SHORT PAPER

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Regioselective synthesis of 2-arylimidazo[2,1-a] isoquinolines†

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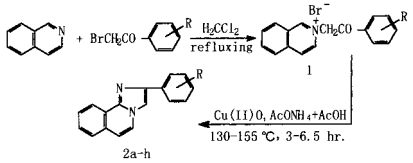
Substituted phenacyl bromides react with isoquinoline to form the corresponding quaternary salts which, when heated in ammonium acetate and acetic acid in the presence of Cu(II)O, undergo regioselective cyclisation to give 2-arylimidazo[2,1-*a*]isoquinolines uniquely.

Keywords: isoquinolines, imidazoles, fused, copper(II) oxidation

2-Arylimidazo[2,1-*a*]isoquinolines have been shown to have biological activity as non-hormonal contragestational agents in both hamsters and rats.[1] The most common method for the synthesis of 2-arylimidazo[2,1-*a*]isoquinolines is the reaction of substituted phenacyl bromides with 1-aminoisoquinoline.[2,3] This procedure, however, is not suitable for large scale preparations because 1-aminoisoquinoline is a costly starting material. A synthesis of 2-phenylimidazo[2,1-*a*]isoquinoline based on the cyclization of phenacylisoquinolinium bromide with ammonium acetate in acetic acid has been reported.[2] However, the yield of target product is low in this case due to the formation of isomer 5,10-dihydro-2-phenylimidazo[1,2-*b*]isoquinoline.[4] Toja has also reported that 2-(4′-chlorophenyl) imidazo[2,1-*a*]isoquinoline could be obtained by running the reaction of the quaternary salt with ammonium acetate in the presence of ferric chloride. But we have found that the reaction needs to be completed in an autoclave[1] and the purification procedure is difficult because excess ferric chloride is used. Herein we report a new method for regioselective synthesis of 2-arylimidazo[2,1-*a*]isoquinolines by conducting the reaction in the presence of Cu(II)O (Scheme 1).

Although the exact structure of complex is unclear, we believe that the Cu(II) ion reacts with the isoquinolinium salt to form a complex which makes the cyclisation occur at the most electrophilic site (1-position), avoiding the competing reaction at the 3-position of the isoquinolinium salt (Table 1).



Scheme 1

General procedure: A solution of isoquinoline (2.84 g, 22 mmol) and phenacyl bromide (5.0 g, 25 mmol) in methylene chloride (25 ml) was refluxed for 3 h. After cooling to room temperature, phenacyl isoquinolinium bromide (7.1 g, 98%) was filtered, washed with methylene chloride (15 ml × 2), and dried.

A mixture of the quaternary salt (2.36 g, 7.2 mmol) obtained above, ammonium acetate (5 g, 65 mmol) and Cu(II)O (0.87 g 10 mmol) in acetic acid (15 ml) was placed in a bottle under nitrogen at 140 °C for 3 h. After cooling, 50 ml of water was added and the mixture was shaken. The precipitated solid was filtered, washed with water (20 ml × 3) and then transferred to a beaker. To the solid 15 ml of 37% aqueous ammonia was added, stirred vigorously and then extracted with chloroform (15 ml × 3). Evaporation of the solvent and recrystallisation of the solid residue from methanol gave 1.28 g (73%) of 2-phenylimidazo[2,1-*a*]isoquinoline.

2-(4′-Ethoxyphenyl)imidazo[2,1-a]isoquinoline (**2h**): m.p. 166–167.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.45 (3H, t, *J* 6.98), 4.09 (2H, m, *J* 6.98), 6.98 (2H, d), 7.03 (1H, d, *J* 7.15), 7.56 (1H, t), 7.63, (1H, t), 7.70 (1H, d, *J* 7.84), 7.74 (1H, s), 7.89 (1H, d, *J* 7.18), 7.93 (2H, d), 8.73 (1H, d, *J* 7.70); IR (KBr) ν (cm^{-1}) 2950, 1620, 1560, 1490, 1380, 1240, 1050, 790, 740, 700. *m/z* 288 (M^+, 100%).

Table 1 Synthesis of 2-arylimidazo[2,1-a]isoquinolines **2a–h**

No.	R	T/°C	Time/h	Yield[a]/%	m.p./°C
2a	H	140–150	3.0	73	140–141 (Lit.[1] 148–150)
2b	4-F	130–140	4.0	69	163–164 (Lit.[1] 162–164)
2c	4-Cl	130	3.0	75	188–190 (Lit.[1] 193–194)
2d	3,4-Cl_2	130–135	3.5	76	160–162 (Lit.[1] 160–161)
2e	4-Br	130	3.0	65	197–198 (Lit.[1] 205–206)
2f	4-Me	130–140	5.5	48	157–158 (Lit.[1] 161–163)
2g	4-OMe	140	6.5	25[b]	176–178 (Lit.[1] 177–179)
2h	4-OEt	140–155	5.0	36[b]	166–167.5

[a:] Isolated yield. [b:] Purified by column chromatography (methylene chloride : chloroform = 1:1).

Experimental

^{1}H NMR spectral data were determined in $CDCl_3$ on a Bruker 500 MHz spectrometer with $SiMe_4$ as the internal standard. *J* values are given in Hz. IR spectra were recorded on a Shimadzu IR-460 instrument. Mass spectral data were obtained by electron ionization on HP5989B spectrometer.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

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