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$Ga(OTf)_3$-promoted condensation reactions for 1,5-benzodiazepines and 1,5-benzothiazepines

Xiang-Qiang Pan [a], Jian-Ping Zou [a,*], Zhi-Hao Huang [a], Wei Zhang [b,*]

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou University, 1 Renai Street, Suzhou, Jiangsu 215123, China
[b] Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA

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ABSTRACT

Condensation reactions of *o*-phenylenediamine and two equivalents of acetophenone under gallium(III) triflate catalysis produce biaryl-substituted 1,5-benzodiazepines. Similar reactions of *o*-phenylenediamine or *o*-aminothiophenol and *o*-hydroxy chalcones lead to formation of functionalized 1,5-benzodiazepines and 1,5-benzothiazepines in good to excellent yields. The *ortho*-hydoxy group of chalcones is crucial for this unprecedented condensation process.

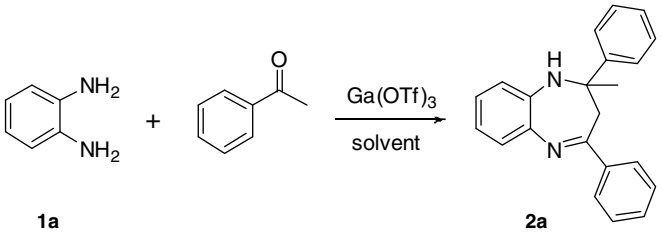
1,5-Benzodiazepines and 1,5-benzothiazepines are privileged heterocyclic ring systems because of their broad and important pharmacological properties.[1] Many functionalized benzodiazepines have been used as analgesic, sedative, anti-convulsant, anti-anxiety, anti-depressive, and hypnotic agents.[2] In addition to their biological activities, they are valuable synthetic intermediates for other heterocyclic compounds such as triazolo-, oxadiazolo-, oxazino-, and furanobenzodiazepines.[3]

A general way to construct the ring skeletons of 1,5-benzodiazepine and 1,5-benzothiazepine is via reactions of *o*-phenylenediamines (*o*-PDA) or *o*-aminothiophenol (*o*-ATP) with ketones,[4] α,β-unsaturated carbonyl compounds, or β-haloketones.[5] Catalysts such as $BF_3{\cdot}Et_2O$, $NaBH_4$, PPA/SiO_2, $MgO/POCl_3$, Amberlyst-15, $Yb(OTf)_3$, Al_2O_3/P_2O_5, AcOH/MW, sulfated zirconia, NBS, and ionic liquids[6] has been used to improve the reaction efficiency.

$Ga(OTf)_3$ is a water-tolerant strong Lewis acid catalyst, which has been used in organic reactions such as Beckmann rearrangement,[7] Friedel–Crafts reactions,[8,9] dehydration of aldoximes,[10] and highly regioselective rearrangement of 2-substituted vinylepoxides,[11] aqueous asymmetric Mukaiyama aldol reactions,[12] and constructions of fused-bicyclolactones[13] and fluorinated five-membered heterocycles.[14] As a part of our continuous effort on the study of the catalytic properties of gallium(III) salts,[15] we report herein a new utility of gallium(III) triflate catalyst for condensation reactions of *o*-phenylenediamine or *o*-aminothiophenol with carbonyl compounds to form functionalized 1,5-benzodiazepines and 1,5-benzothiazepines. Compared to other methods reported in the literature, gallium(III)-promoted reactions are straightforward, give good yields, and also lead to the discovery of a novel transformation for heterocycles.

o-Phenylenediamine and acetophenone were chosen as the substrates for method development reactions (Eq. 1). Table 1 shows the results using different reaction solvents under the conditions

Table 1
$Ga(OTf)_3$-catalyzed reactions of *o*-phenylenediamine and acetophenone[a]



1a **2a** (1)

Entry	Solvent	$Ga(OTf)_3$ (mol %)	Time (h)	**2a** Yield[b] (%)
1	CH_2Cl_2	10	12	56
2	MeOH	10	12	Trace
3	1,4-Dioxane	10	12	Trace
4	CH_3CN	10	4	92
5	CH_3CN	5	12	50
6	CH_3CN	1	24	23
7	CH_3CN	20	4	94
8	CH_3CN	0	12	—[c]

[a] Ambient temperature.
[b] Isolated yield.
[c] Imines were the major product.

* Corresponding authors. Tel./fax: +86 512 65112371 (J.-P.Z.); tel.: +1 617 287 6147; fax: +1 617 287 6030 (W.Z.).
E-mail addresses: wuyanhong@pub.sz.jsinfo.net (J.-P. Zou), wei2.zhang@umb.edu (W. Zhang).

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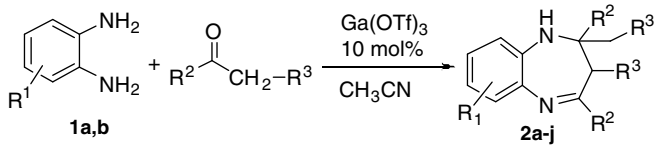
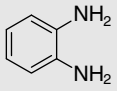
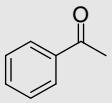
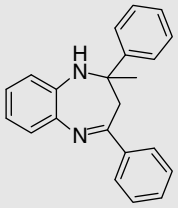
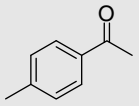
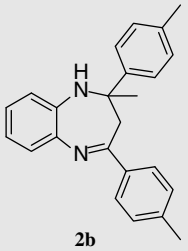
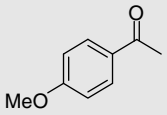
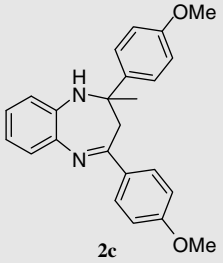
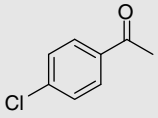
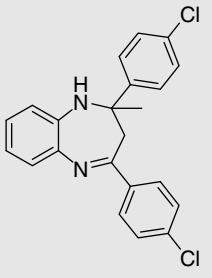
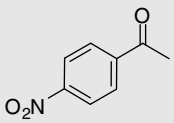
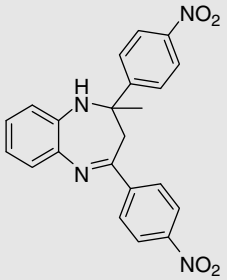
Table 2
1,5-Benzodiazepines from *o*-phenylenediamine and ketones

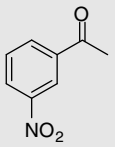
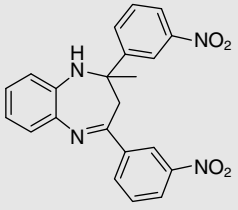
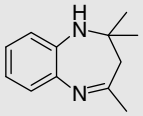
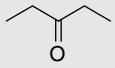
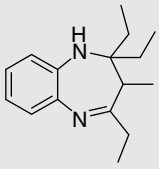
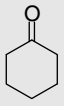
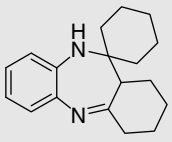
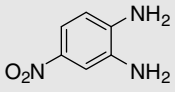
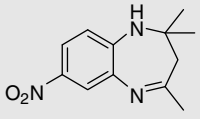


(2)

Entry	*o*-PDA	Ketone	Product **2**[a]	Yield[b] (%)
1	 **1a**		 **2a**	92
2	**1a**		 **2b**	85
3	**1a**		 **2c**	90
4	**1a**		 **2d**	83
5	**1a**		 **2e**	85

(*continued on next page*)

Table 2 (*continued*)

Entry	*o*-PDA	Ketone	Product **2**[a]	Yield[b] (%)
6	**1a**		 **2f**	88
7	**1a**		 **2g**	92
8	**1a**		 **2h**	75
9	**1a**		 **2i**	70
10	 **1b**		 **2j**	86 (91:9)[c]

[a] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectra.
[b] All products were purified by flash column chromatography.
[c] Product ratio was determined by ^{1}H NMR.

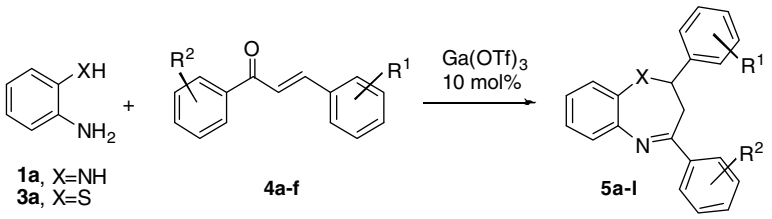
of 10 mol % catalyst and 4–12 h at room temperature. Acetonitrile was found to be a good solvent (Table 1, entry 4). Catalyst loading test was also conducted. It was found that 10 mol % of $Ga(OTf)_3$ was sufficient to catalyze the reaction, and gave 1,5-benzodiazepine in 92% yield (Table 1, entry 4). Increasing the amount of $Ga(OTf)_3$ to 20 mol % did not significantly improve the yield (Table 1, entry 7). However, if the amount of the catalyst was reduced to 5 and 1 mol %, the product yield was reduced to 50% and 23%, respectively (Table 1, entries 5 and 6). In a control reaction without using the catalyst, no desired product was observed after 12 h.

The best condition for the synthesis of 1,5-benzodiazepine was found to be as follows: A mixture of *o*-phenylenediamine (2 mmol), acetophenone (4.5 mmol), and $Ga(OTf)_3$ (0.2 mmol) in 10 mL of MeCN was stirred at room temperature for 4–6 h.[16] This general procedure was used for reactions of *o*-phenylenediamine with different aryl- and alkylketones (Table 2).

Reactions of *o*-phenylenediamine with acetophenones bearing electron-donating and electron-withdrawn substitution groups gave products in good to excellent yields (83–92%) (Eq. 2) (Table 2, entries 1–6). Reactions of alkylketones such as acetone, pentanone-3, and cyclohexanone also gave benzodiazapines (Table 2, entries 7–10), but low yields were obtained from the more hindered alkylketones (Table 2, entries 8 and 9). 4-Nitrobenzene-1,2-diamine was used as the substrate to evaluate the substituent effect on *o*-phenylenediamine. Good product yield (86%) and regioselectivity (91:9) were obtained from this reaction (Table 2, entry 10).

The reaction of α,β-unsaturated ketone (chalcone **4a**) and *o*-phenylenediamine **1a** was carried out to study the reaction scope (Eq. 3). No desired condensation product was detected from the reaction conducted at 60 °C (Table 3, entry 1). We wonder if the amino group is not nucleophilic enough for the addition. Thus, *o*-aminothiophenol was used to replace the *o*-phenylenediamine for the reaction. As we anticipated, 2,4-diphenyl-1,5-benzothiazepine **5b** was isolated at 30% yield (Table 3, entry 2). Even the yield was low, but it encouraged us to further explore the reaction of chalcone derivatives. To our surprise, when 2-hydroxychalcone **4b** was used as the substrate, the reaction with *o*- aminothiophenol

Table 3
Synthesis of 1,5-benzothiazepines/1,5-benzodiazepines from *o*-aminothiophenol/*o*-phenylenediamine and chalcones

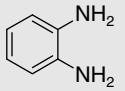
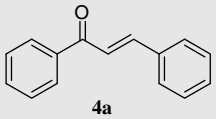
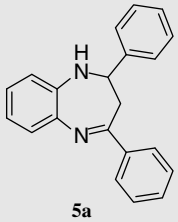
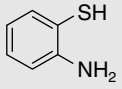
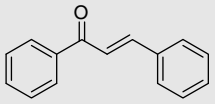
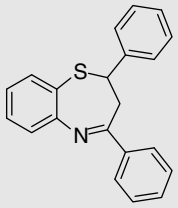
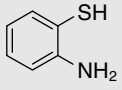
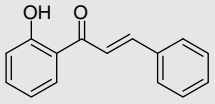
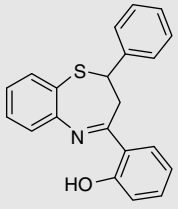
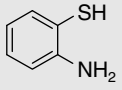
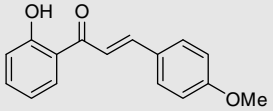
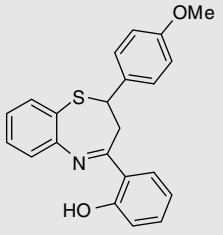
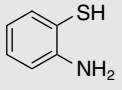
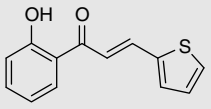
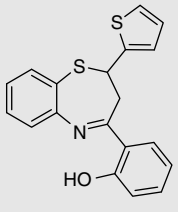
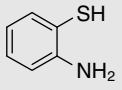
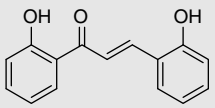
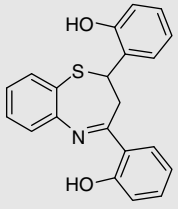


1a, X=NH
3a, X=S

4a-f

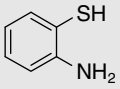
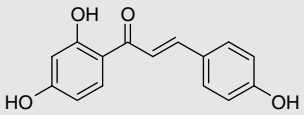
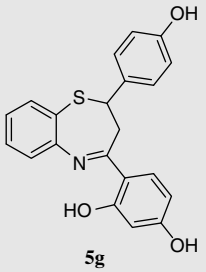
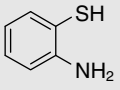
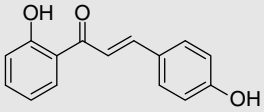
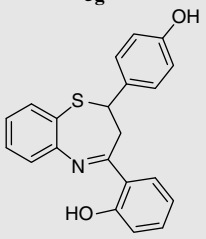
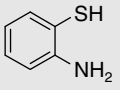
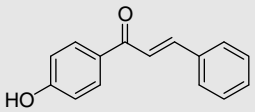
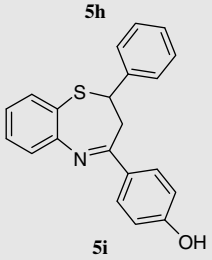
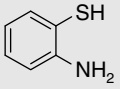
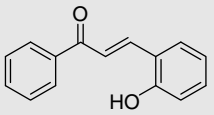
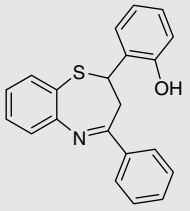
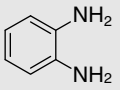
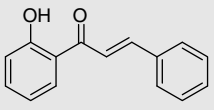
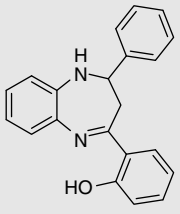
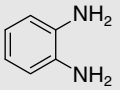
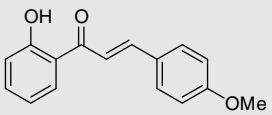
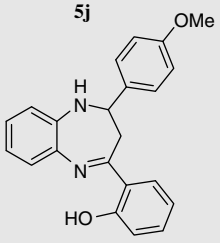
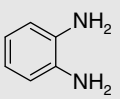
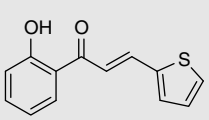
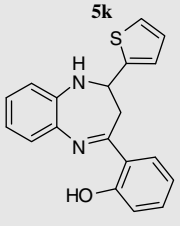
5a-l

(3)

Entry	*o*-PDA/*o*-ATP	Ketone	Product **5**[a]	Yield[b] (%)
1	 **1a**	 **4a**	 **5a**	Trace
2	 **3a**	 **4a**	 **5b**	30
3	 **3a**	 **4b**	 **5c**	95
4	 **3a**	 **4c**	 **5d**	93
5	 **3a**	 **4d**	 **5e**	95
6	 **3a**	 **4e**	 **5f**	91

(*continued on next page*)

Table 3 (*continued*)

Entry	*o*-PDA/*o*-ATP	Ketone	Product **5**[a]	Yield[b] (%)
7	 **3a**	 **4f**	 **5g**	87
8	 **3a**	 **4g**	 **5h**	92
9	 **3a**	 **4h**	 **5i**	35
10	 **3a**	 **4i**		—
11	 **1a**	 **4b**	 **5j**	85
12	 **1a**	 **4c**	 **5k**	84
13	 **1a**	 **4d**	 **5l**	88

[a] Structures were characterized by ^{1}H and ^{13}C NMR and HRMS.
[b] All products were purified by flash column chromatography.

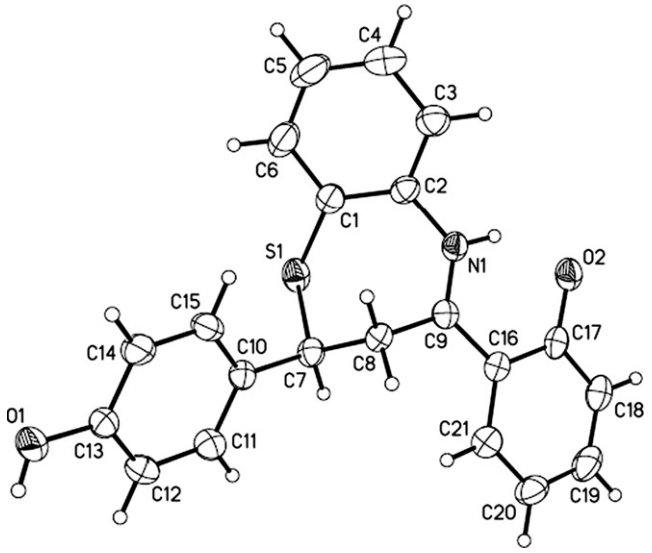


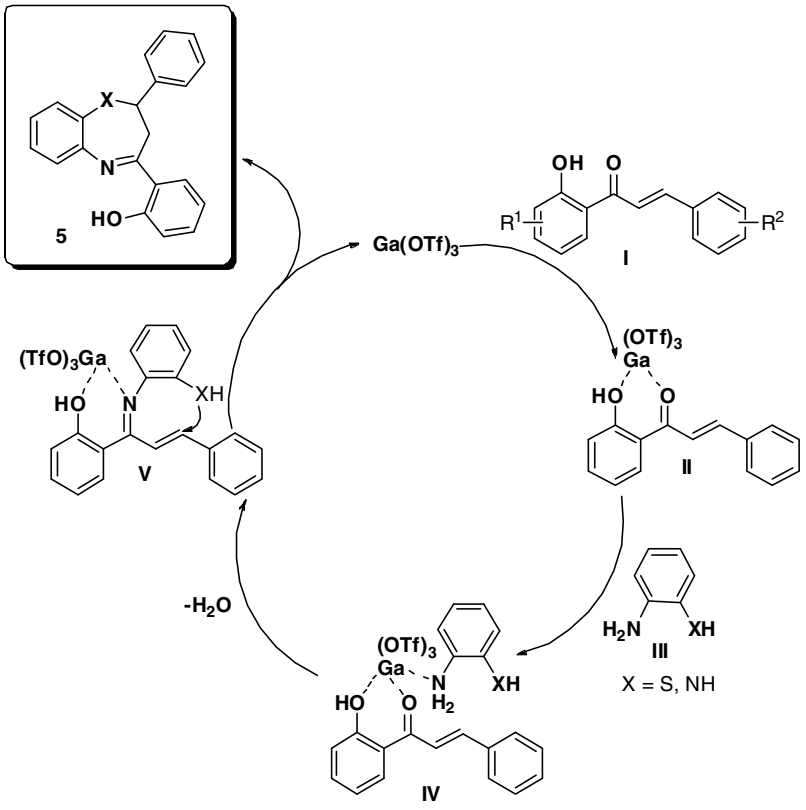
Figure 1. X-ray structure of **5h**.

3a gave the condensation product **5c** in quantitative yield (Table 3, entry 3).[17] To find out the role of the 2-hydroxy group, other 2-hydroxychalcone derivatives were tested (Table 3, entries 4–8). The results showed that these reactions also gave high product yields. Among them, the structure of **5h** was confirmed by X-ray analysis (Fig. 1). To evaluate the influence of the hydroxy group, chalcones with the hydroxy group at different positions were tested. The reaction of 4-hydroxychalcone with *o*-aminothiophenol only gave 35% yield of product (Table 3, entry 9). The reaction of 2′-hydroxychalcone did not afford any product (Table 3, entry 10). Results from these two reactions indicated that the hydroxy at 2-position of chalcone is critical for the condensation reactions. To verify this observation, *o*-phenylenediamine was re-employed for the reaction with 2-hydroxychalcone. Indeed, the reaction proceeded and afforded 1,5-benzodiazepine product in 85% yield (Table 3, entry 11). Reactions of 2-hydroxychalcones **4c** and **4d** with *o*-phenylenediamine also generated products **5k** and **5l** in 84% and 88% yield, respectively (Table 3, entries 12 and 13).

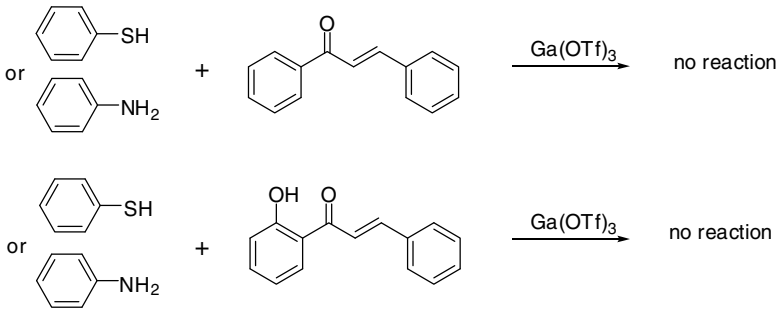
A mechanism for the reaction of *o*-phenylenediamine **1a** or *o*-aminothiophenol **3a** with 2-hydroxychalcone derivatives **4** to form 2,4-disubstituted 1,5-benzodiazepine or 2,4-disubstituted 1,5-benzothiazepine was proposed (Scheme 1). At the first step, catalyst $Ga(OTf)_3$ and 2-hydroxychalcone **I** form complex **II**, which further reacts with **III** to afford complex **IV** and then **V** after losing H_2O. The XH group attacks the C=C bond and leads to the formation of condensation product **5**. In this process the 2-hydroxy group in chalcone has the following two important roles: (1) the 2-hydroxy group involves in the formation of stable complex **III** by chelating with $Ga(OTf)_3$ and facilitates the dehydration process to from complex **V**; (2) the 2-hydroxy makes the α,β-unsaturated carbonyl more reactive toward the addition of XH.

We have also explored the reactions of aniline or thiophenol with chalcone using $Ga(OTf)_3$ as a catalyst. No Michael addition product was observed (Scheme 2).

In summary, $Ga(OTf)_3$ was found to be an effective catalyst for the synthesis of 2,2,4-trisubstituted-1,5-benzodiazepines under mild reaction conditions. $Ga(OTf)_3$ also promotes the reactions of *o*-phenylenediamine and *o*-aminothiophenol with 2-hydroxychalcone derivatives to form 2,4-disubstituted-1,5-benzodiazepines and 2,4-disubstituted-1,5-benzothiazepines through a previously unreported condensation process.



Scheme 1. Proposed mechanism for $Ga(OTf)_3$-catalyzed reaction of 2-hydroxychalcones with *o*-phenylenediamine or *o*-aminothiophenol.



Scheme 2. Reaction condition: chalcone (1.0 equiv), aniline, or thiophenol (1.1 equiv), $Ga(OTf)_3$ (10 mol %), CH_3CN, room temperature, 6 h.

Acknowledgement

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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.2008.06.082.

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16. *A general procedure for synthesis of 2,2,4-trisubstituted-1,5-benzodiazepines* **2** *(Table 2)*: A mixture of *o*-phenylenediamine (2 mmol), acetophenone (4.5 mmol), and $Ga(OTf)_3$ (0.2 mmol) in 10 mL of MeCN was stirred at room temperature for 5–6 h. After completion of the reaction (TLC analysis), the reaction mixture was diluted with water, and extracted with dichloromethane (2×10 mL). The combined organic layer was dried over Na_2SO_4, concentrated to dryness in vacuo, and the residue was purified by column chromatography (eluted with 2:8 EtOAc–petroleum) to afford pure diazepine.
17. *A general procedure for synthesis of 2,4-disubstituted-1,5-benzodiazepines and 2,4-disubstituted-1,5-benzothiaze-pines* **5** *(Table 3)*: A mixture of *o*-aminothiophenol (1.1 mmol), chalcone (1 mmol), and $Ga(OTf)_3$ (0.1 mmol) in 10 mL of MeCN was stirred at 60 °C for an appropriate time. After completion of the reaction (TLC analysis), the residue was purified by column chromatography (eluted with 2:8 EtOAc–petroleum ether) to afford pure thiadiazepine.