Synthesis of 3-Nitro-2-arylimidazo[1,2-*a*]pyridines Using Sodium Dichloroiodide

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Abstract: Moderate to good yields of various 3-nitro-2-arylimidazo[1,2-*a*]pyridines have been easily achieved in the reaction of 2-aminopyridines and nitrostyrenes in the presence of sodium dichloriodide. The procedure is simple and various functional groups are tolerated in this reaction system.

Keywords: 2-aminopyridine, nitrostyrene, iodine reagent, 3-nitro-2-arylimidazo[1,2-*a*]pyridines

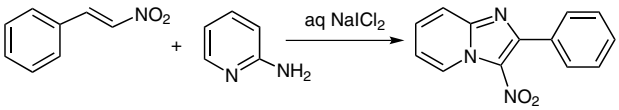
Nitrogen-containing heterocycles are widespread in nature and many synthetic bioactive compounds are based on nitrogen heterocycles;[1] so heterocyclic synthesis continues to provide a focus for the development of novel synthetic methodology.

Imidazopyridines are known to be one of the important class of heterocycles in medicinal chemistry and, within this group of heterocycles, imidazo[1,2-*a*]pyridines derivatives have been widely exploited for as antitubercular,[2] anti-inflammatory,[3] anticancer,[4] anti-HIV,[5] and antimicrobial agents.[6]

Our group is working on novel methodology using iodine reagents[7] and their applications in the synthesis of bioactive compounds.[8] During our studies, we needed to functionalize 3-nitro-2-arylimidazo[1,2-*a*]pyridine as a key compound. Very few examples of syntheses of 3-nitro-2-arylimidazo[1,2-*a*]pyridine have been reported in the literature; these include condensation of 2-aminopyridines with nitrostyrenes;[9a] three-component reactions of 2-aminopyridines, aldehydes and nitromethane,[9b] and Suzuki–Miyaura cross-coupling reactions of 2-chloro-3-nitroimidazo[1,2-*a*]pyridine.[9c] Thus our aim was to develop a simple method for the synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine.

We proposed that this compound could be synthesized using iodine-based reagents. Thus in the initial experiment we carried out the reaction between 2-aminopyridine and nitrostyrene in the presence of aqueous $NaICl_2$ at room temperature in DMF (Scheme 1), but only a very low yield of the desired 3-nitro-2-phenylimidazo[1,2-*a*]pyridine was isolated after extended reaction time. However, a higher yield of the desired product was obtained when the reaction mixture was heated at 80 °C and, after optimization of reaction conditions, the best yield was obtained in 1.5 hours, when 0.1 equivalent of aqueous sodium dichloroiodide was used.

Reactions were also carried out using different solvents such as DMSO, MeOH, EtOH, and MeCN, but very low yields were observed in each case. Thus DMF was deemed the most suitable solvent for this reaction.



Scheme 1 Synthesis of 3-nitro-2-arylimidazo[1,2-*a*]pyridine using aqueous sodium dichloroiodide in DMF

The above method was applied successfully to synthesize various 3-nitro-2-arylimidazo[1,2-*a*]pyridine derivatives, and the results are summarized in Table 1.[10] It was observed that the nature of the substituent on the aromatic rings of nitrostyrenes had little influence on the yields of the products. All the nitrostyrenes with electron-donating or electron-withdrawing groups gave moderate to good yields of the corresponding 3-nitro-2-arylimidazo[1,2-*a*]pyridines.

The substrate scope of 2-aminopyridines was further investigated and similar results were observed. It is interesting to observe that 5-chloro-2-aminopyridine was found to produce the desired product while 6-chloro-2-aminopyridine proved to be inert (Table 1, **3m** vs. **3n**).

In summary, we have successfully developed a novel and efficient system for the synthesis of 3-nitro-2-arylimidazo[1,2-*a*] pyridines. In this system, readily available nitrostyrenes and 2-aminopyridines were utilized in the presence of aqueous sodium dichloroiodide. Various functional groups are well tolerated in this reaction system and gave moderate to good yields.

Acknowledgment

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References and Notes

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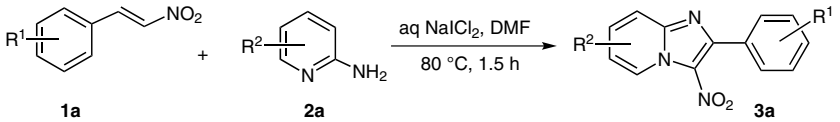
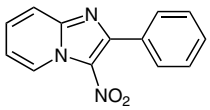
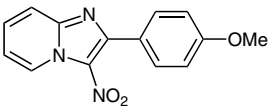
Table 1 Synthesis of Various 3-Nitro-2-arylimidazo[1,2-*a*]pyridine Compounds Using Aqueous Sodium Dichloroiodide[a]



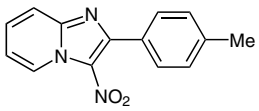
1a **2a** **3a**



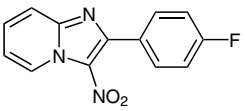
85% **3a**



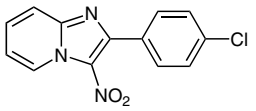
82% **3b**



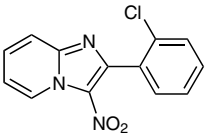
87% **3c**



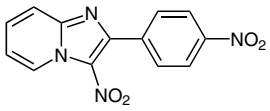
85% **3d**



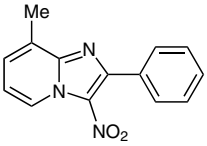
80% **3e**



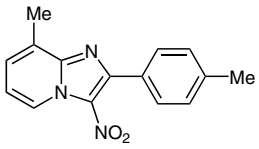
85% **3f**



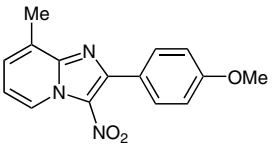
75% **3g**



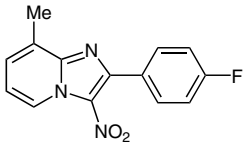
83% **3h**



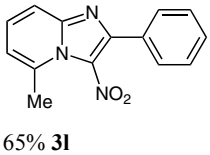
78% **3i**



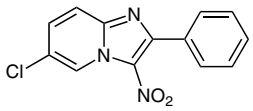
76% **3j**



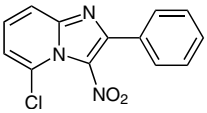
71% **3k**



65% **3l**



69% **3m**



0% **3n**

[a] Reaction conditions: nitrostyrene (1.2 mol), 2-aminopyridine (1 mol), aq $NaICl_2$ (0.1 mol) in DMF at 80 °C.
[b] Isolated yields after column chromatography. Structures were confirmed by comparison of IR, ^1H NMR and mp with literature reports.

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(10) **Typical Procedure**
A mixture of nitrostyrene (1.2 equiv), 2-aminopyridine (1 equiv), and aq $NaICl_2$ (0.1 equiv) in DMF was stirred at 80 °C for 1.5 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with EtOAc and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The product was then purified using silica gel column chromatography (EtOAc–hexane).

3-Nitro-2-phenylimidazo[1,2-*a*]pyridine (3a)
Yellow solid; mp 170–172 °C (lit.[9a] 172–174 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 7.2 Hz, 1 H, H-5), 7.92–7.89 (m, 2 H, H-2′ and H-6′-Ph), 7.84 (d, *J* = 8.8 Hz, 1 H, H-8), 7.68–7.64 (m, 1 H, H-7), 7.52 (t, *J* = 2.0 Hz, 3 H, H-3′, H-4′, and 5′-Ph), 7.28 (t, 1 H, H-6). IR (KBr): 3061, 3034, 1630, 1531, 1481, 1369, 1219, 929, 761, 694 cm^{-1}.

2-(4-Methoxyphenyl)-3-nitroimidazo[1,2-*a*]pyridine (3b)
Yellow solid; mp 167–169 °C (lit.[9a] 168–170 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, *J* = 6.8 Hz, 1 H, H-5), 7.92 (d, *J* = 8.8 Hz, 2 H, H-2′ and 6′-Ph), 7.79 (d, *J* = 8.8 Hz, 1 H, H-8), 7.63 (t, *J* = 8.0 Hz, 1 H, H-7), 7.24 (d, *J* = 6.8 Hz, 1 H, H-6), 7.07 (d, *J* = 8.8 Hz, 2 H, H-3′ and 5′-Ph), 3.87 (s, 3 H, OCH_3). IR (KBr): 3016, 2922, 1608, 1541, 1481, 1369, 1211, 921, 758 cm^{-1}.

2-(4-Fluorophenyl)-3-nitroimidazo[1,2-*a*]pyridine (3d)
Yellow solid; mp 224–226 °C (lit.[9c] 227–228 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (d, *J* = 6.8 Hz, 1 H, H-5), 7.88–7.82 (m, 3 H), 7.69–7.65 (m, 3 H), 7.31–7.27 (m, 1 H). IR (KBr): 3061, 3030, 1604, 1537, 1487, 1334, 1220, 837, 763 cm^{-1}.

3-Nitro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (3g)
Yellow solid, mp 216–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 7.0 Hz, 1 H, H-5), 8.30 (d, *J* = 8.9 Hz, 2 H, H-2′ and 6′-Ph), 8.13 (d, *J* = 8.9 Hz, 2 H, H-3′ and 5′-Ph), 7.73 (t, *J* = 8.2 Hz, 1 H, H-7), 7.66 (d, *J* = 9.2 Hz, 1 H, H-8), 7.37 (t, *J* = 7.0 Hz, 1 H, H-6). IR (KBr): 3074, 3032, 1635, 1599, 1514, 1481, 1334, 856, 758 cm^{-1}.

2-(4-Methoxyphenyl)-8-methyl-3-nitroimidazo[1,2-*a*]pyridine (3j)
Yellow solid; mp 148–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 7.2 Hz, 1 H, H-5), 7.94 (d, *J* = 8.8 Hz, 2 H, H-2′ and 6′-Ph), 7.43 (d, *J* = 6.8 Hz, 1 H, H-7), 7.15 (t, *J* = 6.8 Hz, 1 H, H-6), 7.03 (d, *J* = 8.8 Hz, 2 H, H-3′ and 5′-Ph), 3.84 (s, 3 H, OCH_3), 2.71 (s, 3 H, CH_3). IR (KBr): 3030, 2922, 1610, 1611, 1580, 1472, 1369, 1238, 1149, 1031, 827, 754 cm^{-1}.

2-(4-Fluorophenyl)-8-methyl-3-nitroimidazo[1,2-*a*]pyridine (3k)
Yellow solid; mp 194–198 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 6.95 Hz, 1 H, H-5), 7.96–7.92 (m, 2 H, H-2′ and 6′-Ph), 7.46 (d, *J* = 7.2 Hz, 1 H, H-7), 7.20 (t, *J* = 7.1 Hz, 3 H, H-6, H-3′, and 5′-Ph) 2.73 (s, 3 H, CH_3). IR (KBr): 3053, 2918, 1607, 1539, 1479, 1366, 1238, 1157, 837, 746 cm^{-1}.

5-Methyl-3-nitro-2-phenylimidazo[1,2-*a*]pyridine (3l)
Yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (t, 2 H, H-2′ and 6′-Ph), 7.74 (s, 1 H, H-4′-Ph), 7.57 (d, *J* = 8.8 Hz, 1 H, H-8), 7.44 (t, 2 H, H-3′ and 5′-Ph), 7.37 (t, *J* = 7.4 Hz, 1 H, H-7), 7.15 (d, *J* = 6.8 Hz, 1 H, H-6), 2.61 (s, 3 H, CH_3). IR (KBr): 3061, 3030, 2920, 1674, 1537, 1483, 1344, 1226, 1153, 947, 825, 775 cm^{-1}.

