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Efficient Synthesis of 4-Aminoquinazoline and Thieno[3,2-*d*]pyrimidin-4-ylamine Derivatives by Microwave Irradiation

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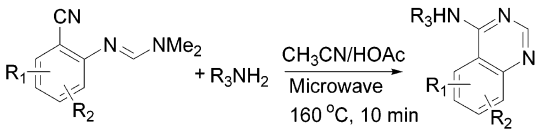
ABSTRACT



A simple, efficient, and high-yielding synthesis of quinazolin-4-ylamine and thieno[3,2-*d*]pyrimidin-4-ylamine derivatives is reported under microwave irradiation conditions. Reaction conditions including temperature, solvent, and reaction time have been studied. An efficient parallel workup procedure was developed to generate a small library (23 compounds) in a short time period.

4-Aminoquinazoline and its derivatives are useful as fungicides and as antiinflammatory, antimicrobial, and antihypertensive agents.[1] In particular, they are potent and highly selective inhibitors of tyrosine kinase.[2] Therefore, in recent years, the synthesis of 4-aminoquinazolines has attracted much attention.[3]

Traditional preparation of 4-aminoquinazolines involves the reaction of amines and 4-chloroquinazolines. The 4-chloroquinazolines were synthesized by chlorination of the corresponding quinazolinones that were in turn prepared by heating anthranilamides with formic acid, triethyl orthoformate, or formamide.

Microwave-assisted organic synthesis has had a significant impact on synthetic organic chemistry since 1986, with the introduction of controlled, precise microwave reactors.[4] The advantages of microwave irradiation include not only improving classical reactions, shortening reaction times, improving yields, and suppressing byproduct formation as compared with conventional thermal heating but also promoting new reaction types for drug discovery and process chemistry.[5]

In a search for novel compounds with pharmaceutical value and expanding application of formamidines in organic synthesis,[6] we wish to report herein a straightforward and high-yielding synthesis of 4-aminoquinazoline and thieno-

(1) Johne, S. *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; 1986; Vol. 29, pp 99−140.

(2) For recent review, see: (a) Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093−1095. (b) Bridges, A. J. *Chem. Rev.* **2001**, *101*, 2541−2572. (c) Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R.; Davis, R.; Koehn, R. E.; Greenberger, L. M.; Wang, Y. F.; Wissner, A. *J. Med. Chem.* **2001**, *44*, 2719−2734. (d) Berger, M.; Albrecht, B.,; Berces, A, Ettmayer, P.; Neruda, W.; Woisetschläger, M. *J. Med. Chem.* **2001**, *44*, 3031−3038.

(3) (a) Reference 2c. (b) Rocco, S. A.; Barbarini, J. E.; Rittner, R. *Synthesis* **2004**, *3*, 429−435 and references cited therein.

(4) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* **1986**, *27*, 279−282.

(5) For recent reviews on microwave-assisted chemistry, see: (a) Perio, B.; Dozias, M.; Hamelin, J. *Org. Process Res. Dev.* **1998**, *2*, 428−430. (b) Cleophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev.* **2000**, *4*, 498−504. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (d) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (e) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (f) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283. (g) Mavandadi, F.; Lidstrom, P. *Curr. Top. Med. Chem.* **2004**, *4*, 773−792.

(6) Cai, L.; Han, Y.; Ren, S. M.; Huang, L. F. *Tetrahedron* **2000**, *56*, 8253−8262.

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[3,2-*d*]pyrimidin-4-ylamine derivatives as promoted by microwave irradiation.

To optimize the conditions, we studied the effects of temperature, reaction time, and solvent. In a typical experiment, a mixture of **1a** and 1.2 equiv of **2a** in 2−3 mL of acetic acid was microwaved and monitored by HPLC, and the results are summarized in Figure 1.

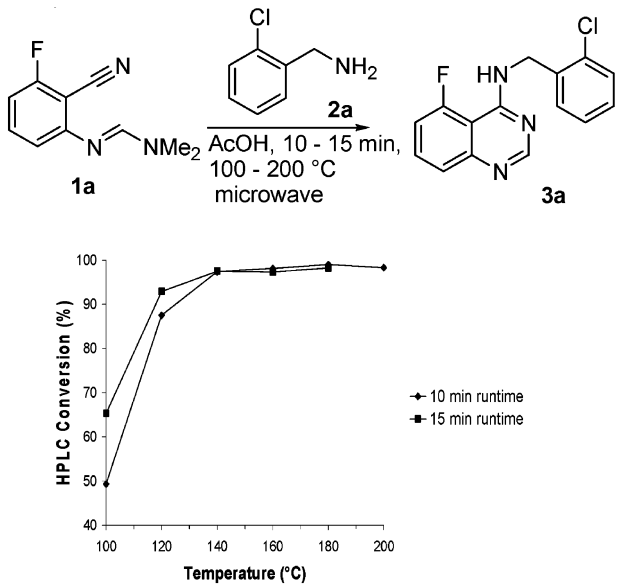


Figure 1. Optimization of reaction conditions: time and temperature effects.

Below 140 °C, the reaction was incomplete with significant amounts of **1a** remaining. At 100 °C, increasing the run time from 10 to 15 min improved the conversion from 49% to 65%, and at 120 °C the conversion increased from 87% to 92%. At 140 °C and above, the products were greater than 97% pure as judged by HPLC.

Isolated yields for a runtime of 10 min were as follows: 140 °C (81%), 160 °C (91%), 180 °C (99%), 200 °C (99%). Isolated yields at 15 min were as follows: 160 °C (88%), 180 °C (95%).

Although the yields and conversions appear to be optimal at >160 °C, a small impurity that is undetected by UV, but appears in the ^{1}H NMR, intensifies as the reaction temperature increases. The optimal combination of yield, HPLC conversion, and NMR purity was determined to be 160 °C, for 10 min.

A study on the effect of acetic acid concentration with varying solvents was conducted with the same substrates as described in Figure 1. Acetic acid concentration was varied from 10 to 40% (v/v), in three different solvents, DMF, THF, and acetonitrile (Figure 2).

In DMF, at 10% acetic acid the ratio of **3a** to **1a** was 1:2. The conversion increased to only 75% with 40% AcOH. In THF, the ratios of **3a** to **1a** were as follows: 10% (5.9:1), 20% (13.3:1), 30% (31.2:1), 40% (44.2:1).

The best results were obtained with acetonitrile as the cosolvent while time and temperature seemingly had a negligible effect. At 180 °C and 10% AcOH the ratio of **3a** to **1a** was 5.5:1. At 160 °C and 15 min run time ratios were as follows: 10% (6.7:1), 20% (12.9:1). Although conversions appear similar at 30% and 40% AcOH, the non-UV-active impurity increases at higher concentration of acetic acid.

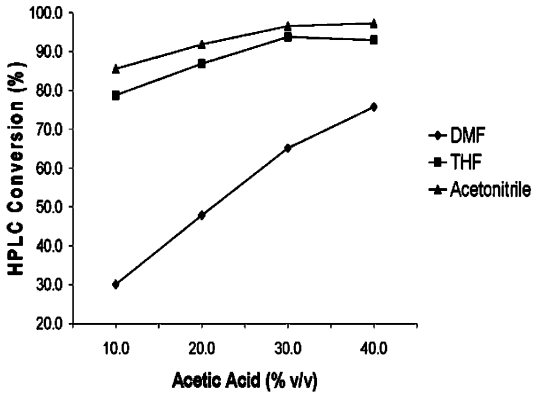
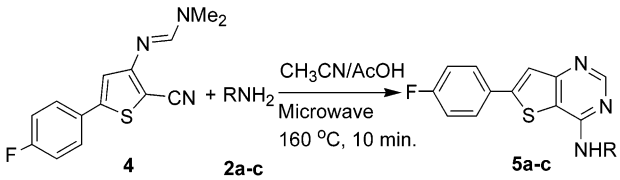


Figure 2. Optimization of reaction conditions: solvent effects.

Scheme 1



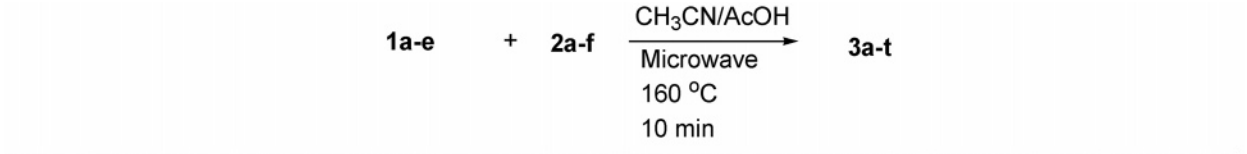
5a: R = 2-chlorobenzyl, 78%
5b: R = 3-trifluromethoxybenzyl, 96%
5c: R = 2-methoxy ethyl, 91%

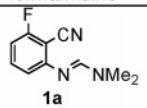
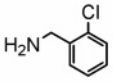
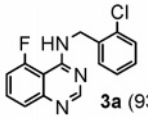
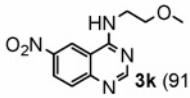
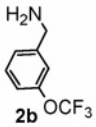
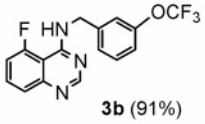
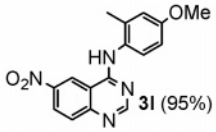
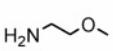
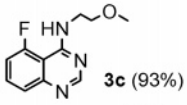
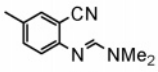
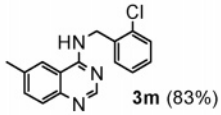
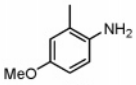
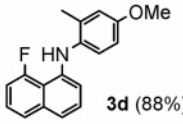
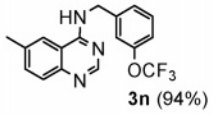
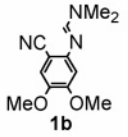
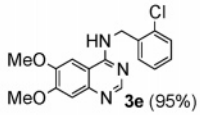
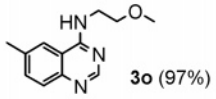
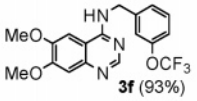
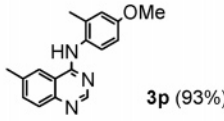
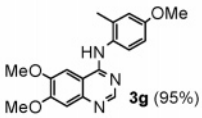
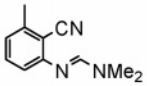
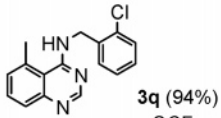
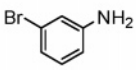
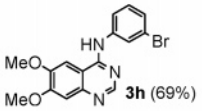
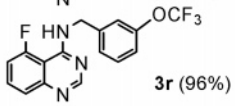
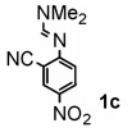
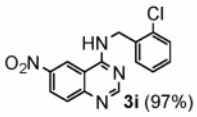
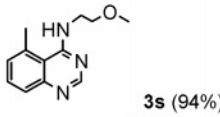
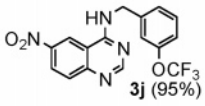
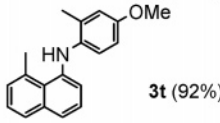
The microwave conditions from Figures 1 and 2 were identified as the preferred reaction conditions and were utilized for the synthesis of a diverse set of 4-aminoquinazoline derivatives. An efficient purification procedure has been developed to purify 20 compounds in a parallel procedure.[7] The reactions of anthancyanoformamidines and amines are general with a variety of electronic and steric subtituents. Benzylamines (**2a**, **2b**), aliphatic amine (**2c**), and electron-rich aniline (**2d**) are effective nucleophiles and gave high yield products. The electron-poor aniline (**2e**) gave moderate yield (**3h**, 69%, entry 8).

In expanding the scope of this chemistry to other heterocyclic compounds, we successfully synthesized thieno[3,2-

(7) **Typical Experimental Procedure.** To a 5 mL microwave reaction vial equipped with a magnetic stir bar were added *N*′-(2-cyano-3-fluorophenyl)-*N*,*N*-dimethylformamidine **1a** (100 mg, 0.52 mmol) and 2-chlorobenzylamine **2a** (90 mg, 0.62 mmol), followed by a 30% solution of glacial acetic acid in acetonitrile (2 mL). The mixture was capped and irradiated in the microwave for 10 min at 160 °C, cooled to ambient temperature, and purified in parallel using the following procedure: the contents of the vial were emptied onto a fritted solid sample cartridge (70 mL) loaded with Hydromatrix (12 g) pretreated with a solution of saturated sodium bicarbonate (20 mL). The solution was eluted directly onto a second solid sample cartridge (70 mL) containing a layer of dry Hydromatrix (4 g) followed by a layer of silica gel (10 g). The cartridges were eluted with ethyl acetate (5 × 20 mL), and the solvent was removed under nitrogen and dried in vacuo to yield **3a** (141 mg, 0.49 mmol, 93%) as a white solid.

Table 1. Synthesis of 4-Aminoquinazoline Derivatives by Microwave Irradiation[a]



entry	formamidine	amine	product (yield[b])	entry	formamidine	amine	product (yield[b])
1	 **1a**	 **2a**	 **3a** (93%)	11	**1c**	**2c**	 **3k** (91%)
2	**1a**	 **2b**	 **3b** (91%)	12	**1c**	**2d**	 **3l** (95%)
3	**1a**	 **2c**	 **3c** (93%)	13	 **1d**	**2a**	 **3m** (83%)
4	**1a**	 **2d**	 **3d** (88%)	14	**1d**	**2b**	 **3n** (94%)
5	 **1b**	**2a**	 **3e** (95%)	15	**1d**	**2c**	 **3o** (97%)
6	**1b**	**2b**	 **3f** (93%)	16	**1d**	**2d**	 **3p** (93%)
7	**1b**	**2d**	 **3g** (95%)	17	 **1e**	**2a**	 **3q** (94%)
8	**1b**	 **2e**	 **3h** (69%)	18	**1e**	**2b**	 **3r** (96%)
9	 **1c**	**2a**	 **3i** (97%)	19	**1e**	**2c**	 **3s** (94%)
10	**1c**	**2b**	 **3j** (95%)	20	**1e**	**2d**	 **3t** (92%)

[a] Reaction conditions: 0.52 mmol of fomamidine, 0.62 mmol of amine, and solvents (2 mL of CH_3CN and 0.6 mL of HOAc), 160 °C, 10 min. Personal Chemistry Synthesizer. [b] Isolated yields. All of 4-aminoquinazoline derivatives have been charaterized by ^1H NMR, ^{13}C NMR, HPLC, HRMS, and mp.

d]pyrimidin-4-ylamines which typically require multiple steps by other methods (Scheme 1).[8]

For comparison, entry 9 in Table 1 has been conducted using an oil bath under otherwise identical conditions (concentration, reaction vessel, temperature, etc.) After tight capping, the vessel was immersed in an oil bath at 160 °C for 10 min. The reaction was then quenched, aqueous workup was conducted, and solvent was concentrated. HPLC conver-

(8) Munchhof, M. J.; Beebe, J. S.; Casavant, J. M.; Beth A. Cooper, Doty, J. L.; R. Higdon, R. C.; Hillerman, S. M.; Soderstrom, C. I.; Knauth, E. A.; Marx, M. A.; Rossi, A.; Sobolov S. B.; Sun, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 21−24.

sion was 87%. A 97% isolated yield for entry 9 in Table 1 (HPLC conversion was 100%) demonstrated that microwave irradiation conditions are superior.

In summary, we have developed an efficient method for the synthesis of 4-aminoquinazoline and thieno[3,2-*d*]pyrimidin-4-ylamine derivatives using microwave irradiation reactions between *N*-(2-cyanophenyl)-*N*,*N*-dimethylformamidine derivatives and amines or *N*-(2-cyanothiophen-3-yl)-*N*,*N*-dimethylformamidine and amines. This procedure is straightforward and high yielding, an advantage over alternate routes which often require multiple steps.

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Supporting Information Available: Experimental procedures and full spectral data for compounds **3a**−**t** and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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