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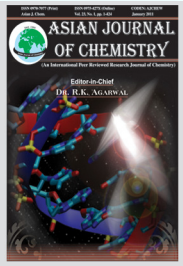

Synthesis of Quinoxalines in Presence of Zinc Triflate

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A simple and efficient method for the synthesis of quinoxaline derivatives has been developed. The reactions were carried out in presence of zinc triflate in acetonitrile reflux. The method is applicable to a variety of diketones and 1,2-phenylenediamines to afford the corresponding derivatives in excellent yields.

Key Words: Diketones, *ortho*-Phenylenediamines, Zinc triflate, Quinoxalines.

INTRODUCTION

Quinoxalines are a versatile class of nitrogen containing heterocyclic compounds and they constitute useful intermediates in organic synthesis. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antibacterial, antiviral, antiinflammatory, anticancer and kinase inhibitors[1-3]. In addition, quinoxaline derivatives have been evaluated as anthelmintic agents, semiconductors, dyes and biocides[4,5]. Therefore, a variety of synthetic strategies have been developed for the preparation of substituted quinoxalines. Conventionally, quinoxalines synthesis can beachieved by the reaction of *o*-phenylenediamine with two-carbon synthones such as α-dicarbonyls[6-11], α-halogeno carbonyls, α-hydroxy-carbonyls[12-14], α-azocarbonyls, epoxides and α,β-dihalides[15-19]. Among the reported procedures, the most common method is the condensation of an aryl 1,2-diamine with 1,2-diketone compounds in refluxing ethanol or acetic acid[20-25] or using different catalysts and reaction conditions[26-29]. However, many of these methods suffer from several drawbacks, such as drastic reaction conditions, use of polar solvents (*e.g.*, AcOH, EtOH, DMSO), expensive and toxic metal catalyst [*e.g.*, $Pd(OAc)_2$ and $RuCl_2(PPh_3)_3$-TEMPO], tedious work up procedures and unsatisfactory yields, which limit their use[30-35]. Therefore, the development of simple and improved method for the synthesis of quinoxalines derivatives would certainly be useful in generating combinatorial libraries for drug discovery.

EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectro meter operating at 70 eV.

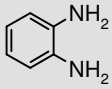
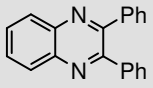
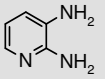
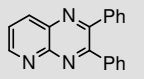
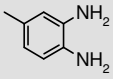
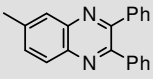
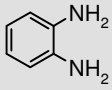
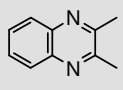
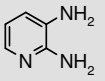
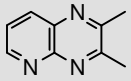
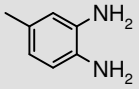
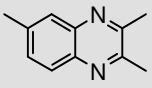
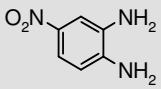
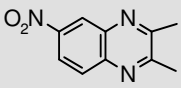
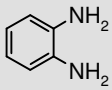
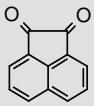
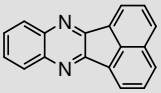
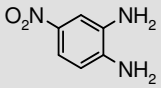
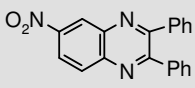
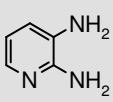
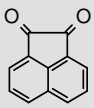
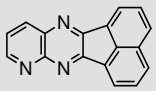
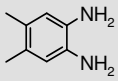
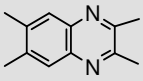
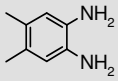
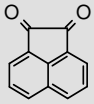
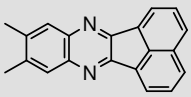
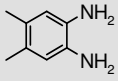
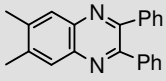
General procedure for the synthesis of quinoxalines: To a mixture of diketone (210 mg, 1.0 mmol) and diamine (128 mg, 1.1 mmol) in acetonitrile (5.0 mL) was added the catalyst zinc triflate (20 % mmol) at room temperature. The resulting reaction mixture was stirred at reflux condition for a period of 4-8 h (Table-1). The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, as indicated by TLC, the solvent was removed from the reaction mixture under reduced pressure. The residue was extracted with ethyl acetate (2 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude products, which were purified by column chromatography using silica-gel (60-120 mesh), while eluting with ethyl acetate and hexane in 3:7 ratio. All the pure products were identified by their IR, ^{1}H NMR and mass spectroscopy data.

Spectral data for selected compounds

Compound (3d): IR (KBr, ν_{max}, cm^{-1}): 3380, 2941, 2885, 1647, 1428, 1397, 1324, 1208, 1164, 1111, 1044, 989, 922, 856, 762, 671. ^{1}H NMR ($CDCl_3$): δ 2.72 (s, 6H), 7.60-7.70 (m, 2H), 7.90-8.01 (m, 2H). EIMS: m/z (%): 158 (m^+ 70), 143 (10), 130 (10), 118 (10), 117 (100), 102 (10), 90 (15), 89 (12), 77 (20), 76 (35), 75 (12), 61 (12), 50 (18), 41 (10).

Compound (3e): IR (KBr, ν_{max}, cm^{-1}, neat): 3376, 2994, 2947, 1641, 1599, 1560, 1461, 1395, 1313, 1238, 1191, 1151, 1108, 1041, 995, 918, 830, 796, 713, 680. ^{1}H NMR ($CDCl_3$): δ 2.78 (s, 3H), 2.83 (s, 3H), 7.58-7.68 (m, 1H), 8.35 (d, 1H,

TABLE-1
ZINC TRIFLATE CATALYZED SYNTHESIS OF QUINOXALINES

S. No	1,2-Diamine	1,2-Diketone	Product*	Reaction time (h)	Yield** (%)
a				4.0	90
b				4.0	85
c				4.0	89
d				5.0	84
e				5.0	82
f				5.0	87
g				6.0	75
h				4.5	90
i				5.5	85
j				5.0	85
k				6.0	86
l				5.0	88
m				4.0	90

*All the products were identified by their ^{1}H NMR, IR and mass. **Yields were isolated and unoptimized.

J = 5.0 Hz), 9.05 (d, 1H, *J* = 3.0 Hz). EIMS: m/z (%): 159 (m^+ 48), 144 (10), 118 (58), 105 (12), 91 (15), 77 (52), 61 (100), 50 (18), 41 (66).

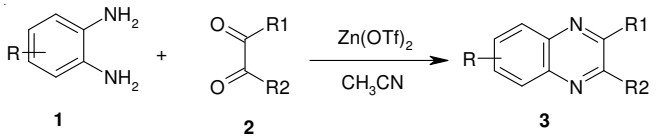
Compound (3h): (KBr, ν_{max}, cm^{-1}): 3387, 3064, 2938, 1661, 1592, 1449, 1323, 1211, 1172, 1110, 1045, 996, 927, 874, 794, 719, 681, 641. ^{1}H NMR ($CDCl_3$): δ 1.48-1.62 (m, 3H), 1.90-2.05 (m, 3H), 2.55 (d, 2H, *J* = 6.0 Hz), 3.08-3.18 (m, 2H), 7.68 (t, 2H, *J* = 6.0 Hz), 7.95 (d, 4H, *J* = 6.0 Hz).

Compound (3k): (KBr, ν_{max}, cm^{-1}): 3383, 2940, 2850, 1620, 1563, 1494, 1442, 1399, 1367, 1325, 1255, 1200, 1158, 1113, 1095, 1044, 988, 907, 833, 769, 677. ^{1}H NMR ($CDCl_3$): δ 7.68-7.72 (m, 1H), 7.82-7.90 (m, 2H), 8.12-8.18 (m, 2H), 8.40 (d, 1H, *J* = 6.0 Hz), 8.01-8.10 (m, 2H), 9.12 (s, 1H). EIMS: m/z (%): 255 (m^+ 25), 233 (56), 225 (18), 211 (33), 194 (15), 178 (30), 171 (65), 149 (20), 131 (25), 115 (15), 105 (100), 75 (28).

Compound (3m): (KBr, ν_{max}, cm^{-1}): 3386, 2939, 2856, 1646, 1428, 1299, 1208, 1108, 1043, 992, 923, 857, 758. ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 6H), 7.81 (t, 2H, *J* = 6.0 Hz), 7.90 (s, 2H), 8.20 (d, 2H, *J* = 6.0 Hz), 8.39 (d, 2H, *J* = 6.0 Hz).

RESULTS AND DISCUSSION

Herein we report a novel and efficient method for the synthesis of quinoxaline derivatives *via* the coupling of aryl-1,2-diamine and diketo carbonyls using a catalytic amount of zinc triflate under mild reaction conditions as shown in the **Scheme-I**.



1 2 3

Scheme-I

Accordingly, treatment of *o*-phenylenediamine (**1**) with benzil (**2**) in the presence of 10 mol % of zinc triflate in acetonitrile at 80-85 ºC afforded the corresponding derivative of 2,3-diphenylquinoxaline (**3a**) in 90 % yield. The reaction was completed within 4 h. This result provided the incentive for further study of reactions with a variety of reactants such as benzil and acenaphthylene-1,2-dione and biacetyl. In a similar manner, the 1,2-diamines including *o*-phenylenediamine, 4-methylbenzene-1,2-diamine, 4-nitrobenzene-1,2-diamine, 4,5-dimethylbenzenediamine and pyridine-2, 3-diamine were reacted smoothly. The scope and generality of this procedure is illustrated in Table-1. In general, the condensation takes place faster, when the reaction was carried out between aromatic diketones and *o*-phenylenediamines. All the reactions were completed with in 4-8 h of reaction time at 80-85 ºC and the obtained products yields were in 75-90 %. The structures of the products were identified by their ^{1}H NMR, IR and mass spectral analysis and compared with literature reports.

In conclusion, we have demonstrated a simple and efficient protocol for the synthesis of quinoxalines using a catalytic amount of zinc triflate at acetonitrile reflux condition via the coupling of diketo carbonyls with 1, 2-diamines. The method is very simple, clean and applicable to a variety of reactants such as aromatic, hetero aromatic and aliphatic systems successfully.

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