Hypervalent Iodine(III) Sulfonate Mediated Synthesis of Imidazo[1,2-*a*]pyridines

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A direct and efficient method for the conversion of alkyl aryl ketones to imidazo[1,2-*a*]pyridines has been developed based on initial formation of α-organosulfonyloxy ketones and their subsequent cyclocondensation by 2-aminopyridines in one-pot conditions.

Keywords: Hypervalent iodine(III) sulfonate; Cyclocondensation; 2-Aminopyridines.

INTRODUCTION

Imidazo[1,2-*a*]pyridines are of interest due to their antiinflammatory,[1] potential antirhinoviral,[2] long-acting local anesthetic[3] and antiulcer agents,[4] for whitening fine fabrics,[5] as anthelmintic or bacteriostatic agents,[6] and as fluorescent materials.[7] They are also versatile intermediates for synthetic transformations.[8]

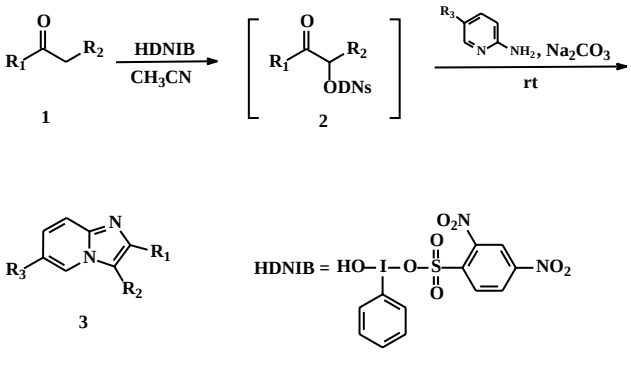
Imidazo[1,2-*a*]pyridines have generally been prepared by the condensation of α-halocarbonyl compound with 2-aminopyridine (Chichibabin reaction).[9] Other methods based on 2-aminopyridine[10] and an alternative strategy of building imidazo[1,2-*a*]pyridines from a variety of substituted imidazoles are also recorded.[11]

Recently, hypervalent iodine(III) reagents have been used extensively in organic synthesis due to their low toxicity, ready availability, and easy handling.[12] As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have reported a modified Pictet-Spengler cyclization of N-sulfonyl-β-phenethylamines with ethyl methylthioacetate using bis(trifluoroacetoxyiodo)benzene (BTI) to prepare ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.[13] We report here a new and direct method for the synthesis of imidazo[1,2-*a*]pyridine (**3**) by the cyclocondensation of 2-aminopyridines with intermediary α-[2,4-(dinitrobenzene)sulfonyloxy] carbonyl compounds (**2**), formed *in situ* from the reaction of [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]-benzene (HDNIB) with aryl methyl ketones (**1**).

RESULTS AND DISCUSSION

The required HDNIB was prepared in satisfactory yields from the reaction of 2,4-dinitrobenzenesulfonic acid with phenyliodine(III) diacetate (PIDA).[14] Treatment of aromatic ketones with HDNIB in CH_3CN at reflux for 1 h produced the α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone intermediates (**2**). Subsequent cyclocondensation by 2-aminopyridines at room temperature in the presence of sodium carbonate gave the corresponding imidazo[1,2-*a*]pyridine derivatives (**3**) in good yields (Scheme I).

Scheme I



The 2,4-dinitrobenzenesulfonyloxy group positioned in the α position to a carbonyl group represents an increas-

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ingly important entity in both mechanistic and synthetic organic chemistry. One of the reasons for this is that the 2,4-dinitrobenzenesulfonyloxy group is a good leaving group, and this accounts for the considerable synthetic utility associated with these groups in functionalization of carbonyl compounds.

Our experiments showed a one-pot procedure for the preparation of imidazo[1,2-*a*]pyridine derivatives (**3**) by cyclocondensation of ketones with HDNIB and 2-aminopyridine in CH_3CN was successful. The results are summarized in Table 1. When the reaction was conducted by replacing HDNIB by HTIB (PhI(OH)OTs, Koser's reagent)[15] under the same conditions, the preparation of 2-phenylimidazo-[1,2-*a*]pyridine (**3a**) needs refluxing for 6 h. This observation clearly demonstrated the leaving ability of –ODNs superior to –OTs in nucleophilic substitution reactions.

In summary, the method described herein provides a good approach for the synthesis of imidazo[1,2-*a*]pyridines by using the reaction of aryl methyl ketones with hypervalent iodine(III) sulfonate (HDNIB) in one-pot conditions and gives good yields.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

2-Phenylimidazo[1,2-*a*]pyridine (3a); Typical procedure

A mixture of acetophenone (120 mg, 1.0 mmol) and HDNIB (468 mg, 1.0 mmol) in acetonitrile (20 mL) was heated at reflux for 1 h. After the reaction mixture was cooled to room temperature, 2-aminopyridine (113 mg, 1.2 mmol) and Na_2CO_3 (60 mg, 0.55 mmol) were added and the mixture was stirred at room temperature for 1 h. Subsequently, the solvent was evaporated off and the residue was chromatographed on a silica gel column eluting with AcOEt-cyclohexane (1:2) to give **3a**, mp 131-133 °C (lit.[15] mp 130-132 °C) yield 80%. IR (KBr) ν: 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.78 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.15-7.19 (m, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.42-7.46 (m, 2H), 7.64 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.87 (s, 1H), 7.94-7.97 (m, 2H), 8.12 (td, *J* = 1.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.1, 112.5, 117.5, 124.8, 125.6, 126.1, 128.0, 128.4, 128.7, 129.9, 133.4, 133.5, 145.6; EI-MS *m/z* (relative intensity) 194 (M^+), 116, 89, 78, 63, 51, 50.

Table 1. Preparation of imidazo[1,2-*a*]pyridines **3a-k**

Entry	R_1	R_2	R_3	Yield(%)
3a	Ph	H	H	80
3b	4-MeC_6H_4	H	H	76
3c	4-MeOC_6H_4	H	H	85
3d	4-FC_6H_4	H	H	87
3e	4-ClC_6H_4	H	H	78
3f	4-BrC_6H_4	H	H	76
3g	2-Furyl	H	H	82
3h	2-Thienyl	H	H	84
3i	Ph	Me	H	75
3j	Ph	H	Cl	77
3k	4-MeOC_6H_4	H	Cl	83

2-(4-Methylphenyl)imidazo[1,2-*a*]pyridine (3b)

mp 145-146 °C (lit.[16] mp 144-145 °C), yield 76%. IR (KBr) ν: 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H), 6.78 (t, *J* = 6.4 Hz, 1H), 7.17 (t, *J* = 8.2 Hz, 1H), 7.24-7.27 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 107.7, 112.5, 117.3, 124.7, 125.5, 125.9, 129.4, 130.5, 137.9, 145.4; EI-MS *m/z* (relative intensity) 208 (M^+), 103, 78, 63, 51.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3c)

mp 137-138 °C (lit.[16] mp 137-138 °C), yield 85%. IR (KBr) ν: 1609, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 3H), 6.74 (dt, *J* = 0.8, 6.8 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 2H), 7.14 (t, *J* = 6.8 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.76 (s, 1H), 7.88 (d, *J* = 9.6 Hz, 2H), 8.08 (td, *J* = 1.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 107.1, 112.1, 114.1, 117.2, 124.3, 125.4, 126.4, 127.2, 145.6, 159.5; EI-MS *m/z* (relative intensity) 225(M^++1), 224 (M^+), 209, 181, 78, 63, 51.

2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine (3d)

mp 159-161 °C (lit.[16] mp 156-160 °C), yield 87%. IR (KBr) ν: 1633 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.82 (dt, *J* = 0.8, 6.8 Hz, 1H), 7.10-7.16 (m, 2H), 7.19-7.24 (m, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.81 (s, 1H), 7.91-7.96 (m, 2H), 8.13 (td, *J* = 1.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.7, 112.6, 115.5, 115.7, 117.4, 124.9, 125.5, 127.7, 129.7, 144.7, 145.5, 163.9; EI-MS *m/z* (relative intensity) 212 (M^+), 185, 107, 78, 51.

2-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine (3e)

mp 206-207 °C (lit.[16] mp 205-206 °C), yield 78%. IR

(KBr) ν: 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.8 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.85 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.1, 112.5, 117.4, 124.9, 125.5, 127.2, 128.8, 132.1, 133.6, 144.5, 145.6; EI-MS *m/z* (relative intensity) 230 (M^++2), 228 (M^+), 193, 192, 114, 89, 78, 75, 63, 51.

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (3f)

mp 209-211 °C (lit.[16] mp 210-212 °C), yield 76%. IR (KBr) ν: 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.80 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.54-7.58 (m, 2H), 7.63 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.81-7.85 (m, 2H), 7.86 (s, 1H), 8.12 (td, *J* = 1.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.2, 112.6, 117.5, 121.9, 125.0, 125.6, 127.5, 131.8, 132.5, 144.5, 145.6; EI-MS *m/z* (relative intensity) 274 (M^++2), 272 (M^+), 193, 192, 78, 63, 51, 50.

2-(2-Furyl)imidazo[1,2-*a*]pyridine (3g)

mp 92-93 °C (lit.[16] mp 92-93 °C), yield 82%. IR (KBr) ν: 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.51-6.52 (m, 1H), 6.79 (dt, *J* = 1.2, 6.8 Hz, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 7.16-7.20 (m, 1H), 7.47 (s, 1H), 7.60 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.80 (s, 1H), 8.11 (td, *J* = 1.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 106.8, 107.8, 111.5, 112.5, 117.2, 125.0, 125.6, 137.8, 142.0, 145.5, 149.4; EI-MS *m/z* (relative intensity) 185 (M^++1), 184 (M^+), 156, 155, 79, 78, 63, 51.

2-(2-Thienyl)imidazo[1,2-*a*]pyridine (3h)

mp 136-137 °C (lit.[17] mp 137-138 °C), yield 84%. IR (KBr) ν: 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.79 (dt, *J* = 1.2, 6.8 Hz, 1H), 7.10 (t, *J* = 4.4 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 4.8 Hz, 1H), 7.48 (d, *J* = 3.6 Hz, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.78 (s, 1H), 8.09 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.4, 112.5, 117.2, 123.7, 124.8, 125.0, 125.3, 127.7, 137.3, 140.7, 145.3; EI-MS *m/z* (relative intensity) 201 (M^++1), 200 (M^+), 155, 78, 69, 63, 51.

3-Methyl-2-phenylimidazo[1,2-*a*]pyridine (3i)

mp 154-155 °C (lit.[16] mp 153-154 °C), yield 75%. IR (KBr) ν: 1629 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.66 (s, 3H), 6.87 (t, *J* = 6.8 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.79-7.81 (m, 2H), 7.92 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 112.0, 115.8, 117.3, 122.8, 123.5, 127.3, 128.3, 128.4, 134.7, 142.3, 144.2; EI-MS *m/z* (relative intensity) 208 (M^+), 207, 103, 84, 79, 78, 63, 51.

6-Chloro-2-phenylimidazo[1,2-*a*]pyridine (3j)

mp 200-201 °C (lit.[18] mp 201-202 °C), yield 77%. IR (KBr) ν: 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.23-7.24 (m, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.44-7.49 (m, 2H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.85 (s, 1H), 7.94-7.97 (m, 2H), 8.22 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.4, 117.6, 120.5, 123.3, 123.8, 126.0, 126.1, 128.2, 128.7, 132.9, 143.8, 146.5; EI-MS *m/z* (relative intensity) 230 (M^++2), 228 (M^+), 116, 89, 77, 63.

6-Chloro-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (3k)

mp 225-226 °C (lit.[17] mp 227-228 °C), yield 83%. IR (KBr) ν: 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.86 (s, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.14 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.59 (d, *J* = 9.6 Hz, 1H), 7.76 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.3, 109.4, 114.2, 117.4, 120.3, 123.2, 125.4, 125.9, 127.3, 128.2, 132.0, 137.6, 146.1, 156.7; EI-MS *m/z* (relative intensity) 260 (M^++2), 258 (M^+), 243, 215, 179, 112.

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