



Gallium(III) triflate-catalyzed [4+2+1] cycloadditions for the synthesis of novel 3,4-disubstituted-1,5-benzodiazepines

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ABSTRACT

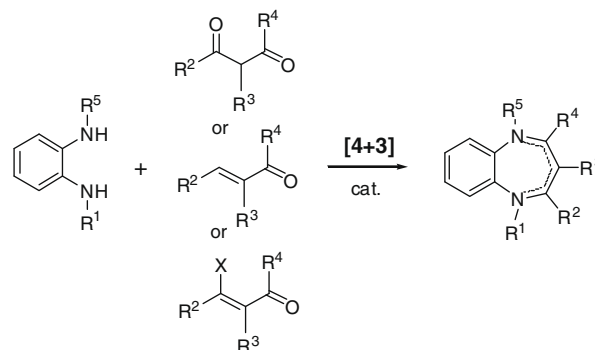
Gallium(III) triflate-catalyzed [4+2+1] cycloaddition of *o*-phenylenediamines and 2 equiv of alkynoate under solvent-free and ultrasonic irradiation conditions afforded novel 3,4-disubstituted-1,5-benzodiazepines in 82–90% yields.

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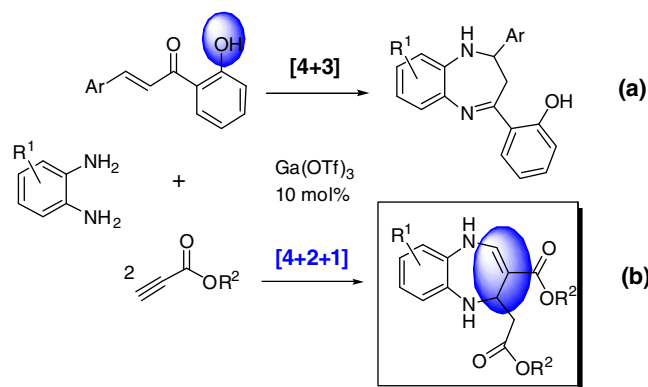
Benzodiazepines are a privileged heterocyclic system. The derivatives of benzodiazepine have a broad range of pharmacological and biological activities.¹ Many of these compounds have been used as analgesic, sedative, anti-convulsant, antianxiety, antidepressive, hypnotic, and antiinflammatory agents.² 1,5-Benzodiazepines are valuable synthetic intermediates for the preparation of other heterocyclic compounds such as triazolo-, oxadiazolo-, oxazino-, furano-, and quinazolino-benzodiazepines.³

1,5-Benzodiazepines can be prepared by cyclization or cycloaddition reactions. The cycloaddition approach is more efficient. [4+3] Cycloadditions of *o*-phenylene-diamines with 1,3-diketones, α,β -unsaturated carbonyl compounds, or β -haloketones have been well established to construct 2,4-disubstituted, 2,2,4-trisubstituted, and 2,2,3,4-tetrasubstituted 1,5-benzodiazepines (Scheme 1).⁴ A wide range of catalysts, such as $\text{BF}_3\cdot\text{OEt}_2$,⁵ polyphosphoric acid,⁶ $\text{CeCl}_3\text{-NaI/SiO}_2$,⁷ I_2 ,⁸ ZnCl_2 ,⁹ SmI_2 ,¹⁰ YbCl_3 ,¹¹ MgO/POCl_3 ,¹² Amberlyst-15,¹³ $\text{Yb}(\text{OTf})_3$,¹⁴ $\text{Ga}(\text{OTf})_3$,¹⁵ $\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$,¹⁶ AcOH/MW ,¹⁷ sulfated zirconia,¹⁸ NBS,¹⁹ Cerium ammonium nitrate(CAN)²⁰, montmorillonite K10,²¹ and ionic liquids,²² have been developed for this kind of cycloaddition reactions.

We have recently introduced gallium(III) triflate ($\text{Ga}(\text{OTf})_3$)-catalyzed [4+3] cycloaddition reactions of *o*-phenylenediamine (*o*-PDA) and *o*-hydroxychalcones for the synthesis of 1,5-benzodiazepines.^{15b} In that work, we found that the *o*-hydroxy group is essential to the condensation process (Scheme 2, a). This observation encouraged us to expand the scope and find alternative electro-



Scheme 1. General [4+3] cycloadditions for the synthesis of substituted 1,5-benzodiazepines.

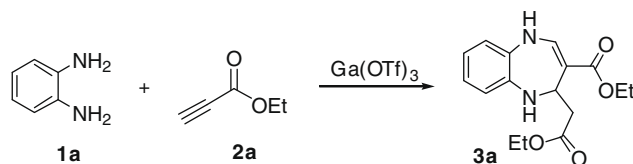


Scheme 2. $\text{Ga}(\text{OTf})_3$ -catalyzed [4+3] and [4+2+1] cycloadditions for the synthesis of 2,4- and 3,4-disubstituted 1,5-benzodiazepines.

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Table 1
Ga(OTf)₃-catalyzed reaction of *o*-phenylenediamines and ethyl propiolate



Entry	1a:2a ratio	Solvent	Ga(OTf) ₃ (mol %)	Temp (°C)	Time (h)	3a, isolated yield (%)
1	1:1	CH ₂ Cl ₂	—	40	24	28
2	1:1	CH ₂ Cl ₂	10	40	24	40
3	1:1	CH ₂ Cl ₂	20	40	24	43
4	1:2	CH ₂ Cl ₂	10	40	36	42
5	1:2.5	CH ₂ Cl ₂	10	40	48	38
6	1:2.5	Solvent-free	—	25	1	Trace
7	1:2.5	Solvent-free	—	25	24	54
8	1:2.5	Solvent-free	10	25	1	87
9	1:2.5	Solvent-free	10	25	10 min	88

philes for the cycloaddition reactions. Our research effort in this direction has led to the discovery of a new cycloaddition reaction. Reported in this paper is the first example of Ga(OTf)₃-catalyzed [4+2+1] cycloaddition of *o*-PDA and alkynoates for the preparation of 3,4-disubstituted-1,5-benzodiazepines containing only a C=C bond without C=N bond in the heterocyclic moiety (Scheme 1, b). To the best of our knowledge, such 3,4-disubstituted-1,5-benzodiazepines represent a new type of 1,5-benzodiazepines and no [4+2+1] cycloadditions have ever been reported for the synthesis of 1,5-benzodiazepines.

The initial reaction of 1:1 *o*-phenylenediamine **1** and ethyl propiolate **2** was performed without any catalyst. After refluxing the reaction mixture in CH₂Cl₂ for 24 h, a major product was isolated in 28% yield, and its structure was characterized to be 3,4-disubstituted 1,5-benzodiazepine **3a** by ¹H NMR, ¹³C NMR, and HRMS analysis (Table 1, entry 1). A literature search revealed that compound **3a** is a new type of 1,5-benzodiazepines. Most 1,5-benzodiazepines are 2,4-disubstituted or 2,2,4-trisubstituted and containing a C=N bond. The 3,4-disubstituted-1,5-benzodiazepine we obtained has a C=C bond, but has no C=N bond. The discovery of a new type of 1,5-benzodiazepines encouraged us to optimize the reaction using Ga(OTf)₃ as a catalyst. At the catalyst loading of 10% and 20%, the product yield was 40% and 43%, respectively (Table 1, entries 2 and 3). Changing the ratio for *o*-phenylenediamine **1** and ethyl propiolate **2** from 1:1 to 1:2 and 1:2.5, and increasing the reaction time to 48 h, the yield had no significant change (Table 1, entries 4–5). Screening of reaction solvents

Table 2
Different catalysts for cycloaddition reaction of *o*-phenylenediamine and ethyl propiolate^a

Entry	Catalyst	Time (min)	3a, isolated yield (%)
1	Ga(OTf) ₃	10	88
2	Yb(OTf) ₃	20	86
3	La(OTf) ₃	10	67
4	Gal ₃	10	n.r
5	AlCl ₃	10	30
6	ZnCl ₂	10	Trace
7	L-Proline	30	44
8	SA	30	14

^a The reactions were all carried out under the conditions of 1 mmol *o*-phenylenediamine, 2.5 mmol ethyl propiolate, 10% mole catalyst, solvent-free, and ultrasonic irradiation at 25 °C.

including acetonitrile, methanol, ethanol, and ethyl acetate also had no significant yield improvement. Surprisingly, the reaction conducted under solvent free conditions for 1 h using 10% Ga(OTf)₃ afforded **3a** in 87% isolated yield (Table 1, entry 8). The same reaction was completed in 10 min under ultrasonic irradiation (Table 1, entry 9).

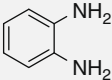
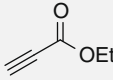
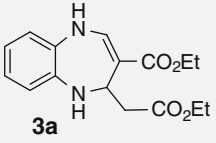
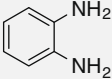
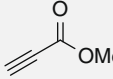
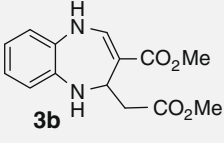
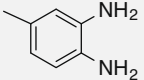
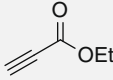
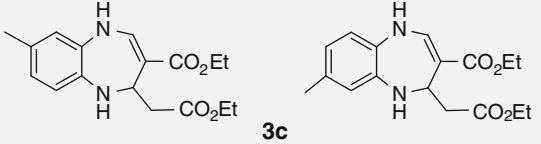
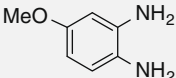
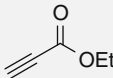
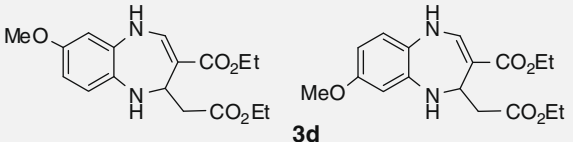
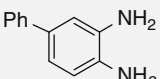
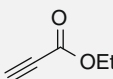
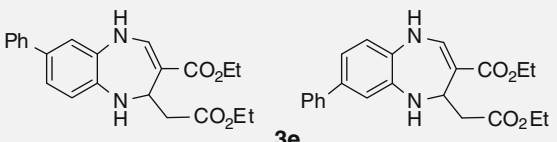
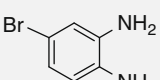
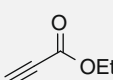
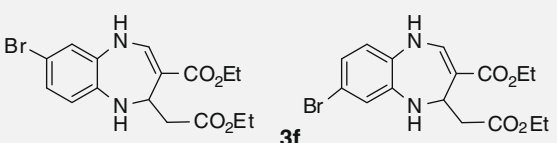
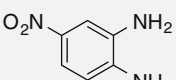
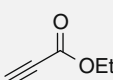
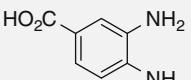
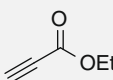
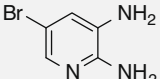
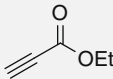
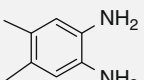
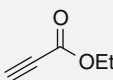
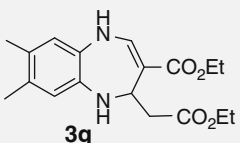
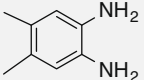
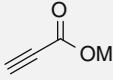
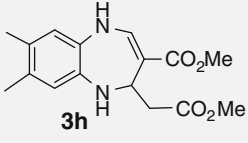
Different catalysts such as Lewis acid, organic molecule, and solid acid (SA) were also tested under solvent-free and ultrasonic irradiation conditions. The results showed that the Ga(OTf)₃ is the best (Table 2, entry 1); Yb(OTf)₃ and La(OTf)₃ are good (Table 2, entries 2, 3); and others are poor. Thus, the optimal reaction conditions for the [4+2+1] cycloaddition reaction are: 1:2.5 *o*-phenylenediamine **1** and alkynoate **2**, 10% Ga(OTf)₃ catalyst, solvent-free, ultrasonic irradiation at 25 °C.²³ This condition has been applied for the synthesis of variety of 3,4-disubstituted-1,5-benzodiazepines **3** shown in Table 3.

As shown in the Table 3, electronic-rich and mono-substituted *o*-phenylenediamines such as 4-methyl-, 4-methoxy-, and 4-phenyl-*o*-phenylenediamines led to the formation of desired products **3c–f** in good yields, but each is a mixture of two unseparable regioisomers (Table 3, entries 3–6). Electron-poor *o*-phenylenediamines containing a NO₂ or CO₂H group and *o*-pyridinediamines could not react with ethyl propiolate (Table 3, entries 7–9). Just like the unsubstituted *o*-phenylenediamine **1a**, disubstituted and symmetrical *o*-phenylenediamine **1i** gave single product **3g** and **3h** in good yields (Table 3, entries 10–11). Interestingly, naphthalene-1,8-diamine **1j** only reacted with 1 equiv of ethyl propiolate **2a** to afford the six-membered ring adduct **4** in 90% yield (Table 3, entry 12).

A proposed reaction mechanism to explain this novel [4+2+1] cycloaddition reaction is shown in Scheme 3. Catalyst Ga(OTf)₃ and ethyl propiolate **2** first forms complex **5**. Both amino groups in **1** attack the C≡C group of 2 equiv of **5** to produce **6**. The cyclization of **5** leads to the formation of benzodiazepine **7**. Final product **3** is generated by releasing two molecules of Ga(OTf)₃ from **7**.

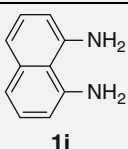
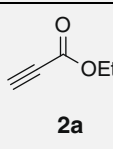
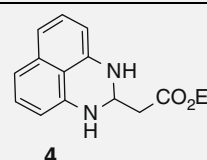
In summary, we have developed a novel [4+2+1] cycloaddition reaction to synthesize a new class of 3,4-disubstituted 1,5-benzodiazepines. The reactions of *o*-phenylenediamines and alkyl propiolates are catalyzed by 10% Ga(OTf)₃ under ultrasonic irradiation, at 25 °C, and solvent-free conditions. Products have two carbonyl groups, two NH groups, and a C=C bond, which can be further functionalized to construct complex heterocyclic compounds.

Table 3
3,4-Disubstituted-1,5-benzodiazepines from the reaction of *o*-phenylenediamines and alkyl propiolates^a

Entry	Diamine 1	Alkynoate 2	Time (min)	Product 3	Isolated yield (%)
1	 1a	 2a	10	 3a	88
2	 1a	 2b	15	 3b	87
3	 1b	 2a	20	 3c	90 ^b
4	 1c	 2a	10	 3d	90 ^b
5	 1d	 2a	25	 3e	85 ^b
6	 1e	 2a	30	 3f	82 ^b
7	 1f	 2a	60	n.r.	
8	 1g	 2a	60	n.r.	
9	 1h	 2a	60	n.r.	
10	 1i	 2a	10	 3g	87
11	 1i	 2b	25	 3h	83

(continued on next page)

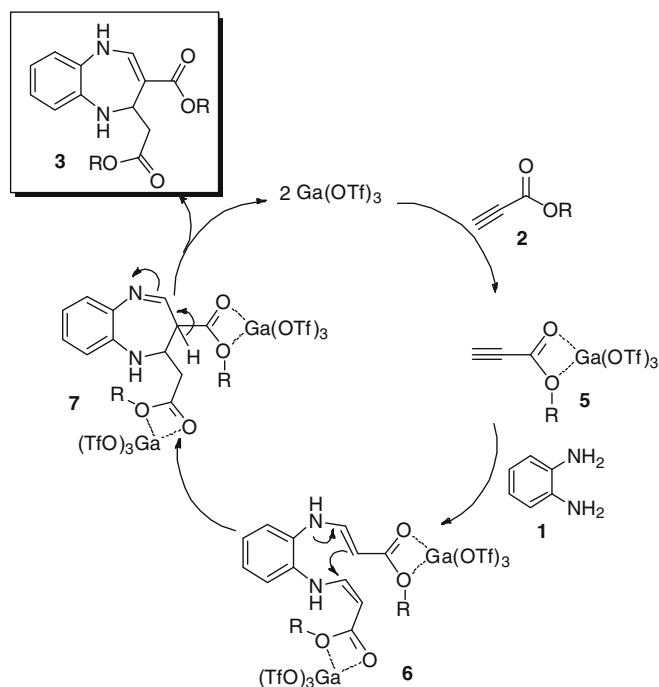
Table 3 (continued)

Entry	Diamine 1	Alkynoate 2	Time (min)	Product 3	Isolated yield (%)
12			30 ^c		90

^a The reactions were carried out under the conditions of 1:2.5 of diamine **1** and alkyl propiolate **2**, 10% Ga(OTf)₃, solvent-free, ultrasonic irradiation at 25 °C unless otherwise noted.

^b Total yield, the two mixtures is about 1:1.

^c Heated at 60 °C.



Scheme 3. Proposed mechanism for Gallium(III) triflate-catalyzed [4+2+1] cycloadditions.

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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.2009.11.049.

References and notes

- (a) Schutz, H. *Benzodiazepines*; Springer: Heidelberg, 1982; (b) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, pp 166–170.
- Randall, L. O.; Kappel, B. In *Benzodiazepines*; Garattini, S., Mussini, E., Randall, L. O., Eds.; Raven Press: New York, 1973; p 27.
- (a) Aversa, M. C.; Ferlazzo, A.; Gionnetto, P.; Kohnke, F. H. *Synthesis* **1986**, 230; (b) Essaber, M.; Baouid, A.; Hasnaoui, A.; Benharref, A.; Lavergne, J. P. *Synth. Commun.* **1998**, *28*, 4097; (c) Xu, J. X.; Wu, H. T.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 84; (d) Zhang, X. Y.; Xu, J. X.; Jin, S. *Chin. J. Chem.* **1999**, *17*, 404; (e) Reddy, K. V. V.; Rao, P. S.; Ashok, D. *Synth. Commun.* **2000**, *30*, 1825; (f) Zhang, W.; Williams, J. P.; Lu, Y.; Nagashima, T.; Chu, Q. *Tetrahedron Lett.* **2007**, *48*, 563.
- (a) Ried, W.; Torinus, E. *Chem. Ber.* **1959**, *92*, 2902; (b) Stahlhofen, P.; Ried, W. *Chem. Ber.* **1957**, *90*, 815.
- Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2657.
- Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun.* **1999**, *29*, 1941.
- Sabitha, G.; Reddy, G. S.; Reddy, K. B.; Reddy, N. M.; Yadav, J. S. *Adv. Synth. Catal.* **2004**, *346*, 921.
- (a) Bandgar, B. P.; Bettigeri, S. V.; Joshi, N. S. *Synth. Commun.* **2004**, *34*, 1447; (b) Chen, W. Y.; Lu, J. *Synlett* **2005**, 1337.
- Pasha, M. A.; Jayashankara, V. P. *Heterocycles* **2006**, *68*, 1017.
- Luo, Y. Q.; Xu, F.; Han, X. Y.; Shen, Q. *Chin. J. Chem.* **2005**, *23*, 1417.
- Wu, J. T.; Xu, F.; Zhou, Z. Q.; Shen, Q. *Synth. Commun.* **2006**, *36*, 457.
- Balakrishna, M. S.; Kaboundin, B. *Tetrahedron Lett.* **2001**, *42*, 1127.
- Yadav, J. S.; Reddy, B. V. S.; Eshwaraian, B.; Anuradha, K. *Green Chem.* **2002**, *4*, 592.
- Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193.
- (a) Huang, Z. H.; Zou, J. P.; Jiang, W. Q. *Tetrahedron Lett.* **2006**, *47*, 7965; (b) Pan, X. Q.; Zou, J. P.; Huang, Z. H.; Zhang, W. *Tetrahedron Lett.* **2008**, *49*, 5302; (c) Cai, J. J.; Zou, J. P.; Pan, X. Q.; Zhang, W. *Tetrahedron Lett.* **2008**, *49*, 7386.
- Kaboundin, B.; Navaee, K. *Heterocycles* **2001**, *55*, 1443.
- Pozarentzi, M.; Stephanidou, S. J.; Tsoleridis, C. A. *Tetrahedron Lett.* **2002**, *43*, 1755.
- Reddy, B. M.; Sreekanth, P. M. *Tetrahedron Lett.* **2003**, *44*, 4447.
- Kuo, C. W.; More, S. V.; Yao, C. F. *Tetrahedron Lett.* **2006**, *47*, 8523.
- Varala, R.; Enugala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, 1009.
- An, L. T.; Ding, F. Q.; Zou, J. P.; Lu, X. H. *Synth. Commun.* **2008**, *38*, 1259.
- Du, Y. Y.; Tian, F. L.; Zhao, W. Z. *Synth. Commun.* **2006**, *36*, 1661.
- A general procedure for the synthesis of 2,3-disubstituted-1,5-benzodiazepines **3**: A mixture of *o*-phenylenediamine (1 mmol), ethyl propiolate (2.5 mmol), and Ga(OTf)₃ (0.1 mmol) was irradiated by ultrasonic wave at 25 °C. After completion of the reaction (TLC analysis), the resultant was diluted by ethyl acetate and directly purified by column chromatography (eluted with 1:6 EtOAc–petroleum) to afford pure product **3**.