for-

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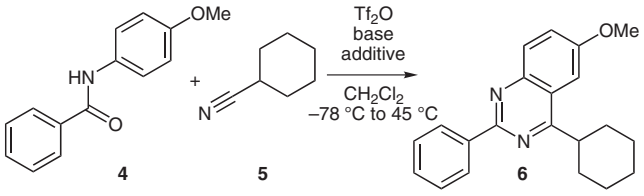
Table 1 Single-Step Conversion of Amide **4** to Quinazoline **6**[a]



Entry	Base additive	Base (equiv)	Yield (%) of **6**
1	none	0	29
2	Et_3N	1.2	0
3	*i*-Pr_2NEt	1.2	14
4	pyridine	1.2	26
5	2,6-lutidine	1.2	28
6	2,4,6-collidine	1.2	19
7	ethyl nicotinate	1.2	59
8	3-bromopyridine	1.2	54
9	2-bromopyridine	1.2	63
10	2-chloropyridine	1.0	72
11	2-chloropyridine	1.2	90
12	2-chloropyridine	3.0	81

[a] Reaction conditions: amide **4** (1 equiv), nitrile **5** (1.1 equiv), Tf_2O (1.1 equiv), base additive, CH_2Cl_2, –78 °C → 45 °C, 16 h.

mation (Table 2, entry 10). Electron-rich and electron-deficient benzonitriles were successfully used as substrates in this chemistry (Table 2, entries 11–13). A variety of *N*-vinyl amides gave access to pyrimidine derivatives with alkyl- or benzonitriles as nucleophiles (Table 2, entries 15–22). In the case of *N*-vinyl amides, often no heating was required; however, less reactive systems benefited from mild warming to 45 °C (Table 2, entry 18).

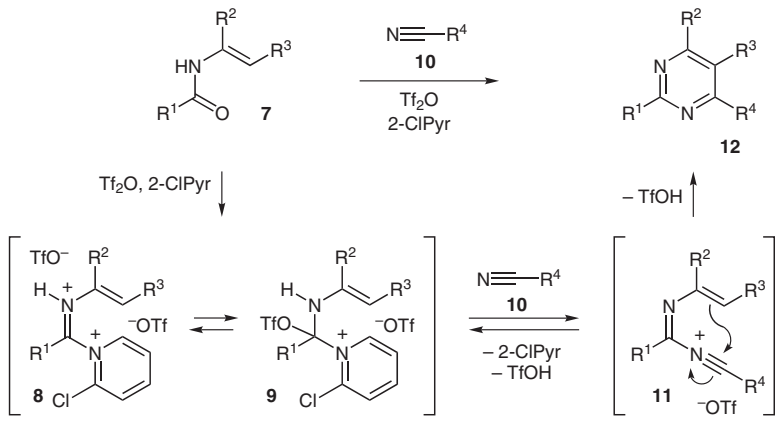
Importantly, an optically active *N*-vinyl amide and an optically active nitrile were converted into the corresponding pyrimidines without any loss in optical activity and without desilylation in the course of the reaction (Table 2, entries 21–22). However, in the case of the less reactive optically active *N*-aryl amides (98% ee) used in entries 23 and 24 of Table 2, the need for heating the reaction mixture to obtain the desired quinazolines afforded products in racemic form.

Minor adjustments of the reaction conditions can extend the scope of this chemistry to less reactive substrates. For example, superstoichiometric amount of the nitrile component was necessary to achieve satisfactory yields with the less reactive substrates (Table 2, entries 9, 18, and 22). Excess nitrile was also beneficial with sterically crowded substrates (Table 2, entry 21). Aliphatic nitriles were more reactive than benzonitrile derivatives when this chemistry was conducted at 45 °C. However, when reactions were heated to 140 °C this observable difference significantly decreased.

An efficient and convergent single-step synthesis of a wide range of pyrimidine and quinazoline derivatives from readily available amide and nitrile substrates is discussed. A wide range of substrates was applicable to this methodology. This methodology does not require isolation of activated intermediates nor does it call for stoichiometric Lewis acid additives post amide activation. Epimerizable *N*-vinyl amide and nitrile substrates may be used as substrates in this chemistry to give the desired azaheterocyclic products without loss in optical activity.

Procedure

The synthesis of pyrimidines and quinazolines directly from the corresponding nitrile and *N*-vinyl or *N*-aryl amides, respectively, is described.



Scheme 2

Table 2 Synthesis of Pyrimidines and Quinazolines

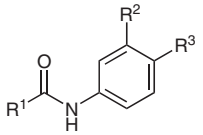
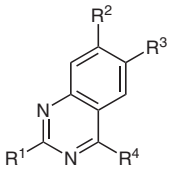
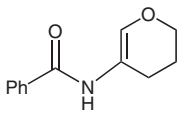
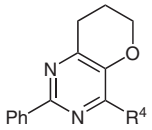
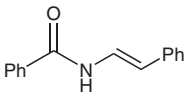
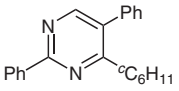
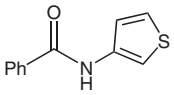
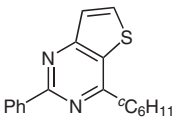
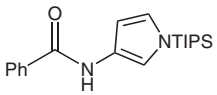
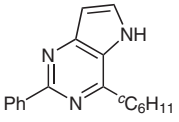
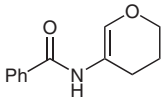
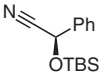
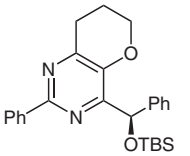
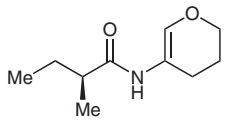
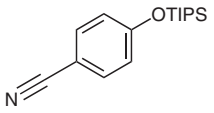
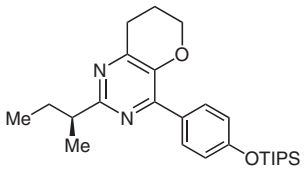
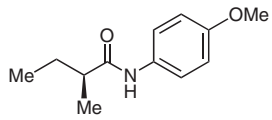
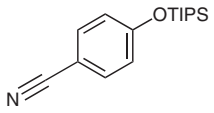
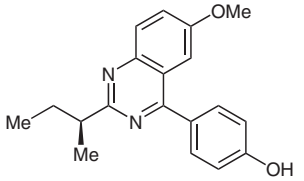
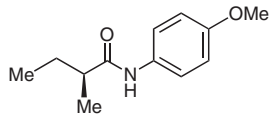
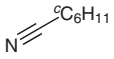
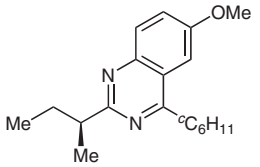
Entry	Amide	Nitrile	Conditions	Yield (%)[a]
				
1	R^1 = Ph, R^2 = H, R^3 = OMe	R^4 = *c*-C_6H_{11}	B	89
2	R^1 = Ph, R^2 = H, R^3 = H	R^4 = *c*-C_6H_{11}	B	71
3	R^1 = Ph, R^2 = CF_3, R^3 = H	R^4 = *c*-C_6H_{11}	C	61
4	R^1 = 4-$MeOC_6H_4$, R^2 = H, R^3 = OMe	R^4 = *c*-C_6H_{11}	B	87[b]
5	R^1 = 4-$NO_2C_6H_4$, R^2 = H, R^3 = OMe	R^4 = *c*-C_6H_{11}	C	69
6	R^1 = *t*-Bu, R^2 = H, R^3 = OMe	R^4 = *c*-C_6H_{11}	C	81
7	R^1 = *c*-C_6H_{11}, R^2 = H R^3 = OMe	R^4 = *c*-C_6H_{11}	C	73
8	R^1 = $N(CH_2CH_2)_2O$, R^2 = H, R^3 = H	R^4 = *c*-C_6H_{11}	C	80
9	R^1 = cyclohex-1-enyl, R^2 = H, R^3 = OMe	R^4 = *c*-C_6H_{11}	B	88[c]
10	R^1 = H, R^2 = H, R^3 = H	R^4 = *c*-C_6H_{11}	C	0
11	R^1 = Ph, R^2 = H, R^3 = OMe	R^4 = 4-$NO_2C_6H_4$	C	86
12	R^1 = Ph, R^2 = H, R^3 = OMe	R^4 = 4-$MeOC_6H_4$	C	88
13	R^1 = Ph, R^2 = H, R^3 = OMe	R^4 = 4-$CO_2EtC_6H_4$	C	74
14	R^1 = Ph, R^2 = H, R^3 = OMe	R^4 = (*E*)-C_6H_4CH=CH	C	68
				
15		R^4 = *c*-C_6H_{11}	A	92
16		R^4 = *t*-Bu	A	86[d]
17		R^4 = $(CH_2)_3C$≡CH	A	77
18		R^4 = *c*-C_6H_{11}	B	 89[c,e]
19		R^4 = *c*-C_6H_{11}	A	 86
20		R^4 = *c*-C_6H_{11}	A	 70[f]
21			B	 71[e,g] (96% ee)

Table 2 Synthesis of Pyrimidines and Quinazolines (continued)

Entry	Amide	Nitrile	Conditions	Yield (%)[a]
22			B	 59[e,g] (93% ee)
23			C	 58[h] (*rac*)
24			C	 85 (*rac*)

[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; Conditions: A = 23 °C, 1 h; B = 45 °C, 16 h; C = microwave, 140 °C, 20 min.
[b] Time = 18 h.
[c] Nitrile = 5.0 equiv.
[d] Gram-scale reaction.
[e] Time = 1 h.
[f] TBAF (1 equiv) was used to desilylate the product.
[g] Nitrile = 3.0 equiv.
[h] TBAF (2 equiv) was used to desilylate the product.

4-*tert*-Butyl-2-phenyl-7,8-dihydro-6*H*-pyrano[3,2-*d*]pyrimidine (3); Typical Procedure

Trifluoromethanesulfonic anhydride (894 μL, 5.41 mmol, 1.10 equiv) was added via a syringe over 3 min to a flame-dried flask containing a stirred mixture of amide **1** (1.00 g, 4.92 mmol, 1 equiv), nitrile **2** (491 mg, 5.90 mmol, 1.20 equiv), and 2-chloropyridine (559 μL, 5.90 mmol, 1.20 equiv) in CH_2Cl_2 (16 mL) at –78 °C. After 5 min, the mixture was placed in an ice-water bath for 10 min and warmed to 0 °C. The resulting solution was allowed to warm to r.t. After 1 h, aq 1 N NaOH (5 mL) was introduced to neutralize the trifluoromethanesulfonate salts. CH_2Cl_2 (50 mL) was added to dilute the mixture and the layers were separated. The organic layer was washed with aq $CuSO_4$ (10% w/w) to remove the 2-chloropyridine, dried (Na_2SO_4), and filtered. 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; column: 12 × 4 cm) on neutralized silica gel to give the pyrimidine **3** as a clear oil; yield: 1.13 g (86%); R_f = 0.67 (EtOAc–hexanes, 20:80).

IR (film): 3065 (w), 2955 (m), 2868 (w), 1558 (m), 1429 (m), 1406 (s), 1366 (m), 1353 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.42–8.37 (m, 2 H, ArH), 7.48–7.38 (m, 3 H, ArH), 4.27 (t, *J* = 5.1 Hz, 2 H, $CH_2CH_2CH_2O$), 2.98 (t, *J* = 6.7 Hz, $CH_2CH_2CH_2O$, 2 H), 2.20–2.14 (m, 2 H, $CH_2CH_2CH_2O$), 1.46 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 154.8, 150.4, 147.6, 138.6, 129.4, 128.5, 127.7, 66.3, 38.2, 28.3, 28.1, 22.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}N_2O$ $[M + H]^+$: 269.1654; found: 269.1653.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.13; H, 7.52; N, 10.34.

Acknowledgment

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