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Gallium(III) triflate-catalyzed synthesis of quinoxaline derivatives

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ABSTRACT

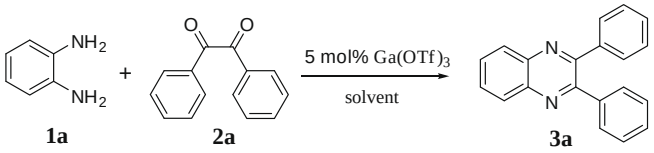
Gallium(III) triflate-catalyzed reactions of phenylene-1,2-diamines and 1,2-diketones produce quinoxalines in excellent to quantitative yields. The reactions proceed with 1 mol % catalyst in ethanol at room temperature. The catalyst can be recycled for at least 10 times.

Quinoxaline is a privileged ring system. Its derivatives have broad biological activities, and have been used as anticancer,[1] antiviral,[2] antibacterial agents,[3] and kinase inhibition agents.[4] In addition to the medicinal applications, quinoxalines have been used as dyes[5] and key intermediates in the synthesis of organic semiconductors.[6]

Over the years, numerous synthetic methods for preparation of quinoxalines have been reported in the literature.[7] Among them, the condensation of 1,2-aryldiamine with 1,2-diketone in refluxing ethanol or acetic acid is a general approach.[8] Research effort has been focused on finding new catalysts to improve the yield of this condensation reaction. In addition to common Lewis acids, many other catalysts including I_2,[9a,9b] SA,[9c] Montmorillonite K-10,[9d] SSA,[9e] $H_6P_2W_{18}O_{62}\cdot 24H_2O$,[9f] $InCl_3$,[9g] $MnCl_2$,[9h] $CuSO_4\cdot 5H_20$,[9i] Zn/L-Proline,[9j] and CAN[9k] have been explored. Oxidative couplings of epoxides and ene-1,2-diamines[10] catalyzed by Bi(0), $Pd(OAc)_2$, $RuCl_2$-$(PPh_3)_3$-TEMPO, and MnO_2 have been reported.[11] The condensation has also been accomplished under catalyst-free conditions, but needs microwave heating.[12] We report here a new method which is catalyzed by $Ga(OTf)_3$, and has advantages of room temperature reaction, extremely high product yields, simple product isolation, and catalyst recovery.

$Ga(OTf)_3$ is a water-tolerant strong Lewis acid, which has broad applications in organic reactions.[13] Recently, we reported a $Ga(OTf)_3$-promoted condensation of 1,2-aryldiamine or 2-aminothiophene with ketones or chalkones to form 1,5-benzodiazepines and 1,5-benzothiazepines.[14] We envisioned that this chemistry could be extended for condensation of 1,2-aryldiamines and 1,2-diketones to form quinoxalines.[15]

The condensation reaction of 1,2-phenylenediamine **1a** and benzil **2a** was carried out in the presence of 5 mol % $Ga(OTf)_3$ at room temperature. Three polar solvents acetonitrile, methanol, and ethanol were evaluated under the same reaction conditions (Scheme 1). It was surprising to find that the reactions in these polar solvents could be completed in as short as 5 min to give quantitative yield of product **3a** (Table 1, entries 1–3). It was also found that reaction in ethyl acetate required a longer time (90 min) and only gave 80% yield of product (Table 1, entry 4). The reaction in water for 30 min resulted product in 85% yield (Table 1, entry 5). Because of high product yield, low toxicity, and good availability, ethanol was chosen as a solvent for further reaction optimization. In the study of catalyst loading, 0.1%, 1%, and 5 mol % of $Ga(OTf)_3$ were tested. Reactions with both 1% and 5 mol % catalysts both gave quantitative yields in 5 min (Table 1, entries 3 and 6),



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

Scheme 1.

Table 1
$Ga(OTf)_3$-catalyzed cycloadditions of *o*-phenylenediamine **1a** and benzyl **2a**

Entry[a]	Solvent	$Ga(OTf)_3$ (mol %)	Time (min)	Yield[b] (%)
1	CH_3CN	5	5	>99
2	MeOH	5	5	>99
3	EtOH	5	5	>99
4	CH_3COOEt	5	90	80
5	H_2O	5	30	85
6	EtOH	1	5	>99
7	EtOH	0.1	30	85

[a] The reaction was performed at rt.
[b] Isolated yield.

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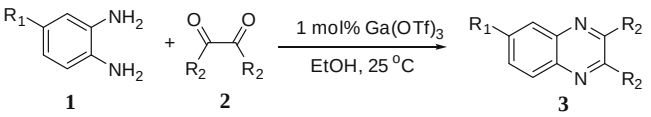
Table 2
The catalytic activity of recycled $Ga(OTf)_3$[a]

Entry	Time (min)	Yield[b] (%)
1	5	>99
2	8	>99
3	10	>99
4	10	>99
5	10	99
6	10	99
7	10	>99
8	10	97
9	10	98
10	10	>99

[a] The reaction was performed at 25 °C.
[b] Isolated yields.

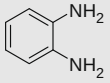
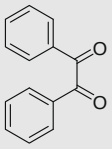
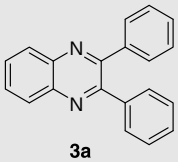
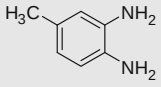
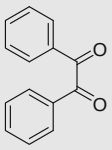
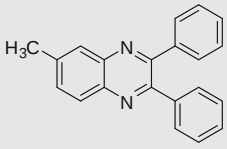
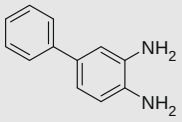
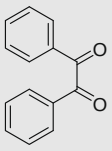
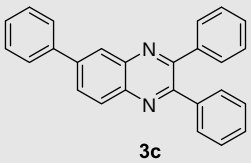
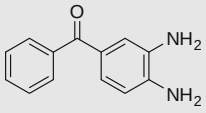
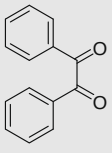
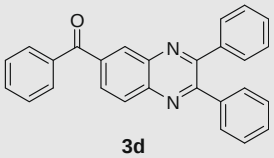
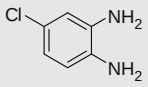
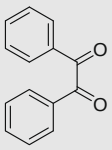
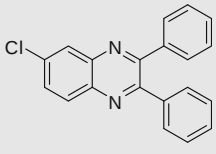
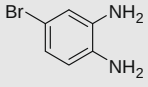
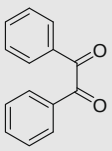
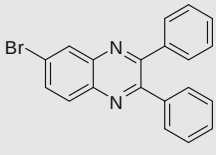


Scheme 2.

whereas 0.1 mol % catalyst loading only gave 85% yield even after a longer reaction time of 30 min (Table 1, entry 7).

The optimized condition for the condensation reaction is as follows: An equimolar amount of **1** and **2** is mixed with 1 mol % $Ga(OTf)_3$ of catalyst in ethanol as a solvent. The reaction is finished in 5 min at room temperature. This general condition was used for other experiment described below.

Table 3
Quinoxaline derivatives from the reaction of 1,2-diamines and 1,2-diketones catalyzed by 1 mol % $Ga(OTf)_3$

Entry	1,2-Diamine	1,2-Diketone	Product[a]	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	5	>99
2	 **1b**	 **2a**	 **3b**	5	>99
3	 **1c**	 **2a**	 **3c**	5	>99
4	 **1d**	 **2a**	 **3d**	20	95
5	 **1e**	 **2a**	 **3e**	10	94
6	 **1f**	 **2a**	 **3f**	10	95

(*continued on next page*)

Table 3 (*continued*)

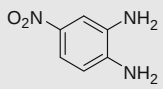
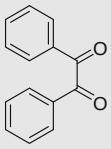
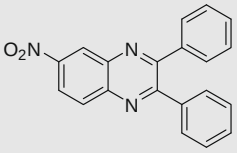
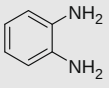
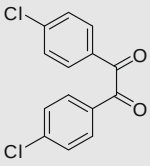
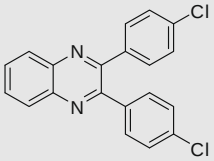
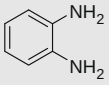
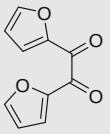
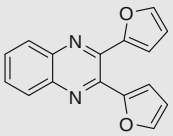
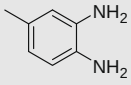
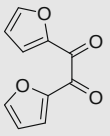
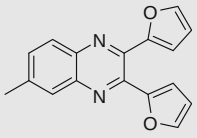
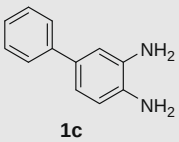
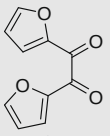
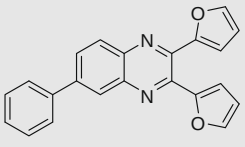
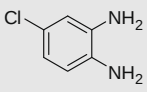
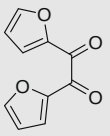
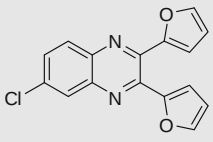
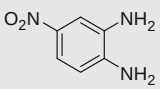
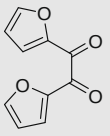
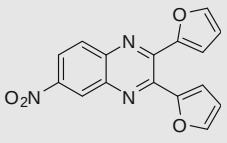
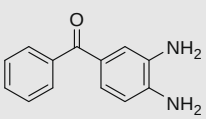
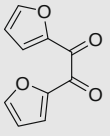
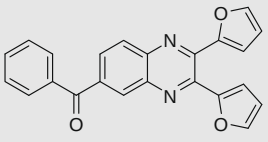
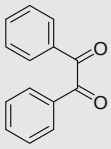
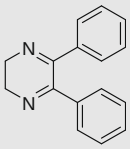
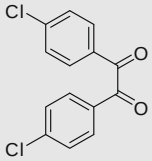
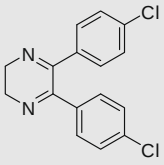
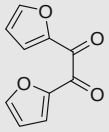
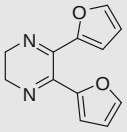
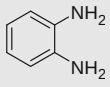
Entry	1,2-Diamine	1,2-Diketone	Product[a]	Time (min)	Yield[b] (%)
7	 **1g**	 **2a**	 **3g**	360	90
8	 **1a**	 **2b**	 **3h**	10	>99
9	 **1a**	 **2c**	 **3i**	10	>99
10	 **1b**	 **2c**	 **3j**	10	>99
11	 **1c**	 **2c**	 **3k**	10	>99
12	 **1c**	 **2c**	 **3l**	10	97
13	 **1g**	 **2c**	 **3m**	240	90
14	 **1d**	 **2c**	 **3n**	10	98

Table 3 (*continued*)

Entry	1,2-Diamine	1,2-Diketone	Product[a]	Time (min)	Yield[b] (%)
15	 **1h**	 **2a**	 **3o**	70	95
16	 **1h**	 **2b**	 **3p**	80	90
17	 **1h**	 **2c**	 **3q**	20	92
18	 **1a**	 **2d**	n.r.[c]	360	–

[a] All products were characterized by ^{1}H, ^{13}C NMR and HRMS spectra.
[b] Isolated yields.
[c] No reaction was observed.

Reducing the amount of catalyst and making it reusable are two important aspects of green chemistry. We developed a catalyst recycle protocol, and also tested the activity of recovered $Ga(OTf)_3$. The procedure is as follows: a mixture of 1,2-aryldiamine and 1,2-diketone (1 mmol each) and $Ga(OTf)_3$ (0.01 mmol) in 3 mL of ethanol was stirred at room temperature for 5–10 min. After completion of the reaction (monitored by TLC), the product was precipitated from the ethanol, and $Ga(OTf)_3$ was left in solvent.[15] The product was collected by filtration, and the filtrate was directly used for the next round of reaction without additional treatment. Within ten cycles, the catalyst showed no significant change on reactivity (Table 2).[16]

The scope of this condensation reaction was evaluated by using different 1,2-aryldiamines and benzil (Scheme 2). Results in Table 3 show that electron-donating groups at the phenyl ring of 1,2-diamine favored the formation of product (Table 3, entries 2 and 3) to give quantitative yields. In contrast, electron-withdrawing groups such as benzoyl, chloro, and bromo gave slightly lower yields (94–95%) (Table 3, entries 4–6). The NO_2 group further reduced the yield to 90%, even the reaction time increased to 6 h (Table 3, entry 7). Reactions of 1,2-di(4-chlorophenyl)ethanedione **2b** and 1,2-di(2-furano)ethanedione **2c** with different 1,2-aryldiamines bearing electron-donating groups afforded products in quantitative yields (Table 3, entries 8–11), while the 1,2-aryldiamines bearing electron-withdrawing groups afforded slightly lower yields (Table 3, entries 12–14). On the other hand, the substituents at the 1,2-diketones had no significant effect on the yield of products. Since only symmetric 1,2-diketones were used for the condensation reactions, no regioisomers were generated as the products.

To test if 1 mol % $Ga(OTf)_3$ could effectively catalyze the reaction of 1,2-alkyldiamines, the reactions of 1,2-ethylenediamine **1h** with **2a**, **2b** and **2c** were carried out, and they all gave excellent yields (90–95%) of dihydropyrazines **3o**–**3q** (Table 3, entries 15–17). Since the reactions were carried out at room temperature, this condition was not strong enough to oxidize the dihydropyrazines to pyrazines. In an attempted condensation reaction of 1,2-phenylene diamine **1a** with 2,3-butanedione **2d**, it was found that the reaction did not take place in 6 h (Table 3, entry 18). Obviously, 1,2-dialkyldiketone is not suitable for the synthesis of quinoxaline derivatives under this general reaction condition.

In summary, a $Ga(OTf)_3$-promoted synthesis of quinoxaline derivatives has been developed. This method has advantages of very mild reaction conditions, simple manipulation, and high product yields. It also has a good aspect of green chemistry since the $Ga(OTf)_3$ catalyst can be easily recovered and reused for at least 10 times without significant change of activity. This protocol may also be applicable for large-scale preparation of quinoxalines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.058.

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15. After completion of this work, we found the following literature in which gallium triflate-catalyzed synthesis of quinoxalinesis was described. Prakash, G. K. S.; Mathew, T.; Vaghoo, H.; Panja, C.; Venkat, A.; Chacko, S.; Olah, G. A. ACS meeting abstract. AN2007:884295CAPLUS.
16. A general procedure for preparation of quinoxaline derivatives **3** and catalyst $Ga(OTf)_3$ recycle: A mixture of 1,2-diamine (1 mmol), 1,2-diketone (1 mmol), and $Ga(OTf)_3$ (0.01 mmol) in 3 mL of ethanol was stirred at room temperature. After completion of the reaction (monitored by TLC), the resultant was cooled with ice-salt bath, filtered to afford pure products **3**, and the filtrate containing $Ga(OTf)_3$ could be directly used by adding reactants. After ten recycles, the catalytic activity of $Ga(OTf)_3$ remained unchanged.