Tetrahedron Letters 54 (2013) 6178–6180

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Recyclable gallium(III) triflate-catalyzed [4+3] cycloaddition for synthesis of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines

Shi-Gang Huang [a], Hai-Feng Mao [a], Shao-Fang Zhou [a], Jian-Ping Zou [a,b,]*, Wei Zhang [c,]*

[a] *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou University, 199 Renai Street, Suzhou, Jiangsu 215123, China*
[b] *Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, China*
[c] *Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA*

ARTICLE INFO

Article history:
Received 9 August 2013
Revised 22 August 2013
Accepted 24 August 2013
Available online 31 August 2013

Keywords:
$Ga(OTf)_3$
Catalysis
[4+3] Cycloaddition
1,3-Diarylpropynones
2,4-Disubstituted-3*H*-benzo[*b*][1,4]diazepines

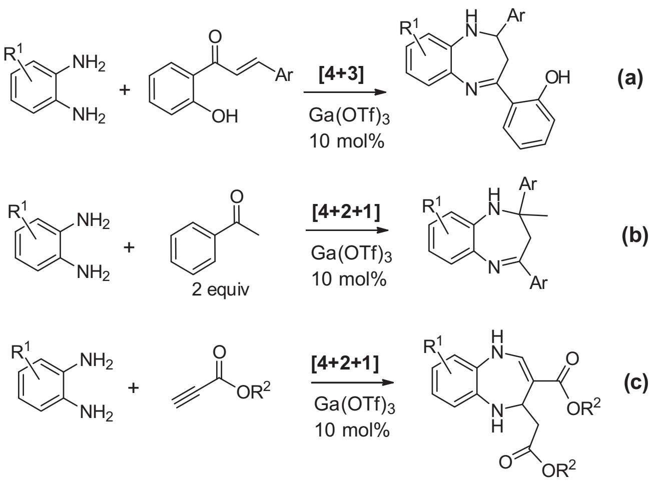
ABSTRACT

Simple and efficient $Ga(OTf)_3$-catalyzed [4+3] cycloaddition of 1,3-diarylpropynones and *o*-phenylenediamines is developed for the preparation of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines. The reaction has advantages of using a green solvent, generating a minimal amount of waste, and easy catalyst recycle.

Compounds containing privileged benzodiazepine ring system have a wide range of pharmacological and biological activities.[1] They have been used as analgesic, sedative, anticonvulsant, anti-anxiety, antidepressive, hypnotic, and antiinflammatory agents.[2] 1,5-Benzodiazepines can be prepared by cyclization or cycloaddition of *o*-phenylenediamines with 1,3-diketones, α,β-conjugated alkenones, or β-haloketones.[3] However, reactions of *o*-phenylenediamines with α,β-conjugated alkynones are limited.[4]

We have recently reported $Ga(OTf)_3$-catalyzed [4+3] and [4+2+1] cycloaddition reactions of *o*-phenylenediamines for the synthesis of benzodiazepines (Scheme 1). The reaction of *o*-phenylenediamines with *o*-hydroxychalcones[5] or acetophenones[6] both afforded 2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines (Scheme 1, a and b). The reaction of *o*-phenyl-enediamines with alkynoates afforded 2,5-dihydro-1*H*-benzo[*b*]-[1,4]diazepines (Scheme 1, c).[7] Introduced in this Letter is a new method for the synthesis of 2,4-disubstituted-3*H*-benzo[*b*]-[1,4]diazepines by [4+3] cycloaddition of *o*-phenylenediamines with 1,3-diarylpropynones.

The initial cycloadditions were carried out using equal molar *o*-phenylenediamine **1a** and 1,3-diphenylprop-2-yn-1-one **2a** at room temperature and in different solvents including CH_3CN, CH_2Cl_2, EtOH, and EtOH/H_2O. It was found that 95% EtOH is a good choice of solvent (Table 1, entry 4). Reactions with different ratios of substrates indicated that 1:1.5 of **1a**:**2a** increased the yield to 71% (Table 1, entry 7). Increase of the reaction temperature to 40 °C further improved the yield to 78% (Table 1, entry 9), but



Scheme 1. [4+3] and [4+2+1] cycloadditions of *o*-phenylenediamines.

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* Corresponding authors.
E-mail addresses: jpzou@suda.edu.cn (J.-P. Zou), wei2.zhang@umb.edu (W. Zhang).

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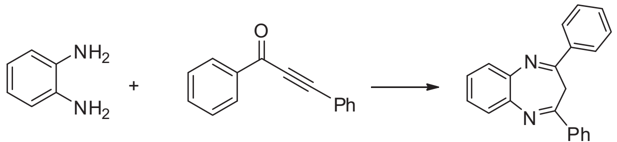
http://dx.doi.org/10.1016/j.tetlet.2013.08.092

the reaction under reflux (78 °C) decreased the yield to 52% (Table 1, entry 10). Increase of the reaction time from 10 to 24 h gave the best yield of 92% (Table 1, entry 11). Reaction without catalyst or with 5 mol % of catalyst gave product in 28% and 77% yields, respectively (Table 1, entries 12 and 13). The effort of reaction optimization revealed that the best condition for the cycloaddition is to use 1:1.5 of **1a**:**2a** with 10 mol % of $Ga(OTf)_3$ in 95% EtOH and at room temperature for 24 h.

Table 1
$Ga(OTf)_3$-catalyzed reactions of **1a** and **2a**[a]

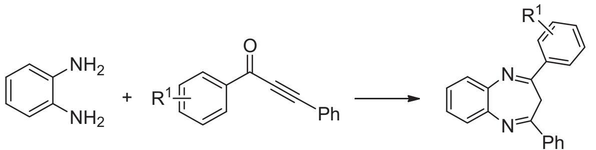


1a **2a** **3a**

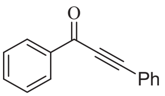
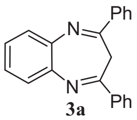
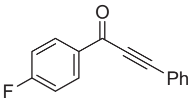
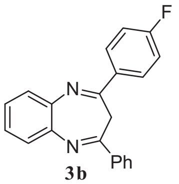
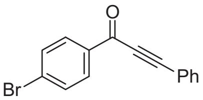
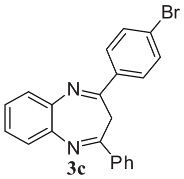
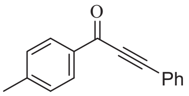
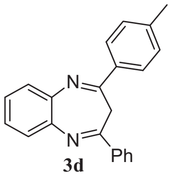
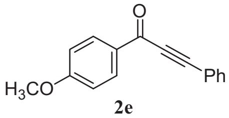
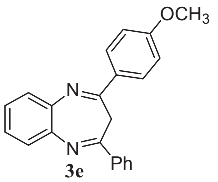
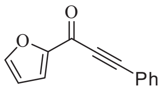
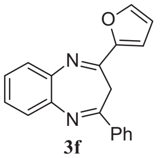
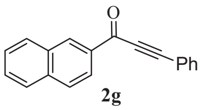
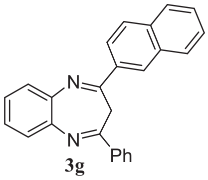
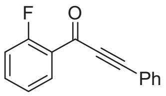
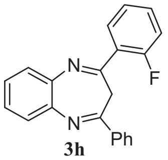
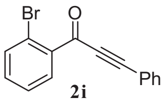
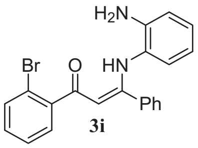
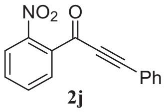
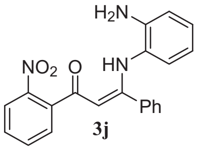
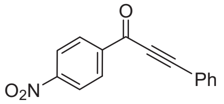
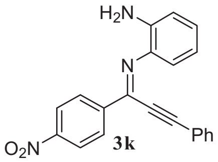
Entry	**1a**:**2a**	Solvent	$Ga(OTf)_3$ (mol %)	Time (h)	Yield[b] (%)
1	1:1	CH_3CN	10	10	Trace
2	1:1	CH_2Cl_2	10	10	Trace
3	1:1	EtOH	10	10	35
4	1:1	95% EtOH	10	10	51
5	1:1	50% EtOH	10	10	38
6	1:1.2	95% EtOH	10	10	60
7	1:1.5	95% EtOH	10	10	71
8	1:2	95% EtOH	10	10	72
9	1:1.5	95% EtOH	10	10	78[c]
10	1:1.5	95% EtOH	10	10	52[d]
11	1:1.5	95% EtOH	10	24	92
12	1:1.5	95% EtOH	–	24	28
13	1:1.5	95% EtOH	5	24	77

[a] Reactions at room temp.
[b] Isolated yields.
[c] 40 °C.
[d] Reflux.

Table 2
$Ga(OTf)_3$-catalyzed reactions of **1a** and **2a**–**2k**[a]



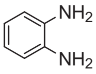
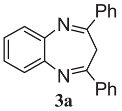
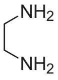
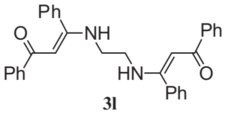
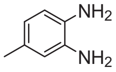
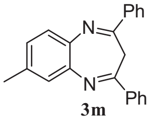
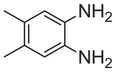
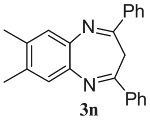
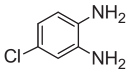
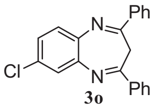
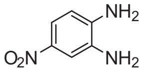
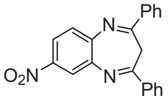
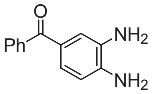
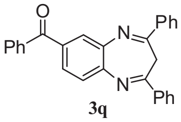
1a **2a-2k** **3a-3k**

Entry	Propynone **2**	Product **3**	Yield[b] (%)
1	 **2a**	 **3a**	92
2	 **2b**	 **3b**	91
3	 **2c**	 **3c**	95
4	 **2d**	 **3d**	74
5	 **2e**	 **3e**	42
6	 **2f**	 **3f**	94
7	 **2g**	 **3g**	45
8	 **2h**	 **3h**	97
9	 **2i**	 **3i**	92
10	 **2j**	 **3j**	86
11	 **2k**	 **3k**	92

[a] Reaction conditions: 1 mmol **1a**, 1.5 mmol **2**, 10 mol % $Ga(OTf)_3$, 25 °C for 24 h.
[b] Isolated yield.

To evaluate the generality and scope of the reaction, a series of 1,3-diarylpropynones **2** were employed for the cycloaddition reactions. It was found that 1,3-diarylpropynones **2** bearing *para*-F and *para*-Br on the 1-phenyl ring are favorable for the formation of benzodiazepines **3** (Table 2, entries 2 and 3), whereas those bearing electron-donating groups such as CH_3, OCH_3, and Ph are unfavorable (Table 2, entries 4, 5, and 7). Reactions of 1-furyl-3-phenylpropynone **2f** gave product **3f** in 94% yield (Table 2, entry 6). Reactions of *ortho*-substituted 1,3-diarylpropynones with Br and NO_2 on the 1-phenyl ring only gave Michael addition products without cyclization (Table 2, entries 9 and 10) except for the F-substituted substrate **2h** (Table 2, entry 8). Interestingly, we found that **2k** with

Table 3
Cycloaddition of diamines **1** and **2a**[a]

Entry	Diamine **2**	Product **3**	Yield[b] (%)
1	 **1a**	 **3a**	92
2	 **1b**	 **3l**	47
3	 **1c**	 **3m**	93
4	 **1d**	 **3n**	96
5	 **1e**	 **3o**	89
6	 **1f**	 **3p**	72
7	 **1g**	 **3q**	47

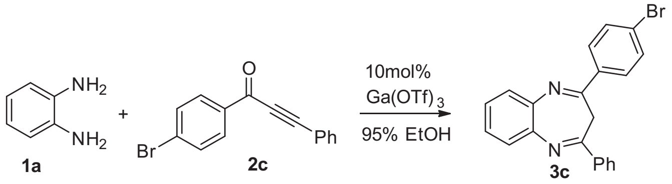
[a] Reaction conditions: 1 mmol **1**, 1.5 mmol **2**, 10%mol $Ga(OTf)_3$, 25 °C for 24 h.
[b] Isolated yield.

para-NO_2 substituted 1-phenyl afforded imine **3k** (Table 2, entry 11). It may attribute to the *para*-NO_2 on the 1-phenyl ring which made the carbonyl group more electrophilic.

The scope and limitations of the reaction of diamines **1** were also explored. The reaction of ethylenediamine **1b** with **2a** only gave Michael addition product **3l** (Table 3, entry 2). Among the substituted *o*-phenylenediamines **1**, those with electron-donating groups such as CH_3 are favorable for the cycloaddition (Table 3, entries 3 and 4). Weak electron-withdrawing groups such as Cl have little effect on yield (Table 3, entry 5). However, those bearing a strong electron-withdrawing group such as NO_2 and carbonyl afforded products with significantly reduced yield (Table 3, entries 6 and 7).

The catalyst reusability was also investigated. A mixture of *o*-phenylenediamine **1a** (1 mmol), 1-(4-bromophenyl)-3-phenylprop-2-yn-1-one **2c** (1 mmol), and $Ga(OTf)_3$ (0.1 mmol) in 3 mL of 95% EtOH was stirred at room temperature for 24 h. After completion of the reaction as monitored with TLC, product **3c** was precipitated out from the reaction solvent while $Ga(OTf)_3$ was left in the solution. After the product was collected by filtration, the catalyst in the filtrate was directly used for the next reaction without further treatment. This process was repeated ten times and the catalyst maintained good and consistent activity (Table 4).

Table 4
Recycling of $Ga(OTf)_3$ catalyst[a]



Round	Time (h)	Yield[b] (%)
1	24	95
2	24	96
3	24	96
4	24	94
5	24	95
6	24	95
7	24	95
8	24	94
9	24	96
10	24	95

[a] The reactions were performed at 25 °C.
[b] Isolated yield.

In summary, a simple and efficient method for the preparation of 2,4-disubstituted-3*H*-benzo[*b*][1,4]diazepines by $Ga(OTf)_3$-catalyzed [4+3] cycloaddition of *o*-phenylenediamines with 1,3-diarylpropynones has been developed. The reactions are conducted in 95% EtOH at room temperature. In addition to mild reaction conditions, simple manipulations, using renewable green solvent, and minimal waste disposal, the catalyst $Ga(OTf)_3$ can be easily separated from the product simply by filtration and can be reused without further treatment for at least 10 times.

Acknowledgments

J.P.Z. thanks the National Natural Science Foundation of China for financial support (No. 20772088, 21172163) and A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.092.

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