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Ketones as a new synthon for quinoxaline synthesis

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Dedicated to the late Professor Yoshihiko Ito for his distinguished achievements in chemistry

Abstract—*o*-Phenylenediamines react with an array of ketones in PEG-400 at 60 °C under an atmosphere of air in the presence of KOH to afford the corresponding quinoxalines in good yields.
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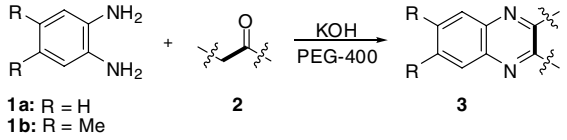
Many synthetic methods have been developed and documented for quinoxalines due to their intrinsic pharmacological and biological activities.[1] Conventional quinoxaline synthesis can be achieved by the reaction of *o*-phenylenediamines with two-carbon synthons such as α-dicarbonyls, α-halogenocarbonyls and α,β-dihalides.[2] *o*-Nitrosoaminobenzenes and benzofuroxans are also used as substitutes for *o*-phenylenediamines to form quinoxalines. Besides such a conventional route, metal-catalyzed reactions for quinoxaline skeletons have also been attempted as alternative methods because of the facility and efficiency of reaction and the wide availability of two-carbon synthons. It is known that α-hydroxy ketones are oxidatively cyclized with *o*-phenylenediamines in the presence of transition metals such as Mn, Pd, Ru and Cu to give quinoxalines.[3–6] Epoxides are also used as a two-carbon synthon in bismuth-catalyzed oxidative cyclization with *o*-phenylenediamines to afford quinoxalines.[7] As a part of our ongoing studies on N-heterocyclization,[8–11] we also reported on the synthesis of quinoxalines via a ruthenium-catalyzed oxidative cyclization of vicinal-diols with *o*-phenylenediamines in the presence of a base and a sacrificial hydrogen acceptor.[12] These circumstances led us to seek for a new two-carbon synthon for quinoxaline synthesis. Herein, this report describes a new synthetic approach for quinoxalines from *o*-phenylenediamines and ketones as two-carbon synthons (Scheme 1).



1a: R = H
1b: R = Me

2 **3**

Scheme 1.

The results of several attempted cyclization of *o*-phenylenediamine (**1a**) with propiophenone (**2a**) are listed in Table 1. Treatment of equimolar amounts of **1a** and **2a** in PEG-400 in the presence of KOH at 60 °C for 40 h afforded 2-methyl-3-phenylquinoxaline (**3a**) in 41% isolated yield (run 1).[13] The molar ratio of [**2a**]/[**1a**] affected the yield of **3a**. In atom economy point of view, the molar ratio of [**2a**]/[**1a**] = 2 is the choice of preference for the effective formation of **3a** (run 2). The yield of **3a** increases with prolonging the reaction time up to 60 h (runs 2–4). When the reaction was carried out under an atmosphere of argon, a slightly decreased yield of **3a** was obtained (run 5). Higher reaction temperature rather resulted in lower yield of **3a** (run 6). Among the solvents examined under [**2a**]/[**1a**] = 2, PEG-400 in terms of product **3a** yield revealed to be the solvent of choice (runs 2, 7–11). The molar ratio of [KOH]/[**1a**] = 3 was required for the effective formation of **3a**, using equimolar amount of KOH relative to **1a** resulting in a lower yield of **3a** (run 12). However, the presence of KOH was essential for the effective formation of **3a**. When the reaction was carried out in the absence of KOH, the cyclization did not occur at all towards **3a** (run 13).

Keywords: Cyclization; Ketones; *o*-Phenylenediamines; Poly(ethylene glycol); Quinoxalines.
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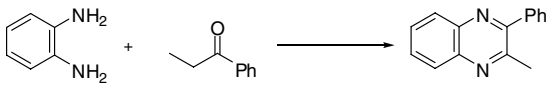
Table 1. Optimization of conditions for the reaction of **1a** with **2a**[a]



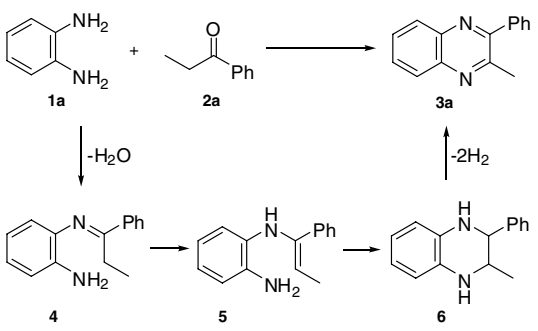
1a **2a** **3a**

Run	[**2a**]/[**1a**]	KOH (mmol)	Solvents	Temperature (°C)	Time (h)	Isolated yield (%)
1	1	3	PEG-400	60	40	41
2	2	3	PEG-400	60	40	60
3	2	3	PEG-400	60	20	33
4	2	3	PEG-400	60	60	72
5[b]	2	3	PEG-400	60	60	64
6	2	3	PEG-400	100	40	43
7	2	3	Toluene	60	40	38
8	2	3	Dioxane	60	40	45
9	2	3	DMSO	60	40	2
10	2	3	THF	60	40	54
11	2	3	1,2-Dimethoxyethane	60	40	56
12	2	1	PEG-400	60	40	51
13	2	—	PEG-400	60	40	0

[a] Reaction conditions: **1a** (1 mmol), solvent (2 mL).
[b] Under an atmosphere of argon.

As to the reaction pathway, although it is not yet fully understood, this, consistent with the product formed, seems to proceed via an initial formation of ketimine **4** by the condensation between **1a** and **2a**, which in turn triggers tautomerization to form enamine **5**. KOH seems to play a role in facilitating such a tautomerization. Subsequent steps seem to be followed by intramolecular hydroamination to form 1,2,3,4-tetrahydroquinoxaline **6** and dehydrogenation to give **3a** (Scheme 2).

Having reaction conditions being established, *o*-phenylenediamines **1** were subjected to react with various ketones **2** in order to investigate the reaction scope and several representative results are summarized in Table 2. The reaction of **1a** with 1-arylpropan-1-ones (**2b** and **2c**) having electron donating and withdrawing substituents on the aromatic ring also proceeds to give the corresponding 2-aryl-3-methylquinoxalines (**3b** and **3c**). Alkyl phenyl ketones (**2d**–**g**) were also cyclized with **1a** to give the corresponding 2-alkyl-3-phenylquinoxalines (**3d**–**g**) in the range of 65–73% yields. The reaction proceeds likewise with alkyl benzyl ketone **2h** to produce 2-isopropyl-3-phenylquinoxaline (**3h**). However, the reaction did not proceed satisfactorily with acetophenone, 2-phenylquinoxaline being formed in only 20% yield. In the reaction of **1a** with 1-phenylbutan-2-one (**2i**), 2-ethyl-3-phenylquinoxaline (**3i**) was obtained in 56% yield without the formation of expected regioisomer, 2-benzyl-3-methylquinoxaline. As shown in Scheme 2, the preferential formation of **3h** to 2-benzyl-3-methylquinoxaline seems to be due to relative resonance stability of intermediate enamine. Lower reaction rate and yield were observed with non-activated dialkyl ketones (**2j** and **2k**). Here again, no regioisomeric quinoxaline was observed with **2j**. Cyclic ketones such as cycloheptanone (**2l**) and cyclooctanone (**2m**) were also reacted with **1a** to give 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline (**3l**) and 6,7,8,9,10,11-hexahydrocycloocta[*b*]quinoxaline (**3m**) in 51% and 61% yields, respectively. Similar treatment of **1b** with alkyl(aryl) ketones (**2a**–**c** and **2g**) afforded the corresponding quinoxalines (**3n**–**q**) in the range of 49–74% yields. The cyclization of **1b** with **2h** resulted in a quantitative yield of quinoxaline **3r**.



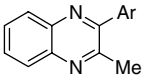
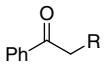
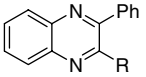
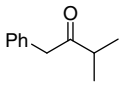
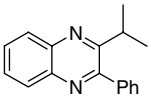
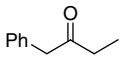
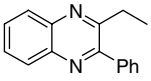
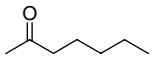
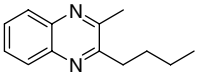
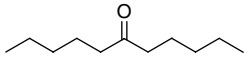
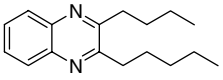
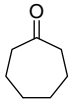
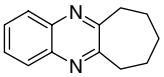
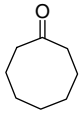
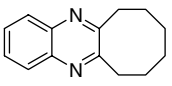
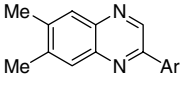
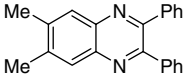
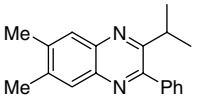
1a **2a** **3a** **4** **5** **6**

Scheme 2.

General experimental procedure: To a 20 mL round-bottomed flask were added *o*-phenylenediamine (1 mmol), ketone (2 mmol), KOH (3 mmol) and PEG-400 (2 mL). The system was stirred at 60 °C for 60 h. The reaction mixture was extracted with chloroform, washed with H_2O several times and dried over Na_2SO_4. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give quinoxaline.

In summary, we have shown that quinoxalines could be synthesized by the reaction of *o*-phenylenediamines with ketones in PEG-400 in the presence of KOH. The present reaction is a straightforward methodology for the synthesis of quinoxalines from readily available starting ketones. Further study of synthetic application for N-heterocycles via an intrinsic enamine intermediate of this reaction is currently under investigation.

Table 2. Synthesis of quinoxalines **3** from *o*-phenylenediamines **1** and ketones **2**[a]

1	Ketones 2	Quinoxalines 3	Isolated yield (%)
			
1a	**2a** Ar = Ph	**3a** Ar = Ph	72
	2b Ar = 4-$OMeC_6H_4$	**3b** Ar = 4-$OMeC_6H_4$	59
	2c Ar = 4-ClC_6H_4	**3c** Ar = 4-ClC_6H_4	54
			
1a	**2d** R = Pr	**3d** R = Pr	73
	2e R = hexyl	**3e** R = hexyl	65
	2f R = phenethyl	**3f** R = phenethyl	68
	2g R = Ph	**3g** R = Ph	67
			
1a	**2h**	**3h**	75
			
1a	**2i**	**3i**	56
			
1a	**2j**	**3j**	30
			
1a	**2k**	**3k**	31
			
1a	**2l**	**3l**	51
			
1a	**2m**	**3m**	61
			
1b	**2a**	**3n** Ar = Ph	54
	2b	**3o** Ar = 4-$OMeC_6H_4$	74
	2c	**3p** Ar = 4-ClC_6H_4	49
			
1b	**2g**	**3q**	71
			
1b	**2h**	**3r**	95

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), KOH (3 mmol), PEG-400 (2 mL), 60 °C, 60 h.

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