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$Ga(ClO_4)_3$-catalyzed synthesis of quinoxalines by cycloaddition of α-hydroxyketones and *o*-phenylenediamines

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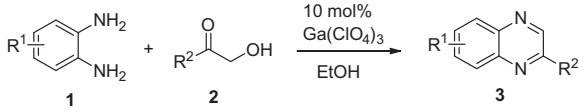
ABSTRACT

A new approach for the synthesis of 2-substituted quinoxalines by $Ga(ClO_4)_3$-catalyzed cycloaddition of α-hydroxyketones and *o*-phenylenediamines is introduced. The reaction is catalyzed by 10 mol % of $Ga(ClO_4)_3$ in EtOH at room temperature. It is performed under simple and mild conditions to afford the product in good yield.

Privileged quinoxaline ring system can be found in a broad range of biological active compounds and functional materials.[1] Quinoxaline derivatives have been used as biocides,[2] medical chemicals,[3] and organic semiconductors.[4] Acid-catalyzed condensation of 1,2-aryldiamines with 1,2-diketones is a primary route to construct the quinoxaline ring.[5] The modification of this reaction has been focused on using 1,2-diketone alternatives and related catalysts.[6] Reactions using 1,2-diketone alternatives such as phenyl epoxides, phenacyl bromides, α-hydroxyketones, and *o*-phenylenediamines with the catalysts such as Bi(0),[7] $HClO_4$/SiO_2,[8] β-cyclodextrin (β-CD),[9] TMSCl,[10] 1,4-diazabicyclo-[2,2,2]-octane (DABCO),[11] transition metals (Mn, Ru, Pd, and Cu),[12] and ion-exchanged molybdophosphoric acid have been reported.[13]

As part of our continuous effort on the development of gallium(III) salts-catalyzed reactions, we have recently reported $Ga(OTf)_3$-promoted synthesis of 1,5-benzodiazepines by the cycloaddition of 1,2-aryldiamine or 2-aminothiophene with ketones or chalkones.[14] We also reported the synthesis of 2,3-substituted quinoxalines by the cycloaddition of *o*-phenylenediamines and diaryl-1,2-diketones.[15] Introduced in this Letter are $Ga(ClO_4)_3$-catalyzed reactions of 1,2-aryldiamines with α-hydroxyketones for the synthesis of 2-substituted quinoxalines (Scheme 1).

o-Phenylenediamine **1a** and 2-hydroxyacetophenone **2a** were selected as the model compounds for the screening of reaction solvent, catalyst, and related reaction conditions (Table 1). When the reaction was carried out with 10 mol % of $Ga(ClO_4)_3$ in EtOH or MeOH, **3a** was obtained in 95% and 96%, respectively, (Table 1, entries 1 and 2). Reactions in other solvents such as MeCN, CH_2Cl_2,



Scheme 1. $Ga(ClO_4)_3$-promoted synthesis of quinoxalines.

Table 1
The reaction of **1a** with **2a** under different conditions[a]

Entry	Catalyst (10 mol %)	Solvent	Time (h)	Yield[b] (%)
1	$Ga(ClO_4)_3$	EtOH	4	95
2	$Ga(ClO_4)_3$	MeOH	4	96
3	$Ga(ClO_4)_3$	CH_3CN	4	62
4	$Ga(ClO_4)_3$	CH_2Cl_2	4	35
5	$Ga(ClO_4)_3$	DMSO	4	71
6	$Ga(ClO_4)_3$	H_2O	4	25
7	$Ga(OTf)_3$	EtOH	4	55
8	$Ga(NO_3)_3$	EtOH	4	Trace
9	$La(OTf)_3$	EtOH	4	72
10	$Yb(OTf)_3$	EtOH	4	75
11	None	EtOH	4	Trace

[a] All the reactions were performed using **1a** (0.5 mmol) and **2a** (0.5 mmol) at 25 °C.
[b] Isolated yield.

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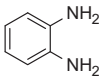
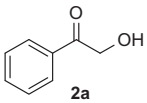
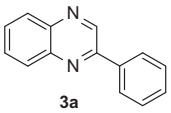
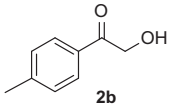
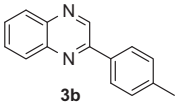
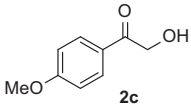
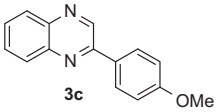
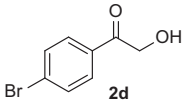
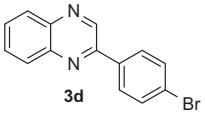
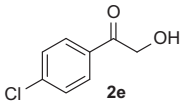
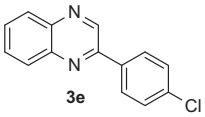
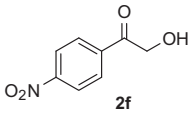
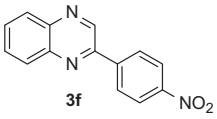
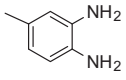
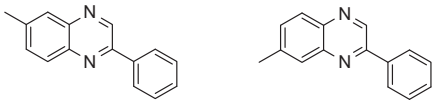
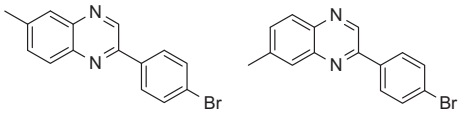
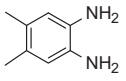
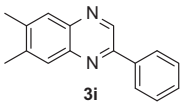
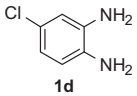
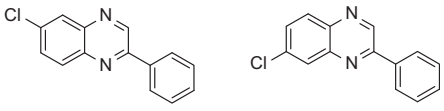
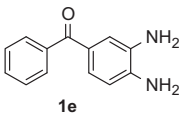
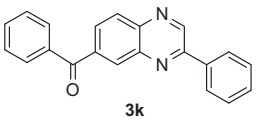
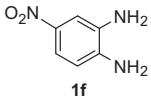
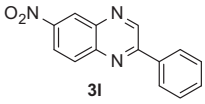
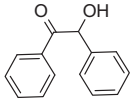
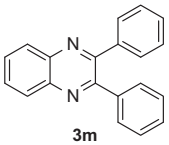
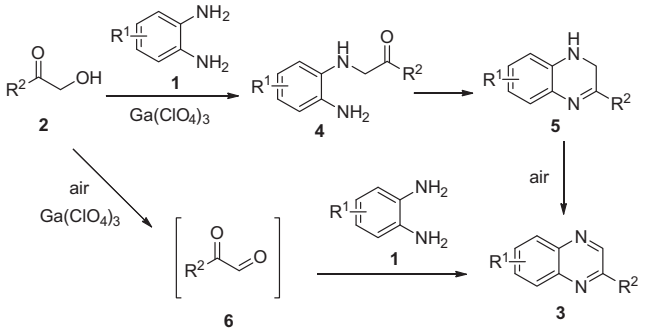
Table 2
$Ga(ClO_4)_3$-catalyzed reactions of diamines and α-hydroxyketones[a]

Entry	1,2-Diamine **1**	α-Hydroxyketones **2**	Product **3**	Yield % (ratio)
1	 **1a**	 **2a**	 **3a**	95
2	**1a**	 **2b**	 **3b**	90
3	**1a**	 **2c**	 **3c**	86
4	**1a**	 **2d**	 **3d**	88
5	**1a**	 **2e**	 **3e**	84
6	**1a**	 **2f**	 **3f**	71
7	 **1b**	**2a**	 **3g** and **3g'**	87 (1:1)
8	**1b**	**2d**	 **3h** and **3h'**	82 (1:1)
9	 **1c**	**2a**	 **3i**	88
10	 **1d**	**2a**	 **3j** and **3j'**	87[b] (2:1)
11	 **1e**	**2a**	 **3k**	75[b]
12	 **1f**	**2a**	 **3l**	61[b]
13	**1a**	 **2g**	 **3m**	70[c]

[a] Reactions were performed using **1** (0.5 mmol) and **2** (0.5 mmol) with $Ga(ClO_4)_3$ (10 mol %) at 25 °C.
[b] Performed at 35 °C.
[c] Reflux.



Scheme 2. Proposed reaction mechanism.

DMSO, and H_2O gave the product in much lower yields (Table 1, entries 3–6). Reactions with other gallium salts or with lanthanum and ytterbium salts in EtOH were also conducted. It was found that $Ga(OTf)_3$ gave 55% yield of **3a** (Table 1, entry 7), whereas, $La(OTf)_3$ and $Yb(OTf)_3$ gave **3a** in 72% and 75%, respectively. Thus, using equal molar substrates of **1a** and **2a** with 10 mol % of $Ga(ClO_4)_3$ in EtOH was selected as the optimized condition for the synthesis of 2-substituted quinoxalines **3**.

Using the optimized condition, we conducted the cycloadditions of various *o*-phenylenediamines **1** and α-hydroxyketones **2** (Table 2). It was found that α-hydroxyketones **2** containing electron-donating and weak electron-withdrawing substitution groups such as Me, MeO, Br, and Cl afforded products in good yields (84–95%) (Table 2, entries 2–5). However, strong electron-withdrawing substitution groups such as NO_2 reduced the yield to 71% yield (Table 2, entry 6). The reactivity and regioselectivity of the substituents on *o*-phenylenediamines **1** were also investigated. It was found that *o*-phenylenediamines **1b** and **1d**, each has a group at the 4-position, afforded corresponding quinoxalines as two isomers (Table 2, entries 7, 8, 10). Interestingly, reactions of **1e** and **1f** yielded the corresponding quinoxalines **3k** and **3l** as single isomers, respectively (Table 2, entries 11 and 12). The reaction of 2-hydroxy-1,2-diphenylethanone **2g** with **1a** was also proceeded smoothly to give 2,3-diphenylquinoxaline **3m** in 70% yield (Table 2, entry 13).

Two possible routes for $Ga(ClO_4)_3$-catalyzed reaction of diamines and α-hydroxyketones are proposed in Scheme 2. The first route involving intermediates **4** and **5** is proceeded through the substitution/cyclization/aromatization steps to form quinoxaline **3**. The reaction is also possible to go through an alternative pathway in which diaryl-1,2-diketone **2** is oxidized to 1,2-diketone **4** and then undergoes cycloaddition with 1,2-aryldiamine **1** to afford product **3**.

In summary, a new $Ga(ClO_4)_3$-catalyzed reaction of diamines with α-hydroxyketones to afford 2-substituted quinoxalines is developed. Compared to the literature methods, this reaction has the advantages of simple manipulation, mild reaction conditions, and high product yields.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.02.113.

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