Iodine-Mediated Efficient Synthesis of 2,3-Dihydro-pyrazines

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Abstract. The synthesis of 2,3-dihydro-pyrazines has been developed by an efficient protocol of annulations of 1,2-diketones and ethylenediamine. A variety of 2,3-dihydro-pyrazines were prepared in high yields in the presence of a catalytic amount of iodine.

Introduction

The synthesis of heterocycles has been received much attention owing to the biological activity of heterocycles [1]. As ones of important N-heterocycles, 2,3-dihydro-pyrazines have shown some significant biological activities, such as DNA strand-breakage activity [2], antibacterial [3], apoptosis induction [4], cytotoxicity [5], and inhibition of enzyme activity [6].

Experimental methodology

To a stirred solution of benzil 1a (2.1 mg, 0.1 mmol) and ethylenediamine (6.2 μl, 0.15 mmol) in CH3CN (1.0 mL) was added I₂ (2.5 mg, 0.01 mmol). The solution was stirred at 60 °C in the air until all the starting material was consumed. The mixture was cooled to room temperature. After evaporation of the solvent, the residue was purified by preparative thin-layer chromatography on silica gel with PE/EtOAc (10/1) as an eluent to give the white solid 5,6-diphenyl-2,3-dihydro-pyrazine (2a), 22.5 mg, 96% yield.

To a stirred solution of 1-phenyl-2-(p-tolyl)ethane-1,2-dione 1b (2.2 mg, 0.1 mmol) and ethylenediamine (6.2 μl, 0.15 mmol) in CH3CN (1.0 mL) was added I₂ (2.5 mg, 0.01 mmol). The solution was stirred at 60 °C in the air until all the starting material was consumed. The mixture was cooled to room temperature. After evaporation of the solvent, the residue was purified by preparative thin-layer chromatography on silica gel with PE/EtOAc (10/1) as an eluent to give the white solid 6-phenyl-2,3-dihydro-pyrazine (2b), 21.4 mg, 86% yield.

To a stirred solution of 1-(4-methoxyphenyl)-2-phenylethane-1,2-dione 1c (2.4 mg, 0.1 mmol) and ethylenediamine (6.2 μl, 0.15 mmol) in CH3CN (1.0 mL) was added I₂ (2.5 mg, 0.01 mmol). The solution was stirred at 60 °C in the air until all the starting material was consumed. The mixture was cooled to room temperature. After evaporation of the solvent, the residue was purified by preparative thin-layer chromatography on silica gel with PE/EtOAc (10/1) as an eluent to give the white solid 5-(4-Methoxylphenyl)-6-phenyl-2,3-dihydro-pyrazine (2c), 23.8 mg, 90% yield.

5,6-Diphenyl-2,3-dihydro-pyrazine (2a). White solid, 22.5 mg (96% yield); mp 155-156 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.38 (m, 4H), 7.34-7.29 (m, 2H), 7.27-7.22 (m, 4H), 3.70 (s, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 45.92, 128.00, 128.23, 129.75, 137.85, 160.41. Data consistent with literature values.[2]
5-Phenyl-6-(p-tolyl)-2,3-dihydro-pyrazine (2b). White solid, 21.4 mg (86% yield); mp 115-116 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42-7.38 (m, 2H), 7.34-7.22 (m, 5H), 7.05 (d, $J = 8.0$ Hz, 2H), 3.68 (s, 4H), 2.30 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.48, 45.84, 45.95, 127.99, 128.00, 128.22, 128.93, 129.68, 135.00, 138.07, 139.92, 160.19, 160.55. HRMS (ESI) calcd for C$_{17}$H$_{17}$N$_2$ (M+H)$^+$, 249.1392, found 249.1389.

5-(4-Methoxyphenyl)-6-phenyl-2,3-dihydro-pyrazine (2c). White solid, 23.8 mg (90% yield); mp 93-94 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45-7.38 (m, 2H), 7.37-7.30 (m, 3H), 7.26 (t, $J = 7.3$ Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 3.77 (s, 3H), 3.67 (s, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 45.78, 46.00, 55.36, 113.59, 128.02, 128.25, 129.68, 129.70, 130.31, 138.25, 159.56, 160.56, 160.88. HRMS (ESI) calcd for C$_{17}$H$_{17}$N$_2$O (M+H)$^+$, 265.1341, found 265.1338.

Experimental Results (2a-2c)

1. $^1$H and $^{13}$C NMR Spectra of Compounds 2a

![NMR Spectra Image]
Fig. 1. $^1$H and $^{13}$C NMR spectra of compound 2a in CDCl$_3$

2. $^1$H and $^{13}$C NMR Spectra of Compounds 2b
Fig.2. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compound 2b in CDCl$_3$

3. $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of Compounds 2c
Conclusion

In conclusion, we developed an efficient iodine-mediated reaction for the synthesis of 2,3-dihydro-pyrazines. Various 2,3-dihydro-pyrazines were prepared in high yields by the annulations of 1,2-diketones and ethylenediamine in the presence of catalytic amount of iodine. A variety of functional groups were tolerated in the present reaction.

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Supplemental data for this article can be accessed on the publisher’s website.

References


