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Thermal cyclization of 3-arylamino-3-(2-nitrophenyl)-propenal Schiff base hydrochlorides followed by triethyl phosphite mediated deoxygenation: a facile synthesis of quindolines

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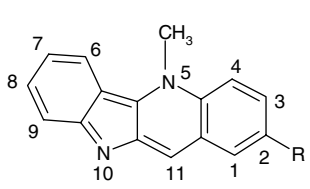
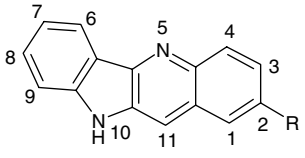
Abstract—A simple and useful method for the synthesis of various 2-substituted quindolines starting from 2-nitroacetophenone is described.

1. Introduction

Cryptolepine **1a** is an important indoloquinoline alkaloid found in *Cryptolepis sanguinolenta* (Lind.), a shrub used in traditional medicine for the treatment of malaria as well as for a number of other diseases[1–3] in central and west Africa.



1a (R=H), **1b** (R=CH_3)
1c (R=Br), **1d** (R=I)



2a (R=H), **2b** (R=CH_3)
2c (R=Br), **2d** (R=I)

Fichter and Boehringer first synthesized cryptolepine in 1906 before its isolation from natural sources.[4] Later on it was synthesized by various other groups,[5–8] of which the preparation by methylation of quindoline by Holt and Petrow (1947)[8a] deserves special mention. There are many synthetic methods available for the construction of tetracyclic indoloquinolines[8] and quindolines.[9]

To develop a general method for the synthesis of various 2-substituted cryptolepines **1**, we undertook the preparation of 2-substituted quindolines **2** starting from 2-nitroacetophenone **3** (Scheme 1). Two important steps involved in the synthesis are: regioselective thermal cyclization of enaminoimine hydrochloride **5** and generation of a nitrene intermediate followed by insertion into a sp^2 C–H bond.

Thus, when 2-nitroacetophenone **3** was treated with $POCl_3$ in DMF, it underwent a Vilsmeier–Haack reaction to produce the β-chlorocinnamaldehyde **4**,[10] with the nitro group remaining intact. The chloroaldehyde **4** upon reaction with 2.2 equiv of aniline in 2 N ethanolic HCl at 0 °C produced the corresponding enaminoimine hydrochloride **5a** in very good yield. Thermal cyclization of **5a** at 200–250 °C produced 2-(2-nitrophenyl)quinoline **6a** as the major isolable product. The desired quindoline **2a** was synthesized by heating **6a** with triethyl phosphite (TEP) at 160 °C. This step involves intramolecular annulation through a nitrene intermediate.[9]

We also synthesized various 2-substituted quindolines **2b–d** following the above mentioned procedure.

The experimental results are summarized in Table 1. Cryptolepines **1a–d** could be obtained from quindolines **2a–d** by heating with methyl iodide in acetone in the presence of BaO and KOH.[5]

In conclusion we have developed a simple method for the synthesis of various 2-substituted quindolines from easily accessible starting materials.

Keywords: Quindoline; Cryptolepine.
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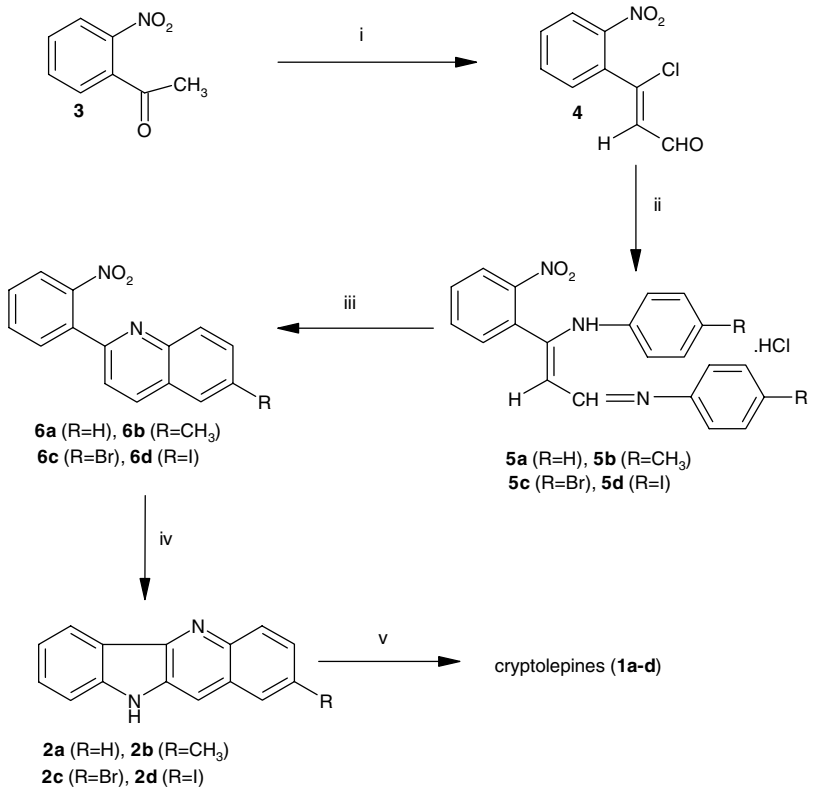

Scheme 1. Reagents and conditions: (i) $POCl_3$, DMF, 0 °C, 1 h then 80 °C, 4 h, 80%; (ii) 2 N ethanolic HCl, arylamine, 0 °C; (iii) heat, 200–250 °C, 5 min; (iv) $P(OEt)_3$, reflux, 4 h; (v) BaO, KOH, acetone, reflux, then CH_3I reflux, 4 h.

Table 1.

Entry	Yield of compound **5** (%)	Yield of compound **6** (%)	Yield of compound **2** (%)	Yield of compound **1** (%)
1	**5a** (92)	**6a** (40)	**2a** (70)	**1a** (71)
2	**5b** (88)	**6b** (37)	**2b** (75)	**1b** (70)
3	**5c** (91)	**6c** (41)	**2c** (68)	**1c** (65)
4	**5d** (90)	**6d** (35)	**2d** (72)	**1d** (73)

Typical experimental procedure for thermal cyclization of **5**: In a test tube the propenal Schiff base hydrochloride **5** was heated at 200–250 °C for 5 min in a preheated salt bath. In the cooler part of the test tube, arylamine hydrochloride was deposited. The residue at the bottom of the test tube was then cooled, washed with cold water and dissolved in benzene (**caution**: carcinogenic). The organic layer was washed well with water, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product **6** thus obtained was purified by column chromatography over silica gel using hexane–ethyl acetate (5:1) as eluent.

Typical experimental procedure for nitrene insertion: In a 5 mL round-bottomed flask, 2-(2-nitrophenyl)quinoline (0.4 mmol) was heated with triethyl phosphite (2 mL) for 4 h. The excess triethyl phosphite was removed by distillation and the crude product was purified by column chromatography over silica gel using hexane–ethyl acetate (3:1) as eluent.

2. Selected spectroscopic data

2.1. Compound 6b

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.54 (s, 3H), 7.45–7.59 (m, 4H), 7.63–7.67 (m, 2H), 7.93–7.96 (m, 2H), 8.10–8.14 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.59, 120.42, 124.39, 126.35, 127.16, 129.18, 131.54, 132.23, 132.55, 135.84, 136.08, 136.99, 146.51, 149.20, 154.53.

ESI MS for $C_{16}H_{12}N_2O_2$ [M], $[M+H]^+ = 265.09$.

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.54; N, 10.60. Found: C, 72.49; H, 4.51; N, 10.71.

2.2. Compound 2a

Yellow solid, mp 250–251 °C (lit.[7a] mp 249–251 °C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 11.39 (s, 1H, NH), 8.42 (d, 1H, $J = 8.4$ Hz), 8.29 (s, 1H), 8.19 (d, 1H,

$J = 8.4$ Hz), 7.99 (d, 1H, $J = 8.2$ Hz), 7.64–7.59 (m, 4H), 7.29 (dd, 1H, $J = 7.17$, 7.17 Hz); ^{13}C NMR (DMSO-d_6, 50 MHz): δ 148.92, 143.98, 142.35, 129.52, 128.44, 128.13, 126.11, 125.15, 123.32, 120.81, 119.69, 117.14, 116.65, 116.44, 115.50; ESI MS: for $C_{15}H_{10}N_2$ [M], $[M+H]^+ = 219.03$.

Acknowledgements

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