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

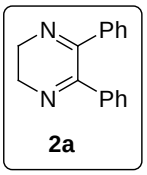
The synthesis of heterocycles has been received much attention owing to the biological activity of heterocycles [1]. As ones of important *N*-heterocycles, 2,3-dihydro-pyrazines have shown some significant biological activities, such as DNA strand-breakage activity [2], antibacterial [3], apoptosis induction [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 CH_3CN (1.0 mL) was added I_2 (2.5 mg, 0.01 mmol). The solution was stirred at 60 ^oC 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.

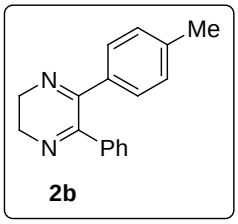
To a stirred solution of1-phenyl-2-(p-tolyl)ethane-1,2-dione **1b** (2.2 mg, 0.1 mmol) and ethylenediamine (6.2 μl , 0.15 mmol) in CH_3CN (1.0 mL) was added I_2 (2.5 mg, 0.01 mmol). The solution was stirred at 60 ^oC in the air until all the starting material was consumed. The mixture was cooled to room 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 henyl -6- (p- tolyl) -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 CH_3CN (1.0 mL) was added I_2 (2.5 mg, 0.01 mmol). The solution was stirred at 60 ^oC 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.



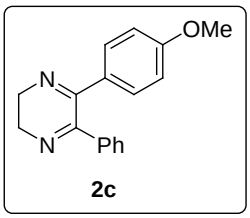
2a

5,6-Diphenyl-2,3-dihydro-pyrazine (2a). White solid, 22.5 mg (96% yield); mp 155-156 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 4H), 7.34-7.29 (m, 2H), 7.27-7.22 (m, 4H), 3.70 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.92, 128.00, 128.23, 129.75, 137.85, 160.41. Data consistent with literature values.[2]



2b

5-Phenyl-6-(p-tolyl)-2,3-dihydro-pyrazine (2b). White solid, 21.4 mg (86% yield); mp 115-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

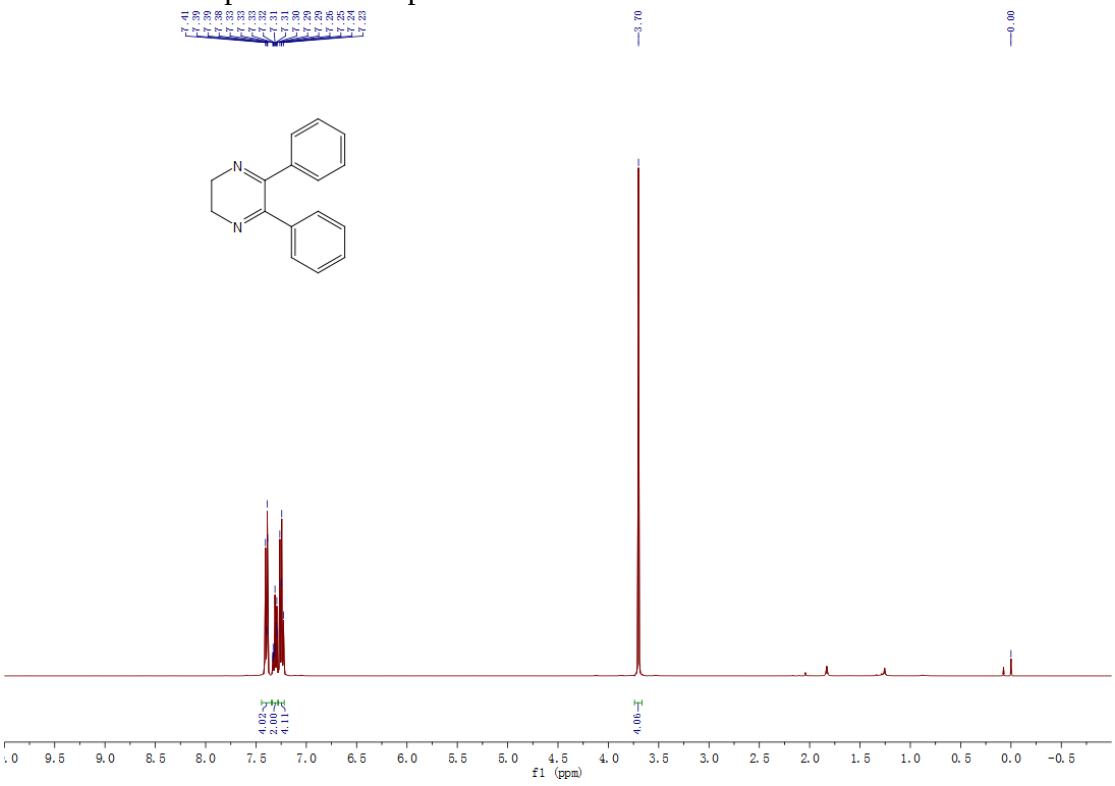


2c

5-(4-Methoxylphenyl)-6-phenyl-2,3-dihydro-pyrazine (2c). White solid, 23.8 mg (90% yield); mp 93-94 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{17}H_{17}N_2O$ $(M+H)^+$, 265.1341, found 265.1338.

Experimental Results (2a-2c)

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



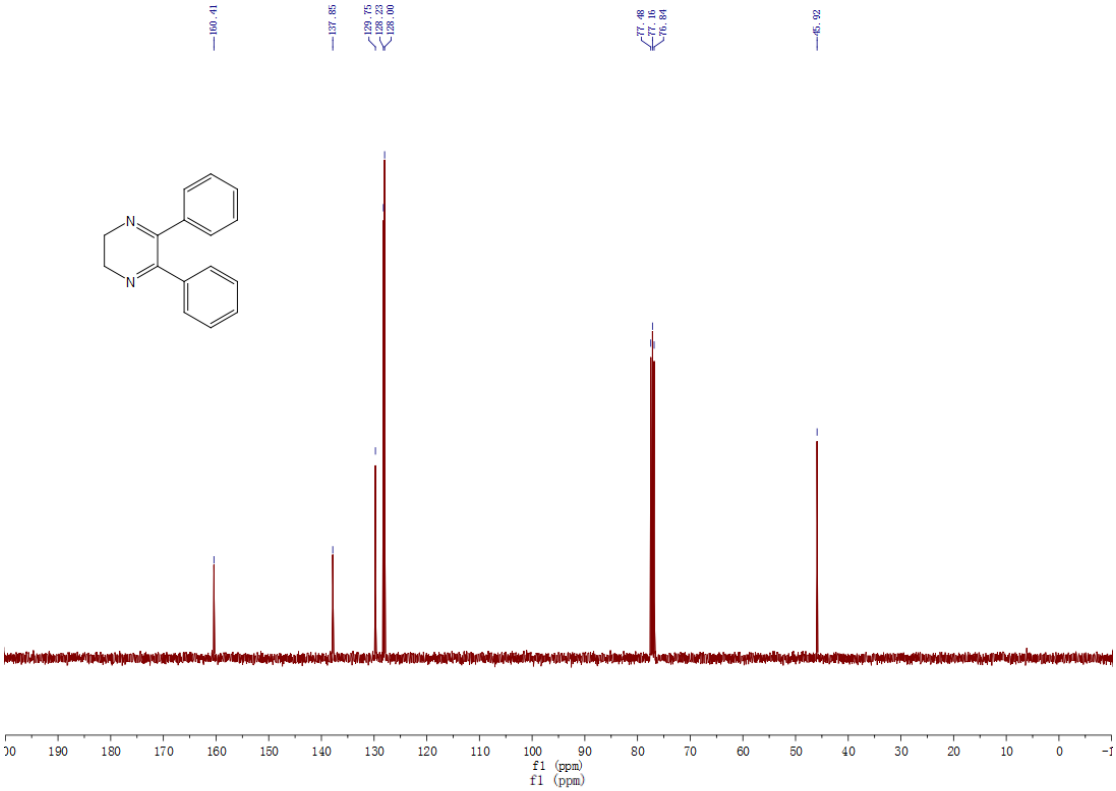
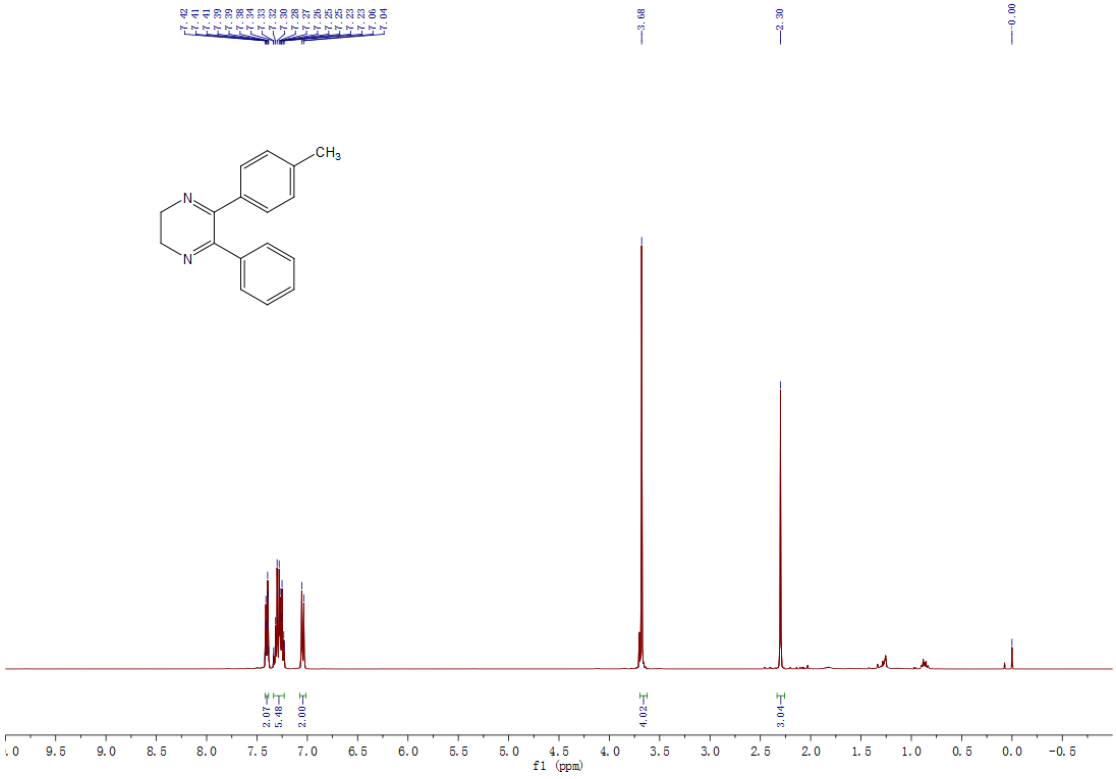


Fig.1. ^{1}H and ^{13}C NMR spectra of compound **2a** in $CDCl_3$

2. ^{1}H and ^{13}C NMR Spectra of Compounds **2b**



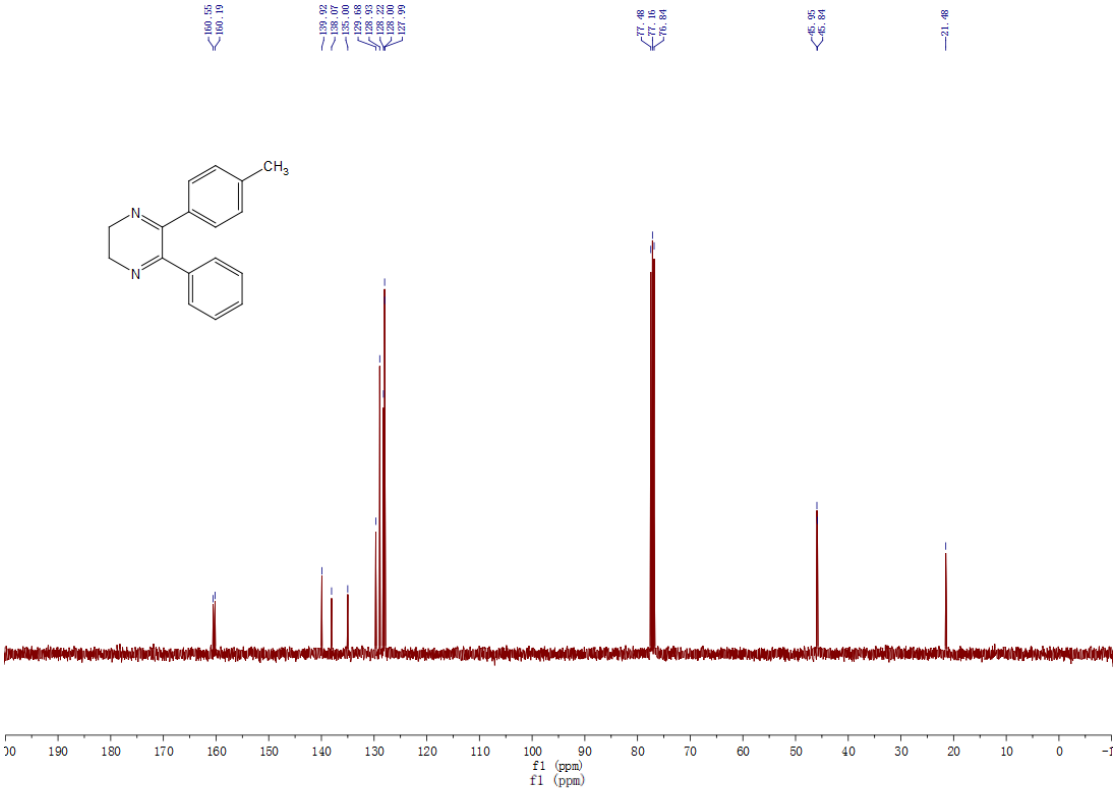
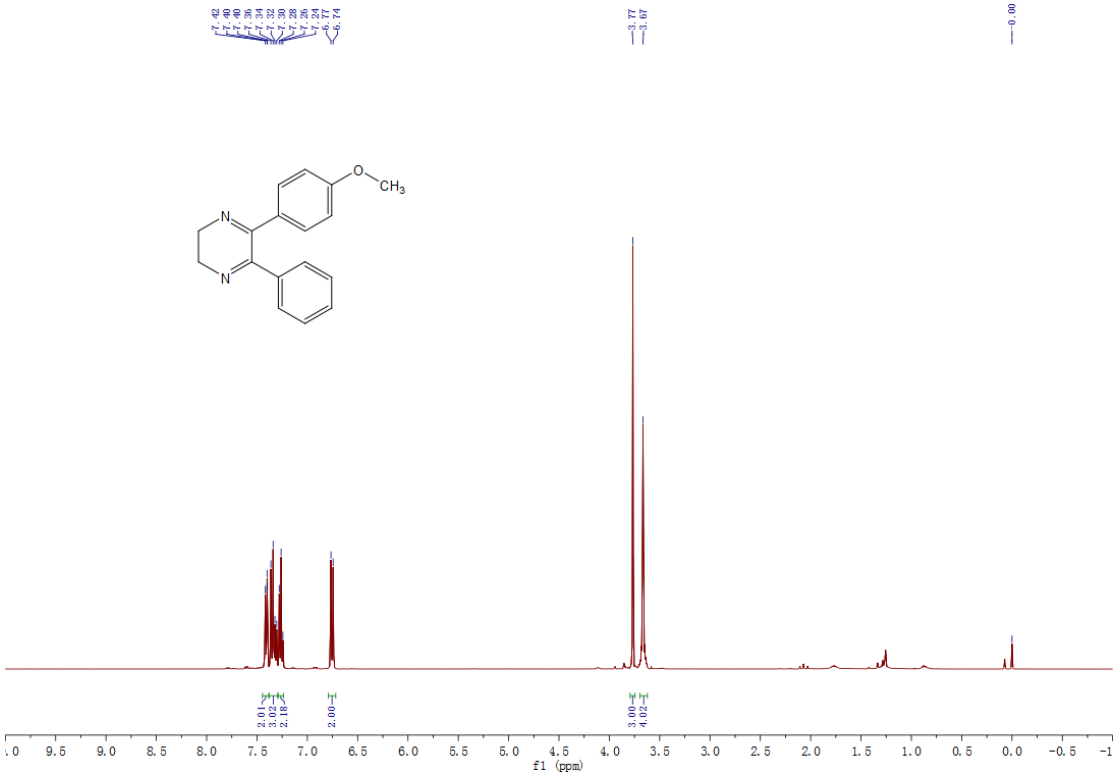


Fig.2. ^{1}H and ^{13}C NMR spectra of compound **2b** in $CDCl_3$

3. ^{1}H and ^{13}C NMR Spectra of Compounds **2c**



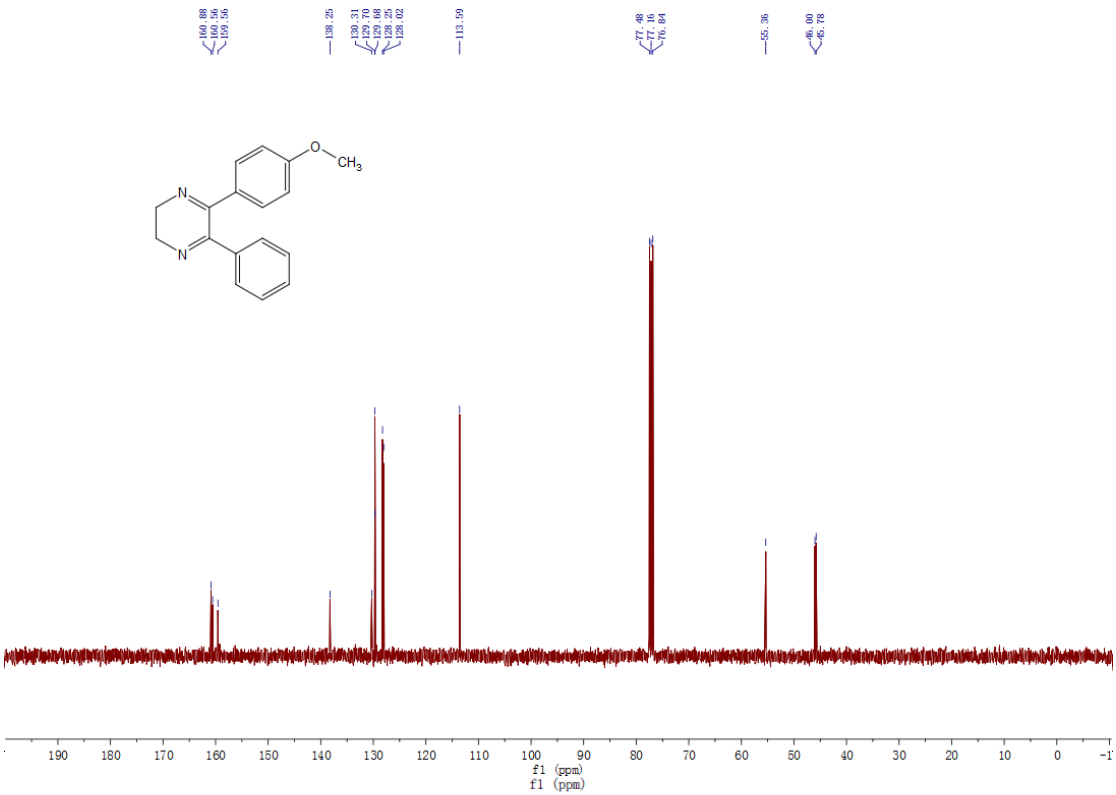


Fig.3. ^{1}H and ^{13}C NMR spectra of compound **2c** in $CDCl_3$

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.

Acknowledgement

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

References

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