Synthesis of 9H-Indeno [1, 2-b] Pyrazine and 11H-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-9H-indeno[1,2-b]pyrazine-2,3-dicarbonitrile, 1-chloro-11H-indeno[1,2-b]quinoxaline and 1-chloro-7-methyl-11H-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 antimicrobial1–5 and anticancer6–12 properties. Several methods used to synthesize quinoxaline and pyrazine derivatives via α-hydroxy carbonyl13 and dicarbonyl compounds14,15 have been reported. Horiuchi and coworkers reported that when α-halo ketones were reacted with 7% NH3 solution, under microwave conditions, pyrazine derivatives, α-hydroxyl ketones and debrominated ketones were formed.16 Kubota and coworkers studied the reaction of 2, 3-diaminomaleonitrile 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-9H-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-11H-indeno[1,2-b]quinoxaline (5) and 1-chloro-7-methyl-11H-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.

Scheme 1

[Diagram showing the reaction scheme]
Experimental

8-Chloro-9H-indeno[1,2-b]pyrazine-2,3-dicarbonitrile 3. A mixture of 2-bromo-4-chloro-1-indanone 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$_2$Cl$_2$. 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$_5$ClN$_4$ (252.02); C, 61.80; H, 1.99; N, 22.17 %).

1-Chloro-11H-indeno[1,2-b]quinazoline 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); 8-Chloro-9H-indeno[1,2-b]pyrazine-2,3-dicarbonitrile 3. A mixture of 2-bromo-4-chloro-1-indanone 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$_2$Cl$_2$. 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$_5$ClN$_4$ (252.02); C, 61.80; H, 1.99; N, 22.17 %).
7.73-7.78 (2H, m, Ar); 8.11-8.20 (3H, m, Ar); δ (75 MHz, CDCl3): 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; νmax (KBr): 1568, 1504, 1460, 1388, 1332, 1116, 852, 785, 734 cm–1. (Found: C, 71.43; H, 3.52, N, 11.21 %. Calc. for C15H9ClN2 (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.

δH (300 MHz, CDCl3): 2.61 (3H, s, CH3); 4.09 (2H, s, CH2); 7.45-7.59 (3H, m, Ar); 7.86 (1H, s, Ar); 7.95-8.17 (2H, m, Ar); δC (75 MHz, CDCl3): 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; νmax (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 C16H11ClN2 (266.06); C, 72.05; H, 4.16; N, 10.50 %).

Identification of products

1H-NMR (300 MHz) and 13C-NMR (75 MHz) spectra were recorded in CDCl3 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 F254 λ 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.

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References

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