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A rapid method for the preparation of 2-substituted oxazolo[4,5-*b*]pyridines using microwave-assisted direct condensation reactions

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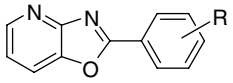
Abstract—The condensation reaction of 2-amino-3-hydroxypyridine with different carboxylic acids by microwave-assisted heating is a fast method for producing libraries based on fused 2-substituted oxazolo[4,5-*b*]pyridines in moderate to good yields.

Oxazoles are rigid and stable structures often found in natural products and widely used in medicinal chemistry. 2-Phenylbenzoxazoles have traditionally been synthesized by heating amino alcohols with benzoic acids in the presence of polyphosphoric acid[1] or trimethylsilyl polyphosphate[2] as dehydrating reagents. Activated acids such as orthoesters and acid anhydrides have been used in the preparation of 2-phenyl-pyrido- and pyrimidino-oxazoles.[3] Our interest lay in the preparation of 2-phenyloxazolo[4,5-*b*]pyridines (**1**, Fig. 1) with different substituents on the phenyl ring. Zhuravlev presented a convenient method to prepare these compounds using palladium catalyzed C-2 arylation of oxazolo[4,5-*b*]pyridine.[4] We particularly wanted to find a rapid way to prepare these compounds via direct condensations of benzoic acids as starting materials.

We first explored the method published by Terashima and Ishii[5] in which boric acid is used as the catalyst to carry out the condensations. Refluxing 3-hydroxybenzoic acid **2a** and 2-aminophenol **3** with 100 mol % of boric acid in *m*-xylene for 18 h with a Dean–Stark apparatus for water removal gave only a 13% yield of compound **5**. Addition of Na_2SO_4 to the reaction mixture to scavenge the water produced in the reaction chemically increased the yield to 37%. Eventually, carrying out the reaction at higher temperature (200 °C) and under pressure (50 psi) in an autoclave overnight gave a satisfactory yield (83%). The same method was then applied for 2-amino-3-hydroxypyridine **4** giving compound **1a** in 58% yield. Scheme 1.



1

Figure 1.

Microwave irradiation has previously been applied in condensation reactions by Bougrin et al.[6] and we decided to apply this method for the preparation of **1a**. The reactions were carried out in a CEM Discover© microwave reactor with varying parameters (Table 1). Reaction times were shortened dramatically, and the best results were obtained without solvent, catalyst or water scavenger with 2 min hold time at 250 °C, giving **1a** in 77% isolated yield (entry 7).

We applied the optimized reaction conditions to different aromatic and aliphatic acids and the results of screening are shown in Table 2.

For some acids the selected temperature (250 °C) was too high and resulted in low yields. These reactions were tested at lower temperature, improving the yield in several cases (entries 3, 4, 6, 7, 8). Some low-yielding reactions were also repeated in the presence of boric acid, since it has been reported to catalyze the condensation under normal heating reactions. Surprisingly, boric acid

Keywords: Direct condensation; Oxazolo[4,5-*b*]pyridine; Microwaves.
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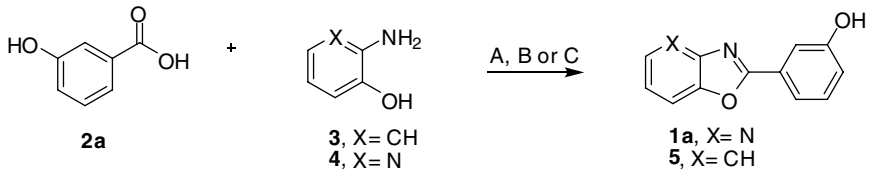
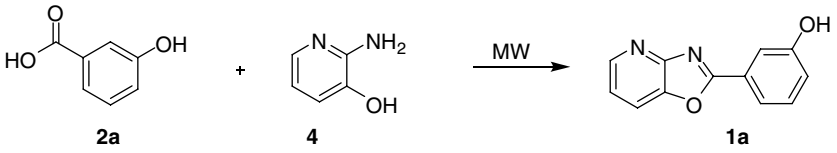


Scheme 1. Reagents and conditions: **2a** (415 mg, 3 mmol, 100 mol %), **3** (330 mg, 3 mmol, 100 mol %), boric acid (185 mg, 3 mmol, 100 mol %), xylene (30 mL). Methods and yields: (A), reflux with a Dean–Stark trap, 18 h, 13% for **5**; (B), Na_2SO_4, reflux 18 h, 37% for **5**; (C), autoclave, 200 °C, 50 psi, 18 h, 83% for **5** and 58% for **1a**.

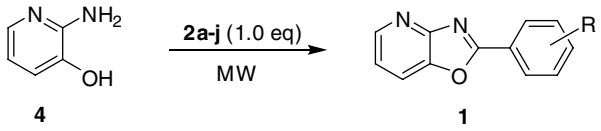
Table 1. Optimization of the condensation reaction of 3-hydroxybenzoic acid **2a** and 2-aminopyridin-3-ol **4**



Entry	Solvent	Temperature and power	Other reagents	Time[a] (min)	Yield[b] (%)
1	*m*-Xylene	200 °C/300 W	H_3BO_3, Na_2SO_4	15	25
2	Toluene	160 °C/1st 150 W, 2nd 300 W	H_3BO_3, Na_2SO_4	2 × 15	0[c]
3	—	200 °C/150 W	H_3BO_3, Na_2SO_4	15	13
4	—	200 °C/300 W	—	15	67
5	—	200 °C/200 W	—	15	40
6	—	250 °C/300 W	—	1	69
7	—	250 °C/300 W	—	2	77
8	—	250 °C/300 W	—	10	12

[a] Hold time is the time at a specific temperature. Ramp time varied from 3 to 10 min.
[b] Isolated yields.
[c] Only the starting materials were detected.

Table 2. The condensation reactions of 2-amino-3-pyridine **4** with acids **2**



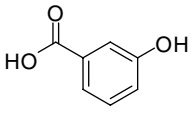
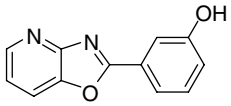
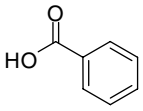
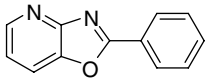
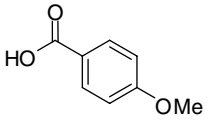
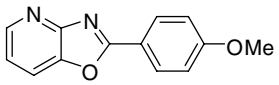
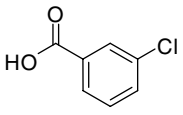
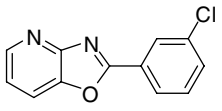
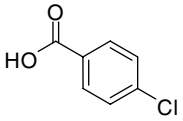
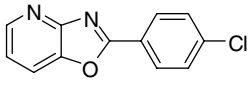
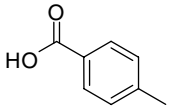
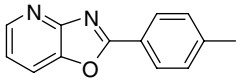
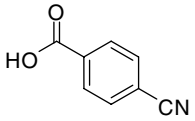
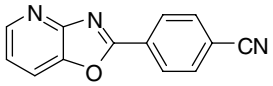
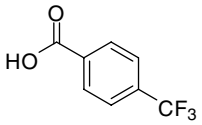
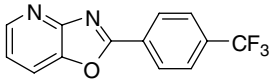
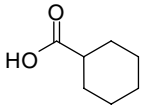
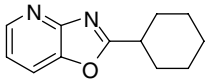
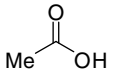
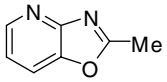
Entry	Acid		Time (min)	*T* (°C)	Product		Yield[a] (%)
1		**2a**	2	250		**1a**	77
2		**2b**	2	250		**1b**	60 (60)
3		**2c**	4 × 2	170		**1c**	Trace (44)
4		**2d**	3	170		**1d**	67
5		**2e**	3	250		**1e**	56

Table 2 (*continued*)

Entry	Acid		Time (min)	*T* (°C)	Product		Yield[a] (%)
6		**2f**	2	170		**1f**	82
7		**2g**	2	170		**1g**	Trace (18)
8		**2h**	4	170		**1h**	58 (40)
9		**2i**	12	250		**1i**	85 (51)
10		**2j**	2	250		**1j**	34 (20)

[a] Isolated yields. Yields in parentheses are for reactions using 100 mol % of boric acid.

was found both to increase the yield in some cases (entries 3, 7) and also to decrease it in others (entries 8, 9, 10).

When 2- and 4-hydroxy-, 4-dimethylamino-, 2-chloro-, 4-acetyl-, and 2-, 3- and 4-nitrobenzoic acids were subjected to the same reaction conditions, none of the desired products were obtained. The main products isolated from the reactions of **4** with 2-, and 4-hydroxy- and 4-dimethylaminobenzoic acid were the decarboxylated products (phenol or *N*,*N*-dimethylaniline, ^{1}H NMR). This implies that the presence of a strong electron donor in the 2- or 4-position of the carboxylic acid results in decarboxylation rather than condensation. With the remaining acids there was no clear main product, only a tar-like material or recovered starting materials.

In summary, 2-substituted oxazolo[4,5-*b*]pyridines are easily produced by microwave-assisted direct condensation. The reactions are fast and operationally simple (solvent-free conditions, easy work-up).

General procedure. The synthesis of **1a** via method C and MW-assisted reaction is presented to illustrate the procedures. Method C: To a 100 mL steel Parr™ pressure vessel, 3-hydroxybenzoic acid **2a** (415 mg, 3.0 mmol), 2-aminopyridin-3-ol **4** (330 mg, 3.0 mmol), H_3BO_3 (185 mg, 3.0 mmol), Na_2SO_4 (4 g, 28 mmol) and *m*-xylene (30 mL) were added. The vessel was closed and heated overnight at 200 °C. The pressure inside the vessel was 50 psi. The mixture was cooled to rt, poured into satd. $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried with Na_2SO_4, filtered and evaporated. The resulting tan solid was recrystallized from EtOAc–Hex (1:1, 50 mL) to yield **1a** (370 mg, 58%) as a white solid. Microwave-assisted reactions were carried out using a CEM Discover™ microwave reactor. A glass tube (10 mL) was loaded with **2a** (110 mg, 1.0 mmol) and **4** (138 mg, 1.0 mmol) and placed into the microwave reactor and irradiated (initially 300 W) at 250 °C for 2 min. After cooling to rt the residual tan solid was dissolved in EtOAc (10 mL). The mixture was evaporated close to dryness and purified by flash chromatography and recrystallization (EtOAc–Hex, 1:1) giving **1a** (165 mg, 77%) as a white solid: mp 203–204 °C, R_f (EtOAc) 0.5; ^{1}H NMR (DMSO, 400 MHz) 10.02 (s, 1H), 8.55 (dd, 1H, $J = 4.9$, 1.4 Hz), 8.24 (dd, 1H, $J = 8.2$, 1.4 Hz), 7.69 (app dt, 1H, $J = 7.7$, 1.2 Hz), 7.64 (t, 1H, $J = 2.0$ Hz), 7.48–7.43 (m, 2H), 7.08 (ddd, 1H, $J = 8.2$, 2.5, 0.9 Hz).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.161.

References and notes

1. (a) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, 427–429; (b) Orlando, C. M., Jr.; Wirth, J. G.; Heath, D. R. *J. Org. Chem.* **1970**, *35*, 3147–3149; (c) Clark, R.; Pessolano, A.; Witzel, P.; Lanza, T.; Shen, T. *J. Med. Chem* **1978**, *21*, 1158–1162.

2. (a) Dotrong, M.; Lovejoy, S. M.; Wolfe, J. F.; Evers, R. C. *J. Heterocycl. Chem.* **1997**, *34*, 817–821; (b) Wang, B.; Vernier, J.-M.; Rao, S.; Chung, J.; Anderson, J. J.; Brodkin, J. D.; Jiang, X.; Gardner, M. F.; Yang, X.; Munoz, B. *Bioorg. Med. Chem.* **2004**, *12*, 17–21; (c) Viaud, M.-C.; Jamoneau, P.; Savelon, L.; Guillaumet, G. *Heterocycles* **1995**, *41*, 2799–2809; (d) Flouzat, C.; Guillaumet, G. *J. Heterocycl. Chem.* **1991**, *28*, 899–906.
3. (a) Doise, M.; Dennin, F.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett.* **1990**, *31*, 1155–1156; (b) Fraser, J.; Tittensor, E. *J. Chem. Soc.* **1957**, 4625.
4. Zhuravlev, F. A. *Tetrahedron Lett.* **2006**, *47*, 2929–2932.
5. Terashima, M.; Ishii, M. *Synthesis* **1982**, 484–485.
6. Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055–8064.