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Synthesis of 9*H*-Indeno [1, 2-*b*] Pyrazine and 11*H*-Indeno [1, 2-*b*] Quinoxaline Derivatives in One-step Reaction from 2-Bromo-4-chloro-1-indanone

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ABSTRACT

The reaction of 2-bromo-4-chloro-1-indanone with 2,3-diaminomaleonitrile, benzene-1,2-diamine and 4-methylbenzene-1,2-diamine in glacial acetic acid gave 8-chloro-9*H*-indeno[1,2-*b*]pyrazine-2,3-dicarbonitrile, 1-chloro-11*H*-indeno[1,2-*b*]quinoxaline and 1-chloro-7-methyl-11*H*-indeno[1,2-*b*]quinoxaline, respectively, in good yield.

KEYWORDS

2-bromo-4-chloro-1-indanone, diaminopyridine, indeno[1,2-*b*]quinoxaline, indeno[1,2-*b*]pyrazine, debromination.

Introduction

Quinoxaline derivatives are an important class of benzo-heterocycles which have received much attention in recent years owing to both their biological properties and pharmaceutical applications, including antimicrobial[1–5] and anticancer[6–12] properties. Several methods used to synthesize quinoxaline and pyrazine derivatives via α-hydroxy carbonyl,[13] and dicarbonyl compounds[14,15] have been reported. Horiuchi and coworkers reported that when α-halo ketones were reacted with 7 % NH_3 solution, under microwave conditions, pyrazine derivatives, α-hydroxyl ketones and debrominated ketones were formed.[16] Kubota and coworkers studied the reaction of 2, 3-diamino-maleonitrile with diones in the presence of oxalic acid in benzene under reflux condition.[17] The synthesis and study of the stability of the quinoxaline derivative, fluoflavine, by a new and highly efficient methodology has been reported.[18] In a previous paper,[19] we have reported an improved synthesis of 4-chloro-1-indanone in four steps from 2-chlorobenzaldehyde and its selective bromination. In this work we utilized 2-bromo-4-chloro-1-indanone as a new candidate for the synthesis of quinoxaline derivatives.

Results and Discussion

Following our previous work,[19] the reaction between 2-bromo-4-chloro-1-indanone **1** and some diamines under acidic conditions was investigated. The reaction of **1** with 2,3-diaminomaleonitrile **2** gave 8-chloro-9*H*-indeno[1,2-*b*]pyrazine-2,3-dicarbonitrile **3** in 37 % yield (Scheme 1).

The reaction of benzene-1,2-diamine (**4a)** and 4-methylbenzene-1,2-diamine (**4b)** with **1,** in glacial acetic acid, gave 1-chloro-11*H*-indeno[1,2-*b*]quinoxaline **(5)** and 1-chloro-7-methyl-11*H*-indeno[1,2-*b*]quinoxaline (**6)** in 77 % and 91 % yield, respectively (Scheme 2). Unfortunately, the debrominated, 1-indanone (**8**), was produced in high yield from the reaction of **1** with diaminopyridines (Scheme 3).

When **1** was reacted with aniline or toluidine under the same conditions, again the debrominated product **8** was formed. This compound was also obtained to the extent of 5 % after 48 h in the absence of any amine or base. In addition, the above reagents in the presence of sodium acetate as catalyst gave a mixture of debrominated product (45 %) and 2-acetoxy derivative in 55 % yield (Scheme 4**)**.

In conclusion, we found that the presence of the electron-donating methyl group in **4b** accelerated the reaction in comparison with that of **4a**. The cyano groups in **2**, because of their electron-withdrawing effect on the amino groups, reduced the rate of reaction and yield, in spite of the long reaction times. With further electron withdrawal, as in **7a** and **7b**, no pyridopyrazine products were obtained, and debromination by nucleophilic reaction at the bromo group became the major pathway.

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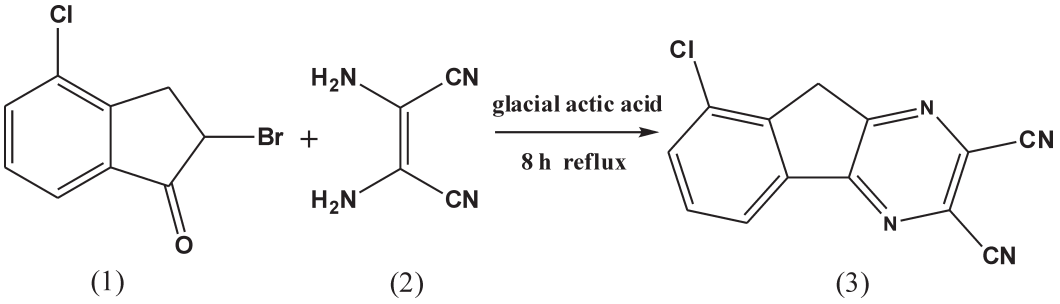
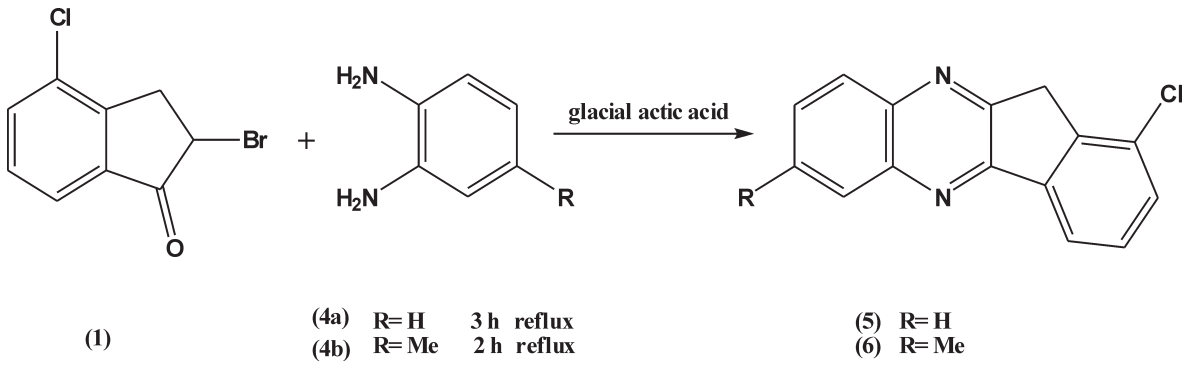
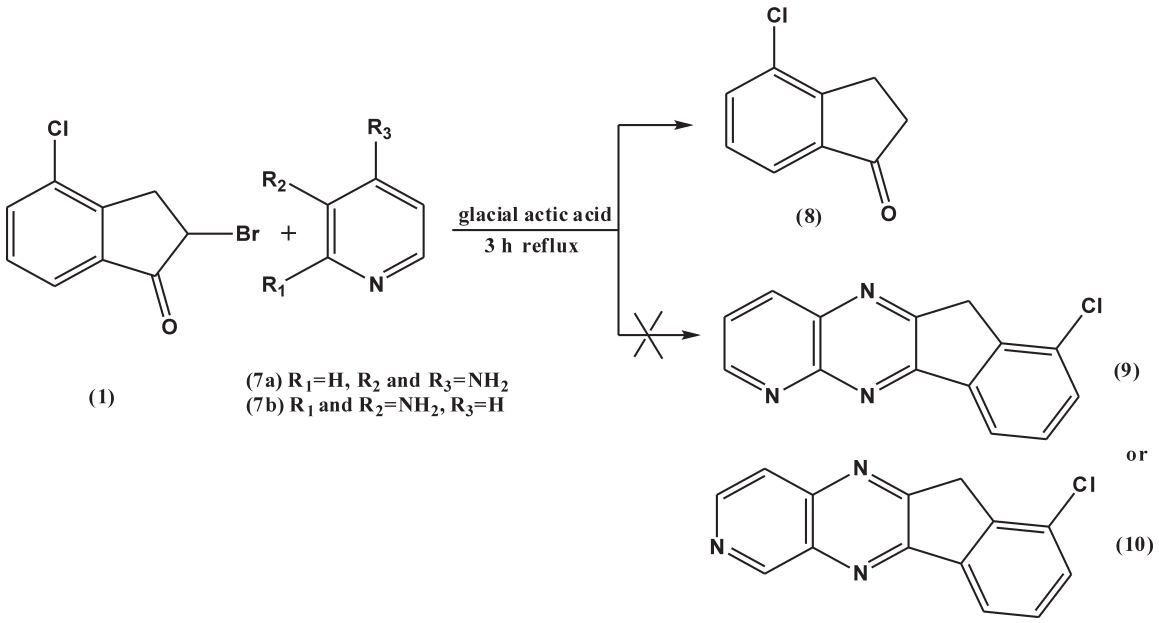


(1) (2) (3)

Scheme 1



Scheme 2



Scheme 3

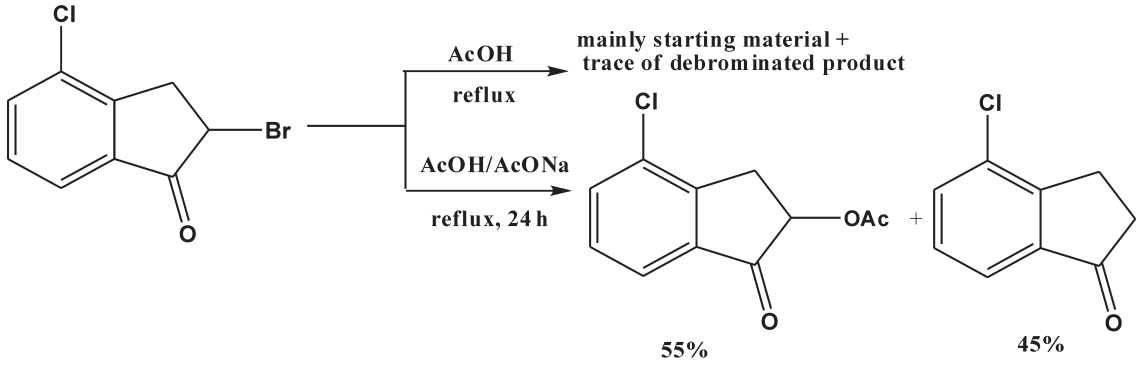
Experimental

8-Chloro-9H-indeno [1,2-b]pyrazine-2,3-dicarbonitrile **3**. A mixture of 2-bromo-4-chloro-1-indanone[19] **1** (152 mg, 0.62 mmol) and 2,3-diaminomaleonitrile **2** (70 mg, 0.64 mmol) was heated at reflux in AcOH (10 mL) for 8 h. The reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2. The extract was dried and evaporated to give compound **3** (57 mg, 37 %) as a dark yellow to brown powder, decomp. 180 °C.

δ_H (300 MHz, $CDCl_3$): 4.28 (2H, s, CH_2); 7.49 (1H, t, *J* 7.8, Ar) ; 7.73 (1H, d, *J* 7.8, Ar); 7.87 (1H, d, *J* 7.8 Hz, Ar); δ_C (75 MHz, $CDCl_3$): 31.19, 116.16, 116.18, 120.56, 123.48, 124.77, 130.24, 130.45, 135.94, 151.97, 153.25, 161.32, 163.89; ν_{max} (KBr): 2236, 1572, 1509, 1444, 1338, 1133, 855, 739, 580 cm^{-1} (Found: C, 61.45; H, 2.05; N, 22.29 %. Calc. for $C_{13}H_5ClN_4$ (252.02); C, 61.80; H, 1.99; N, 22.17 %).

1-Chloro-11H-indeno[1,2-b]quinoxaline **5.** A mixture of 2-bromo-4-chloro-1-indanone **1** (152 mg, 0.62 mmol) and benzene-1,2-diamine **4a** (69 mg, 0.64 mmol) was heated at reflux in AcOH (10 mL) for 6 h. The reaction mixture was poured into water (30 mL) and the precipitated product was collected and washed with water, giving **5** (120 mg, 77 %) as a brown powder, mp 168–170 °C.

δ_H (300 MHz, $CDCl_3$): 4.14 (2H, s, CH_2); 7.47-7.56 (2H, m, Ar);



Scheme 4

7.73-7.78 (2H, m, Ar); 8.11-8.20 (3H, m, Ar); δ_C (75 MHz, $CDCl_3$): 35.47, 120.96, 129.09, 129.20, 129.28, 129.52, 129.58, 130.91, 131.95, 139.13, 141.52, 141.60, 158.47; ν_{max} (KBr): 1568, 1504, 1460, 1388, 1332, 1116, 852, 785, 734 cm^{-1}. (Found: C, 71.43; H, 3.52, N, 11.21 %. Calc. for $C_{15}H_9ClN_2$ (252.05); C, 71.29; H, 3.59; N, 11.09 %).

1-Chloro-7-methyl-11H-indeno[1,2-b]quinoxaline **6.** A mixture of 2-bromo-4-chloro-1-indanone **1** (152 mg, 0.62 mmol) and 4-methylbenzene-1,2-diamine **4b** (78 mg, 0.64 mmol) was heated at reflux in AcOH (10 mL) for 2 h. The reaction mixture was poured into water (30 mL) and the precipitated product was collected and washed with water, giving **6** (150 mg, 91 %) as a light brown powder, mp 174–176 °C.

δ_H (300 MHz, $CDCl_3$): 2.61 (3H, s, CH_3); 4.09 (2H, s, CH_2); 7.45-7.59 (3H, m, Ar); 7.86 (1H, s, Ar); 7.95-8.17 (2H, m, Ar); δ_C (75 MHz, $CDCl_3$): 21.75, 35.47, 120.96, 129.09, 129.20, 129.28, 129.52, 129.58, 130.91, 131.95, 139.13, 141.52, 141.60, 158.47; ν_{max} (KBr): 2917, 1564, 1504, 1462, 1329, 1122, 1033, 829, 736, 580 cm^{-1}. (Found: C, 72.24; H, 4.23; N, 10.38 %. Calc. for $C_{16}H_{11}ClN_2$ (266.06); C, 72.05; H, 4.16; N, 10.50 %).

Identification of products

^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker spectrometer. Chemical shifts (δ) are in parts per million (ppm) relative to TMS, and coupling constants (J) are given in Hertz. Infrared spectra were recorded on a Bruker FT-IR spectrometer using KBr disks. Melting points were determined on a Philips Harris C4954718 apparatus. Microanalyses were performed on a Leco Analyzer 932. Analytical thin-layer chromatography (TLC) was carried out with Merck silica gel 60 F_{254} aluminum sheets.

The routine purification of reagents and solutions was carried out by standard laboratory procedures. All organic extracts were dried with anhydrous sodium sulphate.

Acknowledgements

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