

NITROIMIDAZOLES XI [1]. SYNTHESSES OF DISUBSTITUTED NITROIMIDAZOLYLQUINOLINES

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Abstract

Reaction of substituted-aniline (**8**) with ethyl (1-methyl-5-nitroimidazole-2-carbonyl) acetate (**9**) gave 4-hydroxy-2-(1-methyl-5-nitro-2-imidazolyl)-substituted-quinolines (**10**), which were converted to compound **11** with phosphorus oxychloride. Substituted-2-(1-methyl-5-nitro-2-imidazolyl)-4-methyl-(or phenyl-) quinolines (**14**) were prepared through the reaction of 2-acetyl-5-nitro-1-methyl-imidazole (**13**) with *O*-aminoacetophenones (or *O*-aminobenzophenones) in acid medium.

Introduction

The considerable biological importance of nitroimidazoles has stimulated much work on this heterocycle [2-7]. We recently reported the syntheses of monosubstituted nitroimidazolylquinoline [2]. In the present work, the syntheses of the title compounds as possible effective drugs against tropical diseases are reported [8].

Results and Discussion

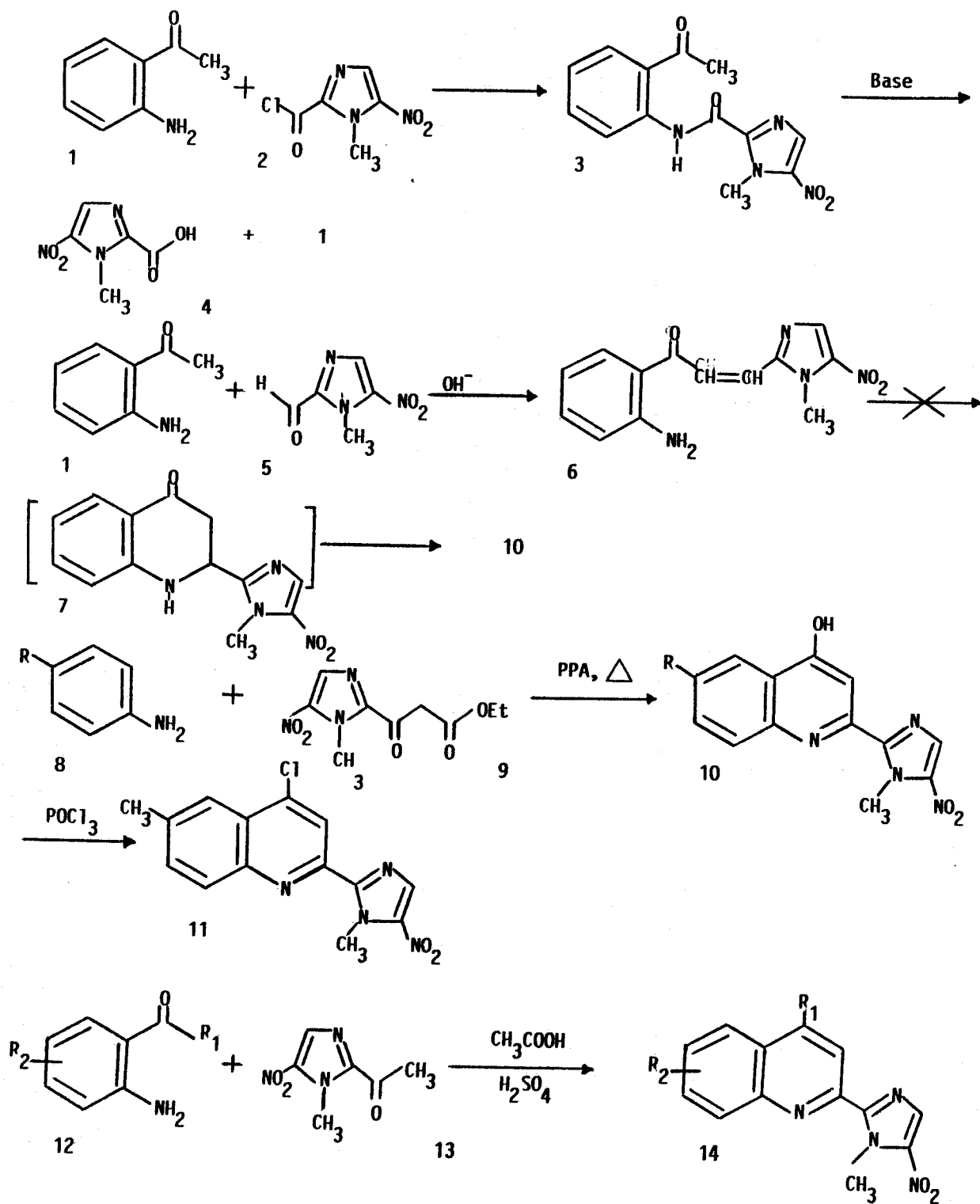
The most common approach employed to synthesize substituted-4-hydroxyquinolines is the condensation of substituted *O*-aminobenzoic acid with a ketone (Nimentowski method) [9] or acetal [10]; condensation of diethyl malonate with iminochloride and subsequent cyclization, hydrolysis and decarboxylation of the intermediate [11]; preparation of 2-aryl-4-aminoquinoline and subsequent diazotization and hydrolysis [12]. All the above reactions failed in our case. Other methods employed for the preparation of the desired compounds are summarized in Scheme 1.

Keywords: Disubstituted nitroimidazolylquinolines; Nitroimidazolylquinolines

Reaction of 2-aminoacetophenone with 1-methyl-5-nitroimidazole-2-carbonyl-chloride (**2**) [13] afforded *N*-[2-acetylphenyl] 1-methyl-5-nitroimidazole-2-carboxamide (**3**). Cyclization of compound **3** under basic conditions did not give the desired compound **10**, instead compound **1** and 1-methyl-5-nitroimidazole-2-carboxylic acid (**4**) [14] were isolated. Cyclization of compound **3** under acid conditions gave only starting material **3**.

Reaction of compound **1** with 1-methyl-5-nitroimidazole-2-carboxaldehyde (**5**) [3] gave 1-(2-aminobenzoyl)-2-(1-methyl-5-nitro-2-imidazolyl)ethylene (**6**). However, this compound did not cyclize to compound **7** under different experimental conditions.

Finally, the desired compound **10** was synthesized through the reaction of substituted-aniline with the β -ketoester (**9**) [3] in polyphosphoric acid at 130-140°C. Reaction of compound **10** [$R=CH_3$], with phosphorus oxychloride gave 4-chloro-2-(1-methyl-5-nitro-2-imidazolyl)-6-methylquinoline (**11**) in high yield. All substituted-4-hydroxy-2-(1-methyl-5-nitro-2-imidazolyl)quinolines (**10**) prepared are summarized in Table 1.



Scheme 1

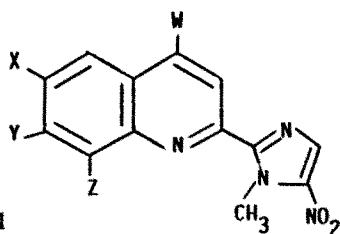


Table 1

Compound No.	W	X	Y	Z	M. P. °C ^a	Yield (%) ^b
10a	OH	Cl	H	H	222-225	15
10b	OH	CH ₃	H	H	280-283	32
10c	OH	H	H	CH ₃	233-235	20
10d	OH	CH ₃ O	H	H	292-295	25
11	Cl	CH ₃	H	H	181-183	94
14a	H	H	H	CH ₃	180-182 ^c	28
14b	CH ₃	H	H	H	169-171	23
14c	Ph	H	H	H	184-186	49
14d	Ph	H	CH ₃	H	210-212	52
14e	Ph	Cl	H	H	198-200	29

a) Unless otherwise stated the compound was crystallized from ethanol.

b) All compounds gave satisfactory C, H, N analyses.

c) This compound was prepared according to Reference [2] and crystallized from petroleum ether.

Substituted-2-(1-methyl-5-nitro-2-imidazolyl)-4-methyl-(or phenyl)quinolines (**14**) could not be synthesized according to Freidlander's method, namely the reaction of *O*-amino-acetophenone (or substituted *O*-aminobenzophenone) with 2-acetyl-5-nitro-1-methylimidazole (**13**) [3] in basic medium. However, these compounds could be synthesized in high yield in acid medium. The structure of all compounds was confirmed by elemental analysis, IR, NMR and mass spectroscopy.

Experimental Section

— Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The UV spectra were recorded using a Perkin-Elmer Model 550 SE. The IR spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The ¹H-NMR spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT-311 spectrometer at 70 eV.

N-(1-Methyl-5-nitro-2-imidazolyl)-*O*-aminoacetophenone (**3**)

To a stirring solution of 1-methyl-5-

nitroimidazole-2-carbonyl chloride (**2**) (1.732 g, 0.01 mole) in dry benzene (10 ml), dry pyridine (5 ml) and *O*-aminoacetophenone (1.35 g, 0.01 mole) in dry benzene (10 ml) was added. The stirring was continued for 2 hours. The precipitate was filtered and washed with water (2×5 ml). The residue was crystallized from acetone to give 2.02 g (70%) of compound **3**; m.p. 246-248°C; IR (potassium bromide): ν 3450 (NH), 3130 (H₄ imidazole), 1690 (C=O), 1660 (C=O), 1539 and 1360 cm⁻¹ (NO₂); ¹H-NMR (CDCl₃); 8.86 (d, 1H, H₆ phenyl), 8.11 (s, 1H, H₄ imidazole), 7.97 (d, 1H, H₃ phenyl), 7.62 (t, 1H, H₄ phenyl), 7.22 (t, 1H, H₅ phenyl), 4.51 (s, 3H, N-CH₃) and 2.80 ppm (s, 3H, CH₃); ms: m/z (%) 288 (M⁺, 99) 273 (94), 258 (20), 245 (100), 242 (30), 229 (90), 227 (24), 216 (56) and 200 (97).

Anal. Calcd. for C₁₃H₁₂N₄O₄: C, 54.17; H, 4.17; N, 19.44. Found: C, 54.02; H, 4.29; N, 19.56.

1-(2-Aminobenzoyl)-2-(1-methyl-5-nitro-2-imidazolyl)ethylene (**6**)

A solution of 1-methyl-5-nitroimidazole-2-carboxaldehyde (0.775 g, 0.005 mole) [15], *O*-aminoacetophenone (0.675 g, 0.005 mole) and 0.6 N sodium hydroxide (5 ml) in ethanol (150 ml) was stirred overnight. The precipitate was filtered and crystallized from methanol to give 0.3 g (22%) of **6**, m.p. 245-248°C; IR (potassium bromide): ν 3460, 3280 (NH₂), 3120 (H-C imidazole), 1645 (C=O), 1545 and 1330 cm⁻¹ (NO₂); NMR (CDCl₃); 8.1 (s, 1H, H₄ imidazole), 8.3-7.3 (m, 4H, phenyl), 6.2 (d, 1H, CH=), 5.40 (d, 1H, CH=) and 4.20 ppm (s, 3H, NCH₃); ms: m/z (%) 272 (M⁺, 11), 243 (33), 193 (26), 184 (37), 147 (70), 131 (67) and 118 (100).

Anal. Calcd. for C₁₃H₁₂N₄O₃: C, 57.35; H, 4.41; N, 20.59. Found: C, 57.53; H, 4.59; N, 20.72.

6-Chloro-4-hydroxy-2-(1-methyl-5-nitro-2-imidazolyl)quinoline (**10a**)

A solution of (1-methyl-5-nitroimidazole-2-carbonyl)acetate (**9**, 482 mg, 2 mmoles) and *O*-chloroaniline (255 mg, 2 mmoles) in polyphosphoric acid (0.8 g) was heated at 158°C for 70 minutes. After cooling, water (10 ml) was added. The solution was made alkaline with a solution of 25% sodium hydroxide (10 ml). The mixture was filtered. The filtrate was acidified with glacial acetic acid and left to stand overnight. The precipitate was filtered, purified by chromatography on small column (silica gel) using chloroform as eluent. The desired compound was crystallized from methanol to give 152 mg (25%) of **10a**; m. p. 222-225°C; NMR (DMSO-d₆): 8.24 (s, 1H, H₄ imidazole), 8.12 (d, 1H, H₅ quinoline,

$J_{5,7}=2.5$ Hz), 7.96 (d, 1H, H_8 quinoline, $J_{7,8}=9$ Hz), 7.73 (q, 1H, H_7 quinoline, $J_{7,8}=9$ Hz; $J_{5,7}=2.5$ Hz), 7.22 (s, 1H, H_3 quinoline) and 4.33 ppm (s, 3H, N- CH_3).

Anal. Calcd. for $C_{13}H_9ClN_4O_3$: C, 51.23; H, 2.96; N, 18.39. Found: C, 51.08; H, 2.83; N, 18.21.

Other 4-hydroxy-2-(1-methyl-5-nitro-2-imidazolyl)-6-(7, or 8-) substituted-quinolines were prepared similarly (Table 1).

4-Chloro-2-(1-methyl-5-nitro-2-imidazolyl)-6-methylquinoline (11)

A stirring mixture of compound 10b (284 mg, 1 mmole) and phosphorus oxychloride (2.5 ml) was heated in an oil bath at 110°C for 2 hours. The excess of phosphorus oxychloride was removed under reduced pressure. To the residue, water (5 ml) was added and neutralized with aqueous sodium hydroxide. The precipitate was filtered and crystallized from ethanol to give 284 mg (94%) of 11, m.p. 181-183°C; NMR ($CDCl_3$): 8.14 (s, 1H, H_4 imidazole), 8.13 (d, 1H, H_5 quinoline, $J_{5,7}=1.8$ Hz), 8.05 (d, 1H, H_8 quinoline, $J_{7,8}=8.6$ Hz), 7.65 (q, 1H, H_7 quinoline, $J_{7,8}=8.6$ Hz, $J_{5,7}=1.8$ Hz), 4.63 (s, 3H, N- CH_3) and 2.23 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{11}ClN_4O_2$: C, 55.54; H, 3.64; N, 18.51. Found: C, 55.63; H, 3.76; N, 18.35.

2-(1-Methyl-5-nitro-2-imidazolyl)-4-methylquinoline (14b)

A stirring solution of 2-acetyl-1-methyl-5-nitroimidazole (1.69 g, 0.01 mole) [3], 2-aminoacetophenone (1.35 g, 0.01 mole) in acetic acid (10 ml) and sulfuric acid (0.1 ml) was refluxed for 20 hours. After cooling, the mixture was added to crushed ice (30 g) and made alkaline with ammonia. The precipitate was crystallized from methanol to give 0.62 g (23%) of 14b, m. p. 169-171°C; NMR ($CDCl_3$): 8.15 (s, 1H, H_4 imidazole), 8.10-7.68 (m, 4H, aromatic), 7.26 (s, 1H, H_3), 4.38 (s, 3H, N- CH_3) and 2.79 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.69; H, 4.48; N, 20.90. Found: C, 62.85; H, 4.36; N, 20.80.

6-Chloro-2-(1-methyl-5-nitro-2-imidazolyl)-4-phenylquinoline (14e)

This compound was prepared from 2-amino-5-chlorobenzophenone and 2-acetyl-1-methyl-5-nitroimidazole similar to 14b in 29% yield, m. p. 198-

200°C; NMR ($CDCl_3$): 8.32 (s, 1H, H_4 imidazole), 8.15 (d, 1H, H_8 quinoline, $J_{7,8}=8.8$ Hz), 7.94 (d, 1H, H_5 quinoline, $J_{5,7}=2.2$ Hz), 7.70 (q, 1H, H_7 quinoline, $J_{7,8}=8.8$ Hz, $J_{5,7}=2.2$ Hz), 7.55 (s, 5H, phenyl) and 4.67 ppm (s, 3H, N- CH_3); ms: m/z (%) 365 (M^+ , 25), 335 (100), 305 (25), 264 (99), 238 (70), 230 (94), 203 (98), 172 (62), 142 (24) and 122 (42).

Anal. Calcd. for $C_{19}H_{14}ClN_4O_2$: C, 62.38; H, 3.83; N, 15.32. Found: C, 62.23; H, 3.71; N, 15.44.

Other 4-alkyl-(or aryl)-2-(1-methyl-5-nitro-2-imidazolyl)quinolines were prepared similarly (Table 1).

Acknowledgements

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