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1*H*-2-Phenylpyrrolo[3,2-*c*]quinoline (**1a**) is made by thermal cyclization of quinol-4-yl hydrazone. Subsequent substitution of the C-3 hydrogen atom of the pyrrole ring of **1a** with chlorine and a formyl group is easily achieved by reacting **1a** with trichloroacetyl chloride and phosphorus oxychloride in DMF, respectively.

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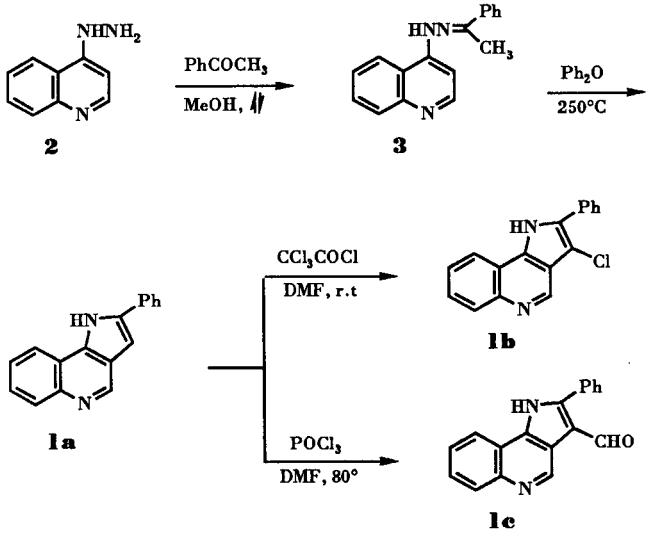
1*H*-Pyrrolo[3,2-*c*]quinolines are of medicinal interest [1,2]. Though syntheses of the ring system have appeared in the literature [2-7], derivatization of the pyrrole ring of pyrrolo[3,2-*c*]quinoline by electrophilic substitution is reported to be difficult [2]. In this communication, we wish to present our results on the synthesis of 1*H*-2-phenylpyrrolo[3,2-*c*]quinoline (**1a**) and facile replacement of the C-3 hydrogen of the pyrrole ring of **1a** by chlorine or a formyl group.

1*H*-2-Phenylpyrrolo[3,2-*c*]quinoline (**1a**) was prepared employing the Fischer indole cyclization method (Scheme 1) [5,6]: thermal cyclization of quinol-4-yl hydrazone **3** in diphenyl ether at 250° afforded **1a** in 70% yield.

Scheme 1

Synthesis of 1*H*-Pyrrolo[3,2-*c*]quinoline and its Derivatization



In the hope of derivatizing the 5-membered ring of **1a** by electrophilic substitution several procedures were applied. Based on the report [8] that the pyrrole nucleus is trichloroacetylated in good yield using trichloroacetyl chloride, a mixture of **1a** and trichloroacetyl chloride was heated in THF in the presence of potassium carbonate or in diglyme, resulting in no reaction. However, reaction of **1a** with trichloroacetyl chloride in DMF at room temperature resulted in 3-chlorination of the pyrrole nucleus of **1a** in excellent yield. This chlorination of the pyrrole nucleus of **1a** with trichloroacetyl chloride/DMF is remarkable in terms of cleanness of the reaction and easy isolation: to our knowledge, chlorination with trichloroacetyl chloride/DMF is unprecedented.

In contrast to a report of failure of the Vilsmeier formylation of 8-methoxy-4-methyl-1-(2-methylphenyl)pyrrolo[3,2-*c*]quinoline [2], the formylation of the pyrrole ring of **1a** to afford **1c** was easily accomplished by reaction with phosphoryl chloride/DMF at 80° followed by hydrolysis at 0°.

The mechanism of chlorination of **1a** with trichloroacetyl chloride/DMF and the applicability of this electrophilic chlorination to other electron-rich systems as well as the synthesis of other substituted 1*H*-pyrrolo[3,2-*c*]quinolines are under investigation.

EXPERIMENTAL

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded at 200 or 250 MHz with TMS as an internal standard. Mass spectral and elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. Compound **2** was prepared according to the method described previously [6].

Acetophenone Quinol-4-ylhydrazone (**3**).

A solution of 4.7 g (30 mmoles) of **2** and 4.0 g (33 mmoles) of acetophenone in 100 ml of methanol was heated to reflux for 22 hours under nitrogen atmosphere and light protection (compound **2** is light-sensitive). After the solvent was evaporated, the yellow solid was triturated with ether and recrystallized from chloroform/petroleum ether to yield 6.1 g (77%) of **3**, mp 189-190°; ^{1}H nmr (DMSO-d_6): δ 8.73 (broad s, 1H), 8.29 (broad s, 1H, NH), 8.07 (d, 1H, J = 8 Hz), 7.9-7.8 (m, 3H), 7.75-7.65 (m, 1H) 7.55-7.4 (m, 5H) and 2.43 (s, 3H).

Anal. Calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 77.86; H, 5.70; N, 15.94.

1*H*-2-Phenylpyrrolo[3,2-*c*]quinoline (**1a**).

To 20 ml of diphenyl ether was added 5.22 g (20 mmoles) of **3** and the mixture was heated at 250° in an oil bath for 6 hours. After cooling, ether was added until the solution became cloudy. Further cooling resulted in the precipitation of the product, which was collected, washed with ether and further purified by column chromatography (silica gel-ethyl acetate) to afford 3.43 g

(70%) of **1a**, mp 289-290°; ^{1}H nmr (DMSO-d_6): δ 12.55 (broad s, 1H), 9.11 (s, 1H), 8.67-8.60 (m, 1H), 8.08-7.99 (m, 3H), 7.68-7.50 (m, 4H), 7.42-7.35 (m, 1H), and 7.23 (s, 1H).

Anal. Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.98; N, 11.47. Found: C, 83.22; H, 5.03; N, 11.38.

1*H*-2-Phenyl-3-chloropyrrolo[3,2-*c*]quinoline (**1b**).

To 1 ml of dry DMF was added slowly 1.12 ml (10 mmoles) of trichloroacetyl chloride at room temperature. After 5 minutes a solution of 0.488 g (2 mmoles) of **1a** in 5 ml of DMF was added dropwise and the mixture was stirred at room temperature for 66 hours. Then tlc (silica gel-ethyl acetate) showed that the reaction was almost complete. The reaction mixture was added to 5 ml of ice water and neutralized with cold 1 *N* sodium hydroxide. The precipitate was collected, washed with water and recrystallized from methanol to afford 0.46 g (83%) of analytically pure **1b**, mp 299-300°; ^{1}H nmr (DMSO-d_6): δ 12.91 (broad s, 1H), 9.08 (s, 1H), 8.62-8.58 (m, 1H), 8.13-8.09 (m, 1H), 7.99-7.95 (m, 2H), 7.72-7.59 (m, 4H), and 7.53-7.47 (m, 1H); ms: m/e (relative intensity) 280 (32), 278 (M^+, 100), 243 (M^+-Cl, 10), 242 (M^+-HCl, 12).

Anal. Calcd. for $C_{17}H_{11}N_2Cl$: C, 73.25; H, 3.98; N, 10.05. Found: C, 73.20; H, 3.81; N, 9.95.

1*H*-2-Phenyl-3-formylpyrrolo[3,2-*c*]quinoline (**1c**).

To 1.5 ml of dry DMF was added slowly 0.93 ml (10 mmoles) of phosphorus oxychloride at room temperature. After 5 minutes, a solution of 0.488 g (2 mmoles) of **1a** in 5 ml of DMF was added and the resulting solution was heated at 80° for 24 hours. After cooling the solution was poured into 75 ml of ice water and neutralized with 1 *N* cold sodium hydroxide. The precipitate was collected and suspended in 25 ml of 1:1 methanol-water and heated to reflux for 30 minutes. Filtration of this while hot yielded 0.44 g (81%) of **1c**, mp 275-276°; ^{1}H nmr (DMSO-d_6): δ 13.38 (broad s, 1H), 10.07 (s, 1H), 9.65 (s, 1H), 8.61-8.57 (m, 1H), 8.15-8.11 (m, 1H), 7.92-7.88 (m, 2H), and 7.76-7.61 (m, 5H).

Anal. Calcd. for $C_{18}H_{12}N_2O$: C, 79.40; H, 4.44; N, 10.29. Found: C, 79.28; H, 4.27; N, 9.97.

REFERENCE AND NOTES

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