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Highly Efficient Synthesis of Quinoxaline Derivatives Catalized by Iridium Complex[1]

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Abstract—A novel iridium complex was used to catalyze a mild reaction of phenylenediamine with propanediol that led to formation of quinoxaline derivatives with moderate to high yields. The reaction diemonstrated strong compatibility with substrates bearing various functional groups.

Keywords: phenylenediamine, propanediol, quinoxaline derivatives, iridium complex

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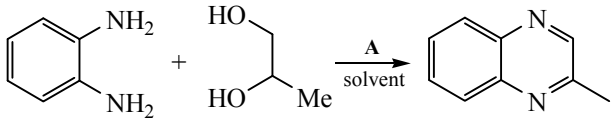
Quinoxaline derivatives attracted close attention of pharmaceutical industry due to their antibacterial [1], antiviral [2], kinase inhibition [3, 4] and anticancer [5] activity. Quinoxalines have been tested as dyes [6, 7], organic semiconductors [8, 9] and building blocks for the synthesis of cavitands [10].

Various strategies have been developed for the synthesis of quinoxalines. The use of θ-phenylene diamine and 1,2-dicarbonyl compounds as starting materials is considered as the conventional method [11]. Later higher yields of the products were achieved by using various catalysts [13–15] and synthetic methods[16–18] that still had some disadvantages. Recently Goldberg and co-workers [19] reported a new type of iridium compound **A** (Scheme 1) which proved to be an efficient catalyst for hydrogenation of carboxylic acids under relatively mild conditions. Herein, we report the iridium catalyzed condensation of phenylenediamines and propanediols that gave quinoxaline derivatives with moderate to high yields.

RESULTS AND DISCUSSION

Initially we targeted development of a new method of synthesis of quinoxaline derivatives from phenylenediamines and propanediols with iridium complex **A** (Scheme 1). 1,2-Phenylenediamine and 1,2-propanediol were selected as the model substrates for testing the reaction. The corresponding product was isolated with 24% yield. (Table 1, entry 1). Following tests of various solvents and bases indicated xylene as the best media and Cs_2CO_3 as most efficient base for the process (Table 1).

Table 1. Screening of optimized reaction conditions for **3a**[a]



1 **2** **3a**

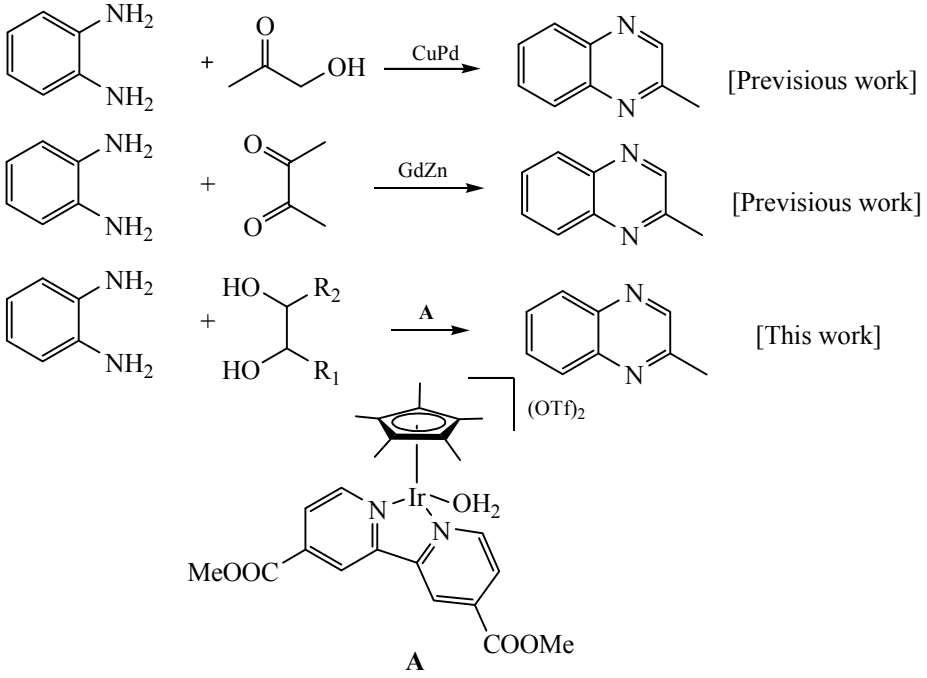
Entry	Base	Solvent	Yield[b], %
1	Na_2CO_3	Toluene	24
2	Na_2CO_3	CH_2Cl_2	<5
3	Na_2CO_3	Benzene	24
4	Na_2CO_3	DMF	<10
5	Na_2CO_3	THF	<10
6	Na_2CO_3	Dioxane	14
7	Na_2CO_3	Xylene	31
8	$NaHCO_3$	Xylene	41
9	KOH	Xylene	16
10	*t*-BuOK	Xylene	44
11	Cs_2CO_3	Xylene	73
12	K_2CO_3	Xylene	39
13	*t*-BuONa	Xylene	51

[a] Conditions: **1** (0.5 mmol, 1.0 equiv), **2** (1.0 equiv), Cat. [Ir] (5 mmol %), base (3.0 equiv), solvent (4 mL), 48 h, reflux.

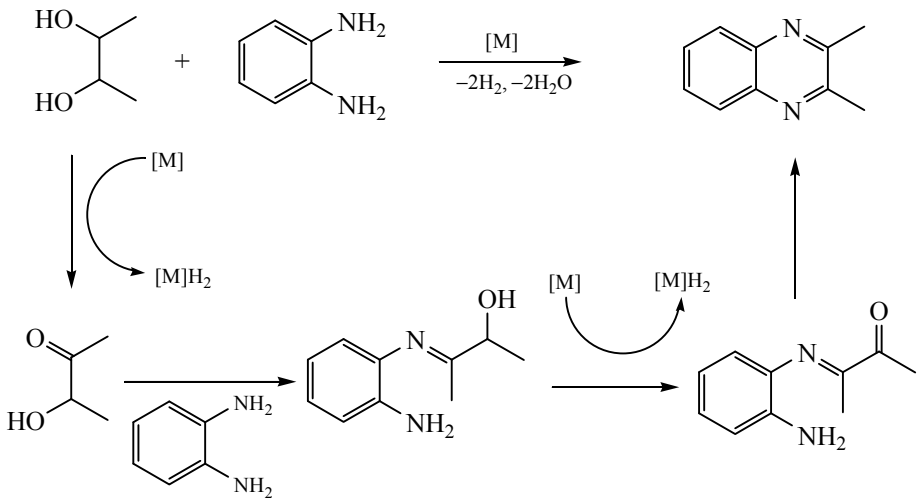
[b] Isolated yields base on **1**.

[1] The text was submitted by the authors in English.

Scheme 1. Some methods for preparation of quinoxalines derivatives.



Scheme 2. Proposed mechanism of the reaction.



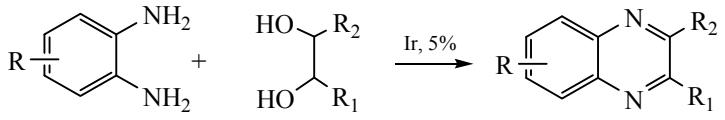
The synthetic data are presented in Table 2.

EXPERIMENTAL

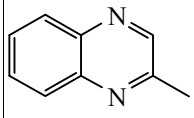
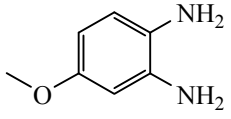
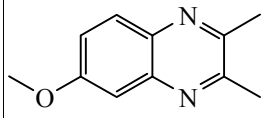
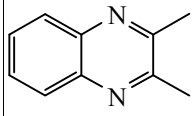
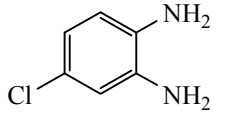
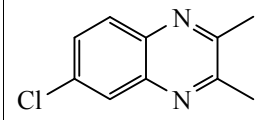
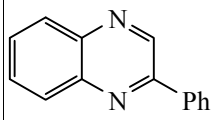
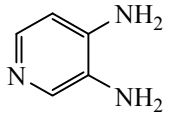
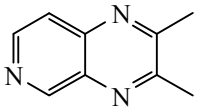
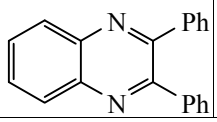
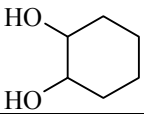
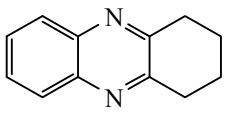
All chemicals were commercially available and used without further purification unless otherwise stated. All solvents were dried and freshly distilled under the atmosphere of nitrogen. The products were separated and purified by column chromatography on silica gel (200–300 or 100–200 mesh) by using petroleum ether (60–90°C) and ethyl acetate as the eluents. All yields are presented for pure products. The reaction progress was commonly monitored by TLC using SiO_2 sheets and compounds were visualized under UV light. The products were verified by ^1H NMR spectra recorded on a Bruker Advance 400 and 300 in $CDCl_3$ using TMS as the reference.

General procedure for the synthesis of 3a. The catalyst **A** (5% mmol, 0.05 mmol), 1,2-phenylene diamine (1 mmol, 1.0 equiv), 1,2-propanediol (1 mmol, 1.0 equiv), Cs_2CO_3 (3.0 equiv) and xylene (4 mL) were

Table 2. Synthesis of quinoxalines derivatives[a]



1 **2** **3**

Comp. no.	Substrate	Product	Yield[b], %	Comp. no.	Substrate	Product	Yield[b], %
3a			73	**3e**			66
3b			71	**3f**			56
3c			65	**3g**			62
3d			58	**3h**			43

[a] Conditions: **1** (1 mmol, 1.0 equiv), **2** (1 equiv), Cat. [Ir] (5% mmol), Cs_2CO_3 (3.0 equiv), xylene (4 mL), 48 h, reflux.
[b] Isolated yields based on **1**.

added to a Schlenk tube under the atmosphere of nitrogen. The mixture was heated for 48 h at 150°C and then cooled down to room temperature. The volatile solvent was evaporated. The residue was purified by column chromatography to give the corresponding product **3a**.

2-Methylquinoxaline (3a). ^{1}H NMR spectrum, δ, ppm: 8.66 s (1H), 7.99 d (1H, J = 8.0 Hz), 7.94 d (1H, J = 8.0 Hz), 7.69–7.59 m (2H), 2.70 s (3H).

2,3-Dimethylquinoxaline (3b). ^{1}H NMR spectrum, δ, ppm: 7.88 d.d (2H, J = 6.0, 3.6 Hz), 7.55 d.d (2H, J = 6.0, 3.6 Hz), 2.62 s (6H).

2-Phenylquinoxaline (3c). ^{1}H NMR spectrum, δ, ppm: 9.22 s (1H), 8.22–7.92 m (4H), 7.67 m (2H), 7.53–7.36 m (3H).

2,3-Diphenylquinoxaline (3d). ^{1}H NMR spectrum, δ, ppm: 8.08 d.d (2H, J = 6.4, 3.2 Hz), 7.66 d.d (2H, J = 6.0, 3.2 Hz), 7.43 d (4H, J = 7.6 Hz), 7.29–7.20 m (6H).

6-Methoxy-2,3-dimethylquinoxaline (3e). ^{1}H NMR spectrum, δ, ppm: 7.76 d (1H, J = 8.8 Hz), 7.23–7.19 m (2H), 3.85 s (3H), 2.60 d (6H, J = 5.2 Hz).

6-Chloro-2,3-dimethylquinoxaline (3f). ^{1}H NMR spectrum, δ, ppm: 7.86 s (1H), 7.80 d (1H, J = 9.2 Hz), 7.50 d.d (1H, J = 8.8, 1.6 Hz), 2.63 s (6H).

2,3-Dimethylpyrido[3,4-b]pyrazine (3g). ^{1}H NMR spectrum, δ, ppm: 9.33 s (1H), 8.66 d (1H, J = 5.6 Hz), 7.74 d (1H, J = 5.6 Hz), 2.71 s (6H).

1,2,3,4-Tetrahydrophenazine (3h). ^{1}H NMR spectrum, δ, ppm: 7.87 d.d (2H, J = 6.4, 3.2 Hz), 7.56 d.d (2H, J = 6.0, 3.2 Hz), 3.07 m (4H), 1.94 m (4H).

CONCLUSIONS

A simple, convenient, mild conditions, and moderate to high yields procedure for the synthesis of quinoxalines has been developed using iridium complex as the catalyst.

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