

Short Note

***N*-[2-Chloro-6-methylquinolin-3-yl)methyl]aniline**

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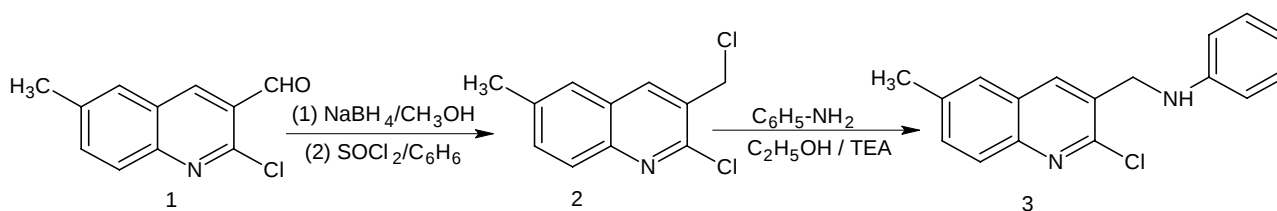
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1. Introduction

Quinoliny amines are important organic compounds which possess a variety of pharmacological activities such as antimalarial, antifungal, hypotensive and antidepressant activity [1-4]. From the various conditions adopted for the synthesis of secondary amines reported in the literature, synthesis *via* nucleophilic substitution is still an important method [5]. As a part of our research programme on quinoline derivatives [6], we report herein the synthesis of *N*-[2-chloro-6-methylquinolin-3-yl)methyl]aniline (Figure 1) by nucleophilic substitution of 2-chloro-3-(chloromethyl)-6-methylquinoline with aniline in absolute ethanol in the presence of triethylamine (TEA) as base.

Figure 1. Synthetic route to the title compound 3.



2. Experimental and Section

The starting material, 2-chloro-3-formyl-6-methylquinoline (**1**), was synthesized by the literature method [7] and it was reduced to 2-chloro-3-(hydroxymethyl)-6-methylquinoline [8] with NaBH₄ in methanol.

2.1. 2-Chloro-3-(chloromethyl)-6-methylquinoline **2**

To a solution of 2-chloro-3-(hydroxymethyl)-6-methylquinoline (0.01 mol, 2.07 g) in dry benzene (30 mL), SOCl₂ (0.013 mol, 1.54 g) was added and the mixture was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in ether, washed with sodium bicarbonate solution (10%, 25 mL) and twice with water (25 mL), dried over sodium sulphate and concentrated *in vacuo* to give a residue which was crystallized from methanol. Yield, 85%; mp 140 °C, light brown colored crystals. ¹H-NMR (300 MHz, CDCl₃) δ: 2.53 (s, 3H, CH₃), 4.87 (s, 2H, CH₂), 7.55-7.57 (m, 2H, H-5 and H-7), 7.92 (d, 1H, H-8, *J* = 7.5 Hz), 8.17 (s, 1H, H-4). ¹³C-NMR (CDCl₃, 75 MHz) δ: 21.48 (CH₃), 43.17 (CH₂), 125.91, 127.12, 127.93, 129.06, 135.76, 141.13, 147.16, 149.31. FAB-MS: 226 (M)⁺, 227 (M+1)⁺, 228 (M+2)⁺, 190 (M-HCl)⁺. Anal. Calcd for C₁₁H₉Cl₂N: C, 58.43; H, 4.01; N, 6.19. Found: C, 58.30; H, 4.03; N, 6.22%.

2.2. *N*-[(2-Chloro-6-methylquinolin-3-yl)methyl]aniline **3**

To a solution of compound **2** (0.01 mol, 2.26 g) and aniline (0.01 mol, 0.93 g) in 30 mL of absolute ethanol, 1 mL of triethylamine (TEA) was added and the mixture was refluxed for 13 h. The contents of the flask were reduced to half of its volume and left overnight. The crystalline mass obtained was filtered, washed with water, dried and recrystallized from ethanol. Yield, 78%; mp 175-176 °C, yellow crystals. ¹H-NMR (300 MHz, CDCl₃) δ: 2.51 (s, 3H, CH₃), 4.20 (s, 1H, NH, D₂O-exchangeable), 4.59 (s, 2H, CH₂), 6.67 (d, 2H, H-2' and H-6', *J* = 7.3 Hz), 6.77 (t, 1H, H-4', *J* = 7.1 Hz), 7.14-7.19 (m, 2H, H-3' and H-5'), 7.53-7.55 (m, 2H, H-5 and H-7), 7.92 (d, 1H, H-8, *J* = 7.8 Hz), 8.09 (s, 1H, H-4). ¹³C-NMR (75 MHz, CDCl₃) δ: 18.97 (CH₃), 46.15 (CH₂), 112.52, 117.03, 126.99, 127.47, 128.22, 130.02, 132.71, 136.49, 143.05, 147.17, 148.19. FAB-MS *m/z*: 283 (M)⁺, 285 (M+2)⁺, 190 (C₁₁H₈ClN⁺). Anal. Calcd for C₁₇H₁₅ClN₂: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.38; H, 5.33; N, 9.96 %.

3. Conclusions

2-Chloro-3-formyl-6-methylquinoline **1** *via* its reduction with solid sodium borohydride in methanol afforded 2-chloro-3-(hydroxymethyl)-6-methylquinoline **2** which on subsequent chlorination with thionyl chloride in dry benzene gave 2-chloro-3-(chloromethyl)-6-methylquinoline **3** as buff colored crystalline solid. The title compound was prepared by refluxing equimolar amounts of compound **2** and aniline in absolute ethanol in the presence of triethylamine in excellent yield. Compounds **2** and **3** were characterized by combined use of FT-IR, ¹H NMR and ¹³C-NMR (Bruker-300 MHz) and mass spectrometry (FAB-MS). In the ¹H-NMR spectrum of compound **2**, the signal due

to CH₂Cl was observed as singlet integrating for two protons at 4.87 ppm. These methylene protons underwent slight diamagnetic shift to 4.59 ppm on substitution with the amino group of aniline in compound **3**. Similarly, in the ¹³C-NMR spectrum of compound **2** the carbon of the CH₂Cl group resonated at 43.17 ppm and underwent a slight paramagnetic shift to 46.15 ppm in compound **3** on substitution. The FAB-MS spectrum of compound **3** showed the molecular ion peak at m/z 283 and an isotopic peak at m/z 285 (M+2) and a fragment peak at m/z 190 of C₁₁H₈CIN⁺.

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Sample Availability: Sample of compound **3** is available from the authors.