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Microwave-assisted organic synthesis of 3-substituted-imidazo[1,5-*a*]pyridines

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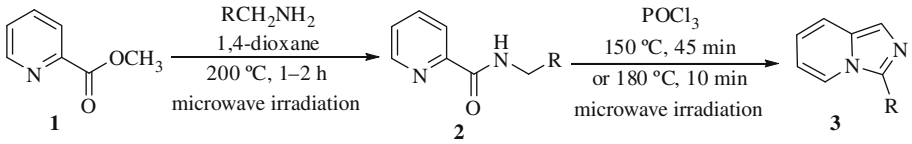
ABSTRACT

3-Substituted-imidazo[1,5-*a*]pyridines were conveniently synthesized in two steps from commercially available picolinic esters under microwave irradiation conditions.

The imidazo[1,5-*a*]pyridine skeleton (2-azaindolizines) has potential applications in organic light-emitting diodes (OLEDs),[1] in organic thin-layer field effect transistors (FETs),[2] and as precursors of *N*-heterocyclic carbenes.[3] Pharmaceutical applications such as cardiotonic agents,[4] aromatase inhibitors in estrogen-dependent diseases,[5] thromboxane A_2 synthetase inhibitors,[6] and angiotensin II receptor antagonists[7] have also been reported in the literature. A variety of methods have been employed in the synthesis of these 2-azaindolizines. Most routes relying on traditional Vilsmeier-type cyclizations of *N*-2-pyridylmethyl amides are only modestly efficient.[8–10] *N*-2-Pyridylmethyl thioamides have also been cyclized with dicyclohexylcarbodiimide,[11] mercuric salts,[12] and iodine/pyridine.[13] These general methods either give low to moderate yields, require harsh prolonged thermal reaction conditions giving tarry materials, or use environmentally toxic reagents. Other methods of preparing 2-azaindolizines include the use of imine derivatives,[14] benzotriazoles,[15] 2,2′-pyridils,[16] and dipyridylketones.[17] Recently, an oxidative condensation-cyclization of aldehydes and aryl-2-pyridylmethylamines in the presence of elemental sulfur as an oxidant afforded a variety of 1,3-diarylated imidazo[1,5-*a*]pyridines[18], and a one-pot synthesis of imidazo[1,5-*a*]pyridines starting from a carboxylic acid and 2-methylaminopyridines using propane phosphoric acid anhydride (T3P) in ethyl or *n*-butyl acetate at reflux allowed the introduction of various substituents at the 1- and 3-positions.[19]

We now report a convenient microwave-assisted organic synthesis of 3-substituted-imidazo[1,5-*a*]pyridines and describe the scope and limitation of this method. Methyl picolinate (**1**) was reacted with various amines under microwave irradiation at 200 °C in anhydrous 1,4-dioxane to give picolinamides **2**,[20] which after isolation were then cyclized in phosphorus oxychloride also under microwave conditions at 150 °C for 45 min or at 180 °C for 10 min to give 3-substituted-imidazo[1,5-*a*]pyridines **3**[21] (Scheme 1).



Scheme 1. Microwave-assisted organic synthesis of 3-substituted-imidazo[1,5-*a*]pyridines.

The reactions of methyl picolinate (**1**) with a series of substituted benzylamines were first investigated and the results are shown in Table 1. *N*-Benzyl picolinamides **2a–e** having hydrogen, halogen, and electron-withdrawing substituents all provided cyclized products **3a–e** in good yields (entries 1–5). The yields for **3a** (R = phenyl, 92%) and **3d** (R = 4-Cl-phenyl, 64%) under microwave conditions were higher than those reported previously for the same thermal reaction of the *N*-benzylpicolinamides in phosphorus pentachloride in chloroform or pyridine where **3a** and **3d** were obtained in yields of 20% and 31%, respectively.[22] *N*-Benzyl picolinamides **2f–h** electron-donating benzylamines such as 4-methoxy, 4-*N*,*N*-dimethylamino, and 3,4-methylenedioxy failed to provide any of the desired cyclized products **3f–h**, respectively (entries 6–8). 2-Methoxybenzylamine (entry 9) afforded cyclized product **3i** in poor yield.

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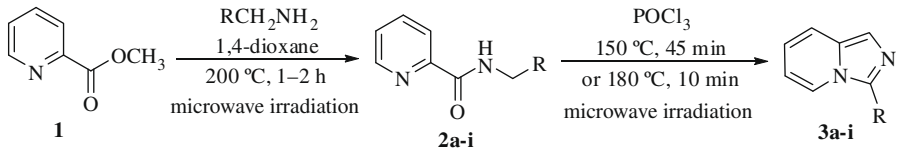
Table 1
Synthesis of picolinamides and conversion to phenyl-substituted imidazo[1,5-*a*]pyridines



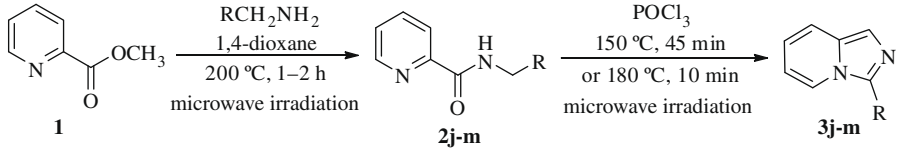
Entry	R	**2** (% yield)	**3** (% yield)
1	Phenyl	**2a** (60)	**3a** (92)
2	4-CF_3-phenyl	**2b** (48)	**3b** (89)
3	4-CN-phenyl	**2c** (37)	**3c** (98)
4	4-Cl-phenyl	**2d** (94)	**3d** (64)
5	4-F-phenyl	**2e** (95)	**3e** (96)
6	4-OMe-phenyl	**2f** (98)	**3f** (NR)
7	4-NMe_2-phenyl	**2g** (37)	**3g** (NR)
8	3,4-Methylenedioxyphenyl	**2h** (97)	**3h** (NR)
9	2-OMe-phenyl	**2i** (63)	**3i** (11)

The introduction of substituents other than phenyl or substituted phenyl groups at the 3-position of the imidazo[1,5-*a*]pyridine ring system were then investigated and the results are shown in Table 2. 4-Pyridylmethylamine (entry 1) gave 3-(4-pyridyl)imidazo[1,5-*a*]pyridine (**3j**) in moderate yield. Aliphatic amines such as ethylglycine hydrochloride (entry 2) and isocyanomethanamine (entry 3) afforded ester and cyano derivatives **3k** and **3l**, respectively. However, 2,2-dimethoxyethanolamine (entry 4) failed to give the acetal product **3m**, which is a useful precursor to the aldehyde functionality.

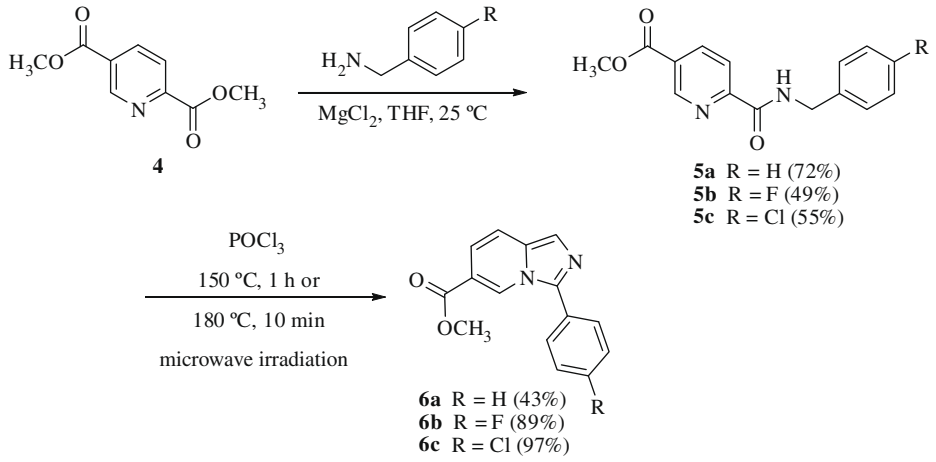
The scope of this method was expanded by investigating substitution on the pyridine ring system. Dimethyl pyridine-2,5-dicarboxylate (**4**) was converted to the picolinamides **5a–c**[23] via a magnesium–chloride-mediated coupling with 4-substituted benzylamines. Microwave irradiation of **7** with phosphorus oxychloride provided methyl 3-substituted-imidazo[1,5-*a*]pyridine-7-carboxylates **6a–c** (Scheme 2). The ester group provides a useful handle for further elaboration of these molecules.

The proposed mechanism of the cyclization step outlined in Scheme 3 was previously presented and validated by deuterium-

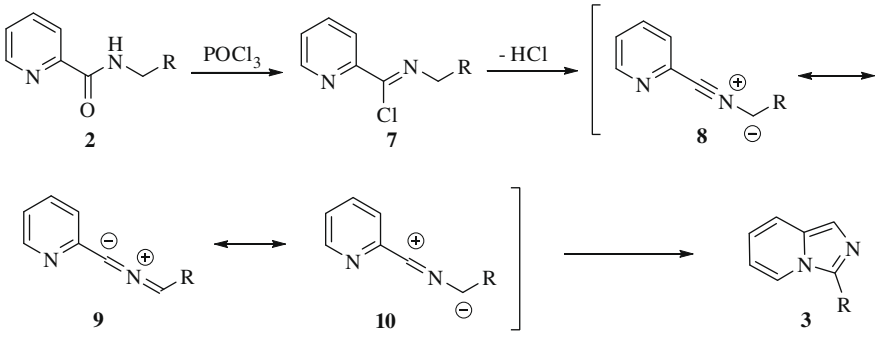
Table 2
Synthesis of picolinamides and conversion to 3-substituted imidazo[l,5-*a*]pyridines



Entry	R	**2** (% yield)	**3** (% yield)
l	4-Pyridyl	**2j** (65)	**3j** (62)
2	CO_2Et	**2k** (45)	**3k** (70)
3	CN	**2l** (36)	**31** (29)
4	$CH(OMe)_2$	**2m** (63)	**3m** (NR)



Scheme 2. Microwave-assisted organic synthesis of methyl 3-substituted-imidazo[1,5-*a*]pyridine-7-carboxylates.



Scheme 3. Proposed mechanism of the cyclization step.

labeling NMR experiments.[22] Picolinamides **2** is converted to imidoyl chlorides **7** which upon loss of hydrogen chloride generates nitrile ylides **8**–**10** in different resonance forms, which then cyclized to 3-substituted-imidazo[1,5-*a*]pyridines **3**.

In conclusion, we have applied a convenient microwave-assisted organic synthesis to the preparation of 3-substituted-imidazo[1,5-*a*]pyridines. The scope and limitations of this method were presented.

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20. A representative procedure for the synthesis of *N*-benzylpicolinamide (**2a**) is presented as follows: Methyl picolinate (**1**, 568 mg, 4.15 mmol) and benzylamine (488 mg, 4.56 mmol) in 1,4-dioxane (2 mL) were heated with stirring at 200 °C for 1 h in the Biotage Initiator™ microwave reactor. After cooling, the contents of the reaction vessel were poured onto water and the aqueous mixture was extracted with methylene chloride. The organic phase was washed with saturated aqueous brine solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes) to give *N*-benzylpicolinamide (**2a**, 529 mg, 60%): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.67 (d, J = 6.1 Hz, 2H), 7.26–7.44 (m, 6H), 7.85 (td, J = 7.7 Hz, 1.7 Hz, 1H), 8.23 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 8.38 (br s, 1H), 8.52 (ddd, J = 4.7 Hz, 1.6 Hz, 0.9 Hz, 1H), ESI-MS: m/z 213 $[M+H]^+$.
21. A representative procedure for the synthesis of a 3-phenylimidazo[1,5-*a*]pyridine (**3a**) is presented as follows: A mixture of *N*-benzylpicolinamide (**2a**, 100 mg, 0.471 mmol) and phosphorus oxychloride (2 mL, 21.5 mmol) was heated with stirring at 150 °C for 45 min in Biotage Initiator™ microwave reactor. After cooling, the mixture was concentrated in vacuo, and water (10 mL) was added to the residue. The pH of the resulting solution was adjusted to 7–8 with concentrated NH_4OH and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes) to give 3-phenylimidazo[1,5-*a*]pyridine (**3a**, 84 mg, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.55 (td, J = 7.4 Hz, 1.2 Hz, 1H), 6.72 (ddd, J = 9.1 Hz, 6.4 Hz, 0.8 Hz, 1H), 7.42–7.56 (m, 5H), 7.80 (dd, J = 3.5 Hz, 1.5 Hz, 2H), 8.26 (dd, J = 7.3 Hz, 0.9 Hz, 1H); ESI-MS: m/z 195 $[M+H]^+$.
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