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A new ruthenium-catalyzed approach for quinoxalines from *o*-phenylenediamines and vicinal-diols

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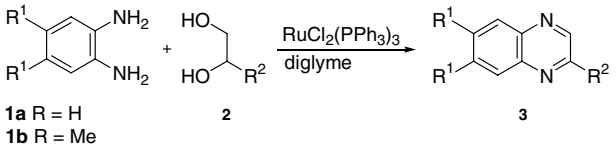
Abstract—*o*-Phenylenediamines react with an array of vicinal-diols in diglyme in the presence of a catalytic amount of a ruthenium catalyst along with KOH to afford the corresponding quinoxalines in good yields.

It is known that quinoxaline plays an important role as a basic skeleton for the design of many pharmacologically and biologically active compounds such as insecticides, fungicides, herbicides and anthelmintics.[1] Conventional quinoxaline synthesis can be achieved by double condensation between *o*-phenylenediamines and 1,2-dicarbonyl compounds. However, the conventional process has frequently suffered from the handling of highly reactive dicarbonyl compounds. As an elegant alternative, it was recently reported that α-hydroxy ketones are oxidatively cyclized with *o*-phenylenediamines in the presence of a transition metal catalyst to give quinoxalines.[1–3] As part of our studies directed towards ruthenium-catalyzed organic syntheses and transformations, we recently found several coupling reactions between carbonyl compounds and alcohols.[4–6] These reactions could be applied to modified Friedländer quinoline synthesis via ruthenium-catalyzed consecutive coupling and cyclization of 2-aminobenzyl alcohol with ketones and secondary alcohols, which is superior to conventional Friedländer method[7–9] in a sense of price and stability of 2-aminobenzyl alcohol.[10–14] Prompted by these findings, we have directed our attention to the synthesis of *N*-heterocycles using such an intrinsic ruthenium-catalyzed oxidative cyclization of alcohols.[15–17] Herein, we report a ruthenium-catalyzed synthesis of quinoxalines from *o*-phenylenediamines and vicinal-diols in the presence of KOH.



1a R = H
1b R = Me

2

3

Scheme 1.

Initial attempts for the oxidative cyclization between *o*-phenylenediamine (**1a**) and 1-phenyl-1,2-ethanediol (**2a**, **2**: $R^2 = Ph$) were examined under several conditions (Scheme 1). Treatment of equimolar amount of **1a** and **2a** in diglyme in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ and KOH at reflux for 20 h afforded 2-phenylquinoxaline (**3a**, **3**: $R^1 = H$; $R^2 = Ph$) in 50% yield (Table 1, run 1). The yield of **3a** was considerably affected by the molar ratio of **2a** to **1a**, [**2a**]/[**1a**] = 2 being the choice of preference for the effective formation of **3a** (run 2). Recently, we observed on the dramatic acceleration of reaction rate by the addition of a hydrogen acceptor for ruthenium-catalyzed coupling of

Table 1. Effect of molar ratio, bases and hydrogen acceptors on $RuCl_2(PPh_3)_3$-catalyzed synthesis of **3a** from **1a** and **2a**[a]

Run	[**2a**]/[**1a**]	Base	Additives	Yield (%)
1	1	KOH	—	50
2	2	KOH	—	75
3	2	KOH	Benzalacetone	82
4	2	KOH	1-Dodecene	76
5	2	—	—	13
6	2	—	Benzalacetone	18

[a] Reaction conditions: **1a** (0.5 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), KOH (2 mmol), additive (1 mmol), diglyme (5 mL), reflux, for 20 h.

Keywords: Cyclization; *o*-Phenylenediamines; Quinoxalines; Ruthenium catalyst; Vicinal-diols.
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secondary alcohols with primary alcohols and oxidative cyclization of 2-aminobenzyl alcohol with secondary alcohols.[6,11] However, the addition of benzalacetone as a hydrogen acceptor at the present reaction resulted in a slightly increased yield of **3a** to 82%, whereas that of 1-dodecene showed no significant change (runs 3 and 4).[18] The presence of KOH was essential for the effective formation of **3a**. Performing the reaction in the absence of KOH resulted in only 13% yield of **3a** (run 5). Here again, a slight increase in the yield of **3a** was observed with the addition of benzalacetone (run 6). It is known that strong bases are used as promoters in transition metal-catalyzed transfer hydrogenation from alcohols.[19]

Having established the reaction conditions, various vicinal-diols **2** were subjected to react with **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. From the reactions between **1a** and 1-aryl-1,2-ethanediol (**2a**–**h**),[20–22] the oxidative cyclized products (**3a**–**h**) were formed in the range of 63–82% yields without any identifiable side product. The product yield was not significantly affected by the position of the substituent on the aromatic ring of **2a**–**h**, whereas the electronic nature of that had some relevance to the product yield. The reaction proceeds likewise with 4,5-dimethyl-1,2-phenylenediamine (**1b**) to give the corresponding quinoxalines (**3i** and **3j**) in similar yields. In the reaction of 1-(2-naphthyl)-1,2-ethanediol (**2i**),[20–22] 2-(2-naphthyl)quinoxaline (**3k**) was also obtained in 75% yield. The reaction of 1-(2-furyl)-1,2-ethanediol (**2j**)[20–22] with **1a** also proceeds to give the corresponding quinoxaline **3l** in 69% yield. 1,2-Diol **2k**, which has an alkyl substituent at carbon bearing hydroxyl group, was also readily oxidatively cyclized with **1a** to afford 2-butylquinoxaline (**3m**) in 68% yield. Internal vicinal-diol **2l**, which has alkyl substituents at both carbons bearing hydroxyl group, was also reacted with **1a** to give 2,3-dimethylquinoxaline (**3n**) in similar yield. From the reaction between **1a** and cyclic 1,2-diol **2m** (cis- and trans-mixture), 6,7,8,9-tetrahydrophenazine (**3o**) was produced in high yield.

Table 2. Ruthenium-catalyzed synthesis of quinoxalines **3** from *o*-phenylenediamines **1** and vicinal-diols **2**[a]

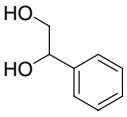
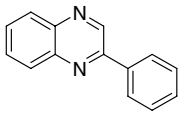
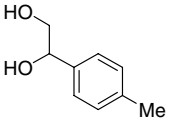
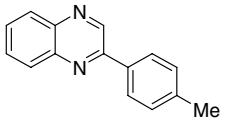
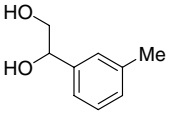
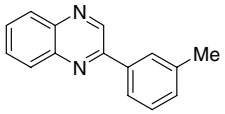
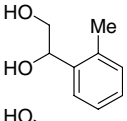
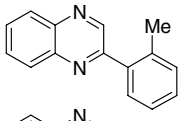
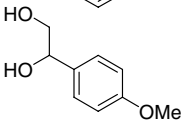
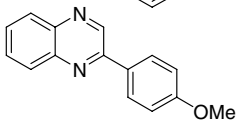
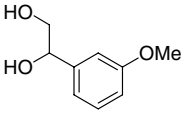
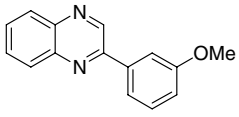
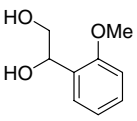
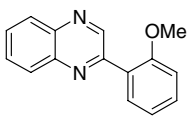
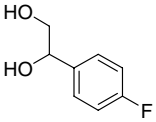
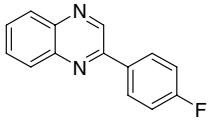
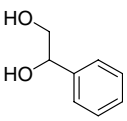
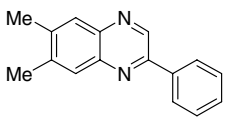
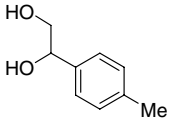
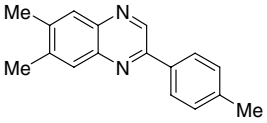
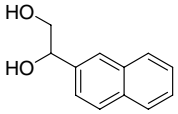
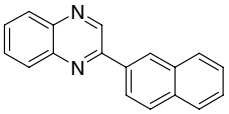
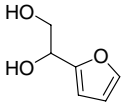
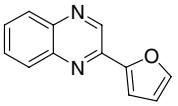
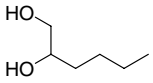
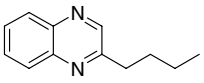
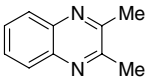
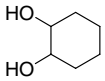
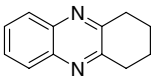
1	Diols 2	Quinoxalines 3	Yield (%)
1a		**2a**		**3a**	82
1a		**2b**		**3b**	80
1a		**2c**		**3c**	76
1a		**2d**		**3d**	81
1a		**2e**		**3e**	73
1a		**2f**		**3f**	76
1a		**2g**		**3g**	72
1a		**2h**		**3h**	63
1b		**2a**		**3i**	84

Table 2 (*continued*)

1	Diols 2		Quinoxalines 3		Yield (%)
1b		**2b**		**3j**	79
1a		**2i**		**3k**	75
1a		**2j**		**3l**	69
1a		**2k**		**3m**	68
1a		**2l**		**3n**	79
1a		**2m**		**3o**	82

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), KOH (2 mmol), benzalacetone (1 mmol), diglyme (5 mL), reflux, for 20 h.

As to the mechanistic aspects for the present reaction, it seems to proceed via an initial oxidation of diols **2** to mono-carbonyls as well as di-carbonyls followed by condensation with diamines. It is known that the oxidation is catalyzed by a ruthenium along with a strong base.[19] Partial enhancement of the reaction by the addition of benzalacetone seems to be due to partial acceleration of the initial oxidation by transfer hydrogenation from **2** to benzalacetone.[19]

General experimental procedure: To a 20 mL round bottomed flask were added *o*-phenylenediamine (0.5 mmol), vicinal-diol (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), KOH (2 mmol), benzalacetone (1 mmol) and diglyme (5 mL). The system was stirred at reflux for 20 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–hexane) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give quinoxalines.

In summary, it has been shown that an array of vicinal-diols undergo an oxidative cyclization with *o*-phenylenediamines in the presence of a catalytic amount of a ruthenium catalyst along with KOH to give quinoxalines in high yields. The present reaction is an alternative synthetic approach for quinoxalines. We believe that this reaction will work as a useful procedure for the direct introduction of quinoxaline skeletones into vicinal-diol containing compounds.

Acknowledgement

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