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A Novel Strategy for the Construction of Functionalized 1,5-Benzodiazepines *via* a Tandem Conjugated Addition/Cyclization Process

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Abstract: A novel approach for the synthesis of functionalized 1,5-benzodiazepine is described. The protocol is triggered by a tandem conjugated addition/cyclization process from the readily available starting materials 1,2-phenylenediamine and ethyl propiolate. The products have secondary amino and ester groups, and a β-enamino ester, which can serve in further functionalizations to produce molecular diversity.

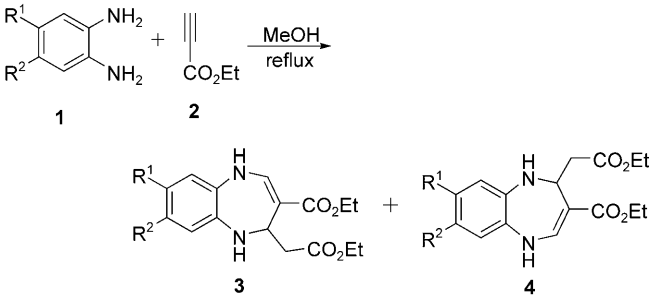
Keywords: 1,5-benzodiazepines; conjugated addition; cyclization; tandem reactions

In recent years, the development of new strategies that provide synthetic efficiency and atom economy has been an important goal of synthetic chemistry, and continues to be a great challenge.[1] Tandem reactions are good candidates for this target as they can serve as a powerful tool for the efficient assembly of complex structures from simple starting materials, with a minimal production of waste.[2]

The chemistry of alkynes constitutes a very attractive research area since the resulting adducts are prone to further transformations.[3] In particular, terminal conjugated alkynes involved in multibond-forming processes have been well documented. Generally, these conversions are initiated by the catalytic conjugated addition of a tertiary amine or phosphine to a terminal conjugated alkynoate, leading to the formation of many new carbon-carbon bonds in one pot.[4,5] In this context, a practical and catalyst-free tandem conjugated addition to synthesize the functionalized 1,5-benzodiazepine system is reported herein. It is noteworthy that the present protocol proceeds readily without the addition of any other reagents or catalysts.

The rapid and efficient synthesis of nitrogen-containing heterocycles remains a great challenge in organic and medicinal chemistry.[6] For instance, 1,5-benzodiazepines have been termed as a privileged structure because of their regular appearance in diverse screening assays and their significant biological activities.[7] Although they were first introduced into the pharmaceutical industry almost 40 years ago, these compounds are still being actively studied.[8] However, a careful literature search showed that most synthetic efforts have been focused on the condensation of *o*-phenylenediamine with carbonyl compounds including methyl ketones, β-halo ketones and α,β-unsaturated ketones.[9] Despite the advances achieved, the application of such methods suffers from poor functional diversity, which limits their more extensive use in the drug industry. It is well known that structural and functional diversity play an important role in the drug discovery process, because they offer means for structural derivatization. Consequently, the development of new synthetic approaches toward 1,5-benzodiazepines that provide additional functional diversity is highly desirable. Herein we report the first synthesis of functionalized 1,5-benzodiazepines from 1,2-phenylenediamine and ethyl propiolate under catalyst-free conditions (Scheme 1).

In our initial experiments, *o*-phenylenediamine **1a** was employed as model substrate to react with ethyl propiolate **2** (Table 1). At room temperature, this mixture produced only a large amount of mono-conjugated addition intermediate without the formation of a seven-membered ring.[10] Fortunately, 1,5-benzodiazepine **3a** was obtained when this reaction was carried out under reflux. A series of reaction parameters were screened and the conversion was found to be



Scheme 1. The tandem conjugated addition/cyclization reaction of 1,2-phenylenediamine and ethyl propiolate.

Table 1. Optimization of reaction conditions.[a]

Entry	Substrate **1a** (equiv.)	Solvent	Time [h]	Yield [%][b]
1	1	MeOH	10	73
2	0.8	MeOH	10	85
3	0.6	MeOH	10	89
4	0.5	MeOH	24	49
5	0.6	EtOH	12	69
6	0.6	THF	24	–[c]
7	0.6	CH_3CN	24	11
8	0.6	DCE	24	17
9	0.6	acetone	24	–[c]
10	0.6	DCM	24	86

[a] All reactions were carried out with 1 mmol of ethyl propiolate **2** in 5 mL solvent under reflux in air.
[b] Yields of product after silica gel chromatography.
[c] A very complex mixture was obtained.

strongly dependent on the reaction conditions. The choice of solvent was especially critical: dichloroethane (DCE) and CH_3CN gave poor yields, while very complex mixtures were obtained when THF and acetone were used (Table 1). It seemed that MeOH and dichloromethane (DCM) gave better results, and MeOH was proven to be the best choice because use of DCM as solvent did not afford the seven-membered ring when an electron-withdrawing group was present in substrate **1**. Interestingly, the amount of 1,2-phenylenediamine added relative to the amount of substrate **2** also influenced the yield of product **3a**. The yield of **3a** increased to 89% when 0.6 equivalent of *o*-phenylenediamine was used, while using 1 equivalent of substrate **1a** gave only a 73% yield (Table 1).

With optimized reaction conditions in hand, we next explored the scope of the reaction. Various substituted 1,2-phenylenediamines **1** were reacted with ethyl propiolate **2** to afford the functionalized 1,5-benzodiazepines and the results are summarized in Table 2. The transformations proceeded smoothly under the optimized conditions to give seven-membered ring products. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and EA, and the structure of compound **4e** was confirmed by a single crystal X-ray analysis (Figure 1).[11] The analysis showed that two isomers **3** and **4** were isolated when the substituents R^1 and R^2 were different (Table 2, entries 2, 3, 5–9, 11, 12). Normally, these two isomers

Table 2. Syntheses of functionalized 1,5-benzodiazepines.[a]

Entry		Substrate **1**	Time [h]	Product	Yield [%][b]
1	**1a**	$R^1=R^2=H$	10	**3a**	89
2	**1b**	$R^1=Cl$, $R^2=H$	7	**3b+4b**	36+54
3	**1c**	$R^1=Br$, $R^2=H$	10	**3c+4c**	35+59
4	**1d**		7	**3d**	90
5	**1e**	$R^1=NO_2$, $R^2=H$	36	**3e+4e**	28+66
6	**1f**	$R^1=CN$, $R^2=H$	16	**3f+4f**	32+57
7	**1g**	$R^1=COOMe$, $R^2=H$	18	**3g+4g**	42+50
8	**1h**	$R^1=COOEt$, $R^2=H$	18	**3h+4h**	38+49
9	**1i**	$R^1=PhCO$, $R^2=H$	22	**3i+4i**	50+39
10	**1j**		6	**3j**	91
11	**1k**	$R^1=CH_3O$, $R^2=H$	7	**3k+4k**	36+60
12[c]	**1l**	$R^1=CH_3$, $R^2=H$	5	**3l+4l**	47+47

[a] *Reactions conditions:* 0.6 mmol diamine **1**, 1 mmol ethyl propiolate **2** in 5 mL MeOH under reflux.
[b] Yields of products isolated after silica gel chromatography.
[c] The ratio of **3l** and **4l** was confirmed from the ^{1}H NMR spectrum.

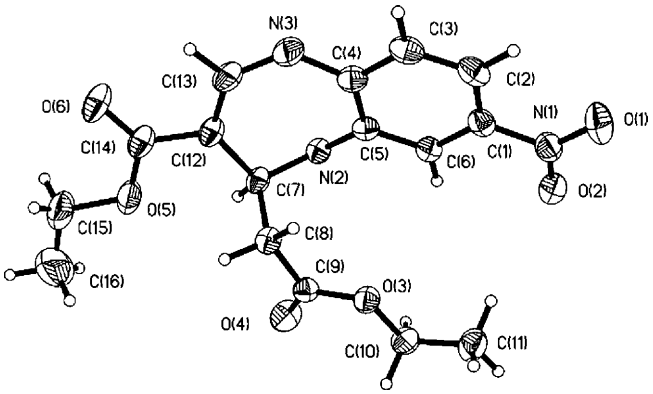
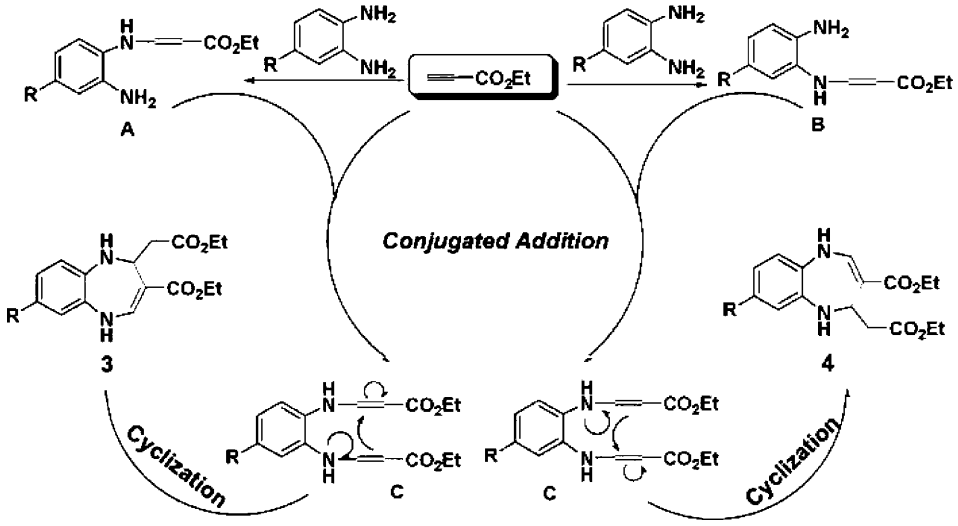


Figure 1. Single-crystal X-ray structure of compound **4e**.

could be separated efficiently by careful silica gel chromatography, and product **4** was usually isolated as the major component.[12] As expected, the above process was affected dramatically by the substituents on the aromatic ring in substrate **1**. Electron-donating substituents such as methyl and methoxy group essentially build up the nucleophilicity of the amino groups, thus facilitating the corresponding conjugated addition and cyclization process (entries 10, 11 and 12). Shorter reaction times were observed in such cases. By contrast, the presence of electron-withdrawing groups disfavors the present conversion. In particular, when a substrate with a strong electron-withdrawing group such as a nitro group was used, the reaction became quite sluggish (entry 5). Substitution of a bromo group slightly affected reaction time. To our delight, symmetrical aromatic diamines led to the formation of the seven-membered ring system **3** exclusively, without the observation of any isomer (entries 1, 4 and 10). For instance, the reaction of **2** with 4,5-dichloro-1,2-phenylenediamine or 4,5-dimethyl-1,2-phenylenediamine was quite clean and high yielding (entries 4 and 10). It should also be noted that when substrate **1l** was used, products **3l** and **4l** could not be separated with the usual methods (entry 12). In such cases, the product ratio was determined from the ^{1}H NMR spectra. Overall, this one-pot, catalyst-free tandem conjugated addition/cyclization process constructs two carbon-nitrogen bonds, one carbon-carbon bond and a seven-membered ring in an efficient and atom-economical manner. Also, the protocol utilizes simple and commercially available materials without the formation of any wastes. The functionalized products which include secondary amino and ester groups, and a β-enamino esters can produce molecular diversity in further functionalizations. Many functionalizations of the enamino ester moiety have been reported, including the reaction with acryloyl chloride and *trans*-β-nitrostyrene to form privileged bicyclic heterocycles.[13] These transformations are being developed in our laboratory, and they will be reported in due course.

A possible mechanism is proposed to account for the formation of the seven-membered ring (Scheme 2). Conjugated addition of 1,2-phenylenediamine to one equivalent of ethyl propiolate leads to the formation of intermediates **A** and **B**, which then undergo further addition of another equivalent of ethyl propiolate to afford **C**. These *in situ*-generated reactive intermediates subsequently experience intramolecular cyclization followed by proton transfer to produce the functionalized seven-membered rings **3** and **4**.

In conclusion, we have described a practical tandem conjugated addition/cyclization process to generate functionalized 1,5-benzodiazepines in an efficient and atom-economical manner. The protocol utilizes simple and commercially available starting materials without formation of any wastes. This pro-



Scheme 2. Proposed mechanism for the formation of **3** and **4**.

cedure represents an operationally very simple yet powerful method for the construction of two carbon-nitrogen bonds, one carbon-carbon bond and a seven-membered ring in a one-pot synthesis. Furthermore, the seven-membered ring compounds have reactive secondary amino and ester groups and enamino esters, which enable further modifications leading to molecular diversity. Thus the present method has the potential to be applied in medicinal and synthetic chemistry. Studies of the reaction mechanism and broadening the scope of the reaction are currently in progress in our laboratory.

Experimental Section

General Procedure for the Synthesis of Functionalized 1,5-Benzodiazepines

1,2-Phenylenediamine **1a** (64.8 mg, 0.6 mmol) was added to a solution of ethyl propiolate **2** (98 mg, 1.0 mmol) in 5 mL MeOH. After being stirred for 10 h under reflux, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatoragraphy on silica gel to afford the desired product **3a**.

Acknowledgements

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[11] CCDC 736154 contains the supplementary crystallographic data for compound **4e** in this paper. These data can be obtained free of charge from The Cambridge

Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[12] It can be easily found from the TLC detection that products **4** are more polar than **3** in nearly all cases.
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