Bromodimethylsulfonium Bromide (BDMS)-Catalyzed Synthesis of 1,5-Benzodiazepines Using a Multi-Component Reaction Strategy

Satavisha Sarkar, Jugal Kishore Rai Deka, Jagadish P. Hazra, Abu T. Khan*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India
Fax +91(361)2582349; E-mail: atk@iitg.ernet.in

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This work is dedicated to the late Dr. Uttara Debi who was compassionate and amicable in nature.

Abstract: A new approach for the synthesis of multi-functionalized 1,5-benzodiazepines is developed starting from *o*-phenylenediamines, β-keto esters and aromatic aldehydes utilizing a one-pot, three-component strategy employing bromodimethylsulfonium bromide as the catalyst. The simple reaction procedure, good yields, mild reaction conditions and applicability to a wide range of substrates are some of the salient features of this protocol.

Key words: multi-component reactions, 1,5-benzodiazepines, *o*-phenylenediamines, bromodimethylsulfonium bromide

The benzodiazepine skeleton continues to generate interest from the pharmaceutical community.[1] Indeed, the concept of 'privileged medicinal structures or scaffolds' was initially coined by Merck researchers during their work on benzodiazepines.[2,3] They exhibit a broad spectrum of pharmacological properties, such as anti-inflammatory, anticonvulsant, anti-anxiety, sedative, antidepressant, hypnotic,[1,4] antibiotic,[5] anticancer[6] and antiviral (HIV) activities,[7] and act as inhibitors of the HIV-1 capsid assembly.[8] Benzodiazepines have been developed as dyes for acrylic fibers[9] and have been used as starting materials for the preparation of triazole[10a] and oxadiazole[10b] derivatives.

Multi-component reactions (MCRs) have emerged as a powerful strategy to construct structurally complex and functionally diverse multi-heterocyclic skeletons with efficient atom-economy.[11]

Strategies for the construction of 1,5-benzodiazepines are generally based on the condensation reactions of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds,[12] β-halo ketones,[13] or ketones.[12a,14] A cycloaddition approach has also been explored using *o*-phenylenediamines and terminal alkynes.[15]

Kita et al. reported the construction of 1,4-diazepines using ethylenediamine, aromatic aldehydes, methyl acetoacetate and *p*-toluenesulfonic acid (PTSA) as the catalyst,[16a] but they were unable to synthesize 1,5-benzodiazepines under these conditions. In 2008, they extended their approach to the synthesis of 1,5-benzodiazepines using *o*-phenylenediamine, aromatic aldehydes and β-keto esters with pentafluorobenzoic acid as the catalyst.[16b] Although Rodriguez et al. similarly established the synthesis of 1,4-diazepines using molecular sieves (4 Å), their strategy for the synthesis of 1,5-benzodiazepines under identical conditions failed.[16c,d] Our group has reported the synthesis of 1,5-benzodiazepines using 2,6-pyridinedicarboxylic acid as an organocatalyst.[16e] Unfortunately, these protocols are limited in scope due to the formation of side products, often lead to low yields, and require extended reaction times, high temperatures, inert atmospheric conditions or use expensive catalysts. Hence, there is scope for the development of new methodologies for the synthesis of 1,5-benzodiazepine scaffolds.

We have reviewed the usefulness of bromodimethylsulfonium bromide (BDMS) as a catalyst as well as a brominating reagent.[17a] Bromodimethylsulfonium bromide displays efficient catalytic properties, as it is capable of generating hydrobromic acid (HBr) *in situ*, and acts as an efficient pre-catalyst for several acid-catalyzed organic reactions.[17b–d] As part of our ongoing efforts to develop new synthetic protocols for the synthesis of biologically active heterocyclic compounds through multi-component reactions, we have explored the utility of bromodimethylsulfonium bromide as an efficient catalyst for the synthesis of 1,5-benzodiazepine derivatives (Scheme 1).

To develop suitable conditions, a trial reaction was performed with *o*-phenylenediamine (1 mmol), ethyl acetoacetate (1 mmol) and 4-chlorobenzaldehyde (1 mmol) using bromodimethylsulfonium bromide (5 mol%) in acetonitrile as the solvent. Monitoring by TLC showed that,

Scheme 1 Bromodimethylsulfonium bromide (BDMS) catalyzed synthesis of substituted 1,5-benzodiazepine derivatives

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after five hours, there was no further change in the reaction. After isolating the major product and analysis by spectroscopic techniques, we identified it as the desired product **4d** (R = Et, R^1 = H, Ar = 4-ClC_6H_4). To optimize the conditions, similar reactions were executed with bromodimethylsulfonium bromide (5 mol%) in different solvents such as ethanol, dichloromethane and 1,2-dichloroethane (Table 1, entries 1–4), with 1,2-dichloroethane being the most suitable. Catalysts including molecular iodine, *p*-toluenesulfonic acid, trifluoroacetic acid (TFA) and L-proline in 1,2-dichloroethane as the solvent led to lower yields (Table 1, entries 7–10). The reaction did not proceed at all in the absence of a catalyst (Table 1, entry 11). Further experimentation established that bromodimethylsulfonium bromide (10 mol%) in 1,2-dichloroethane was the optimal combination (Table 1, entry 5); further increasing the amount of catalyst did not improve the yield (Table 1, entry 6). From the above observations, it is clear that bromodimethylsulfonium bromide plays a specific role compared to other catalysts.

Table 1 Optimization of the Reaction Conditions for the Synthesis of 1,5-Benzodiazepine Derivatives[a]

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	BDMS (5)	MeCN	12	38
2	BDMS (5)	EtOH	12	25
3	BDMS (5)	CH_2Cl_2	6	35
4	BDMS (5)	DCE	5	64
5	**BDMS (10)**	**DCE**	**4.5**	**72**
6	BDMS (15)	DCE	4.5	72
7	I_2 (10)	DCE	6	64
8	PTSA (10)	DCE	12	25
9	TFA (10)	DCE	12	20
10	L-proline (10)	DCE	12	27
11	No catalyst	DCE	24	–

[a] All the reactions were performed with *o*-phenylenediamine (1.0 mmol), ethyl acetoacetate (1.0 mmol) and 4-chlorobenzaldehyde (1.0 mmol).
[b] Yield of isolated product.

Having optimized the reaction conditions, we next examined the generality and scope of this reaction using ethyl acetoacetate and *o*-phenylenediamine and various substituted aromatic aldehydes, which afforded the corresponding products **4a**–**m** in good to moderate yields (Table 2).[18]

Aromatic aldehydes with electron-donating substituents such as methyl and methoxy groups generally gave better yields (**4b**,**c**, Table 2, entries 2 and 3) compared to those with electron-withdrawing substituents (**4d**–**f**, Table 2, entries 4–6). We also performed the reaction with *ortho*- and *meta*-substituted aldehydes (**4g**–**i**, Table 2, entries 7–9), as well as with the sterically hindered naphthaldehyde

Table 2 Synthesis of 1,5-Benzodiazepine Derivatives Using Substituted Aromatic Aldehydes, Ethyl Acetoacetate and *o*-Phenylenediamine[a]

Entry	Ar	Product	Time (h)	Yield (%)[b]
1	Ph	**4a**	4.5	75
2	4-MeC_6H_4	**4b**	4	77
3	4-$MeOC_6H_4$	**4c**	4	78
4	4-ClC_6H_4	**4d**	4.5	72
5	4-BrC_6H_4	**4e**	4.5	74
6	4-FC_6H_4	**4f**	5	70
7	3-FC_6H_4	**4g**	5	71
8	2-ClC_6H_4	**4h**	5	68
9	2-$O_2NC_6H_4$	**4i**	5	65
10	2-naphthyl	**4j**	4.5	71
11	2-furfuryl	**4k**	4.5	72
12	2-thienyl	**4l**	5	74
13	3-indolyl	**4m**	4.5	75

[a] All the reactions were performed with *o*-phenylenediamine (1.0 mmol), ethyl acetoacetate (1.0 mmol) and different aromatic aldehydes (1.0 mmol).
[b] Yield of isolated product.

(**4j**, Table 2, entry 10). Furthermore, the reaction was also carried out with heteroaromatic aldehydes such as furfural, thiophene 2-carboxaldehyde and indole 3-carboxaldehyde, giving moderate yields (**4k**–**m**, Table 2, entries 11–13). Unfortunately, the reaction was unsuccessful with aliphatic aldehydes. When the reaction was carried out with cyclohexanecarboxaldehyde, *o*-phenylenediamine and ethyl acetoacetate, we isolated 2-cyclohexyl-1-(cyclohexylmethyl)-1*H*-benzo[*d*]imidazole (**5**) (see the Supporting Information) in 30% yield, instead of the desired 1,5-benzodiazepine.

Conducting the reaction of *o*-phenylenediamine and benzaldehyde with different acyclic β-keto esters such as methyl acetoacetate or *t*-butyl acetoacetate gave the de-

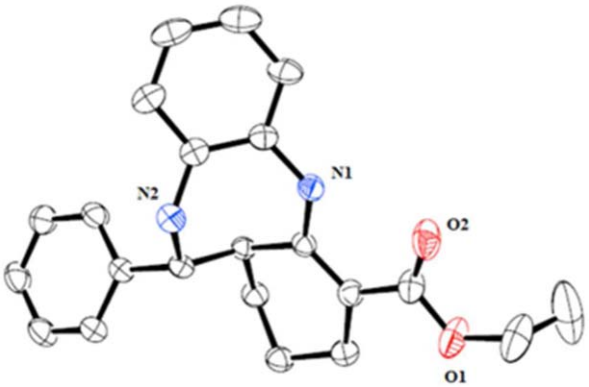


Figure 1 X-ray crystallographic structure of **4q** (CCDC 952358)

Table 3 Reactions of Different β-Keto Esters with Benzaldehyde and *o*-Phenylenediamine for the Synthesis of 1,5-Benzodiazepines[a]

Entry	R	Product	Time (h)	Yield (%)[b]
1	Me	**4n**	4.5	72
2	*t*-Bu	**4o**	5	74
3	CH_2-CH=CH_2	**4p**	5	68

[a] All the reactions were performed with *o*-phenylenediamine (1.0 mmol), benzaldehyde (1.0 mmol) and different β-keto esters (1.0 mmol).
[b] Yield of isolated product.

sired products in good yields (**4n**,**o**, Table 3, entries 1 and 2), whereas allyl acetoacetate produced the corresponding product in a slightly lower yield (**4p**, Table 3, entry 3).

We successfully synthesized 1,5-benzodiazepine derivative **4q** in 77% yield using the cyclic β-keto ester, ethyl 2-oxocyclohexane carboxylate, *o*-phenylenediamine and benzaldehyde. The product **4q** was characterized by single crystal X-ray diffraction (Figure 1).

Extending the scope of this reaction by utilizing a disubstituted aromatic diamine furnished the desired product in good yield (**4r**, 68%). However, mono-substituted diamines gave a mixture of two inseparable regioisomers in approximately 6:4 ratios as determined by ^{1}H NMR spec-

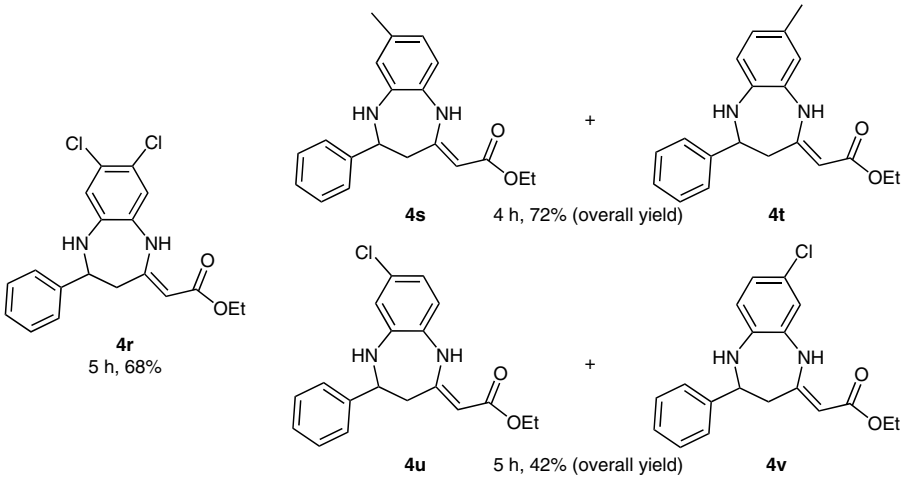
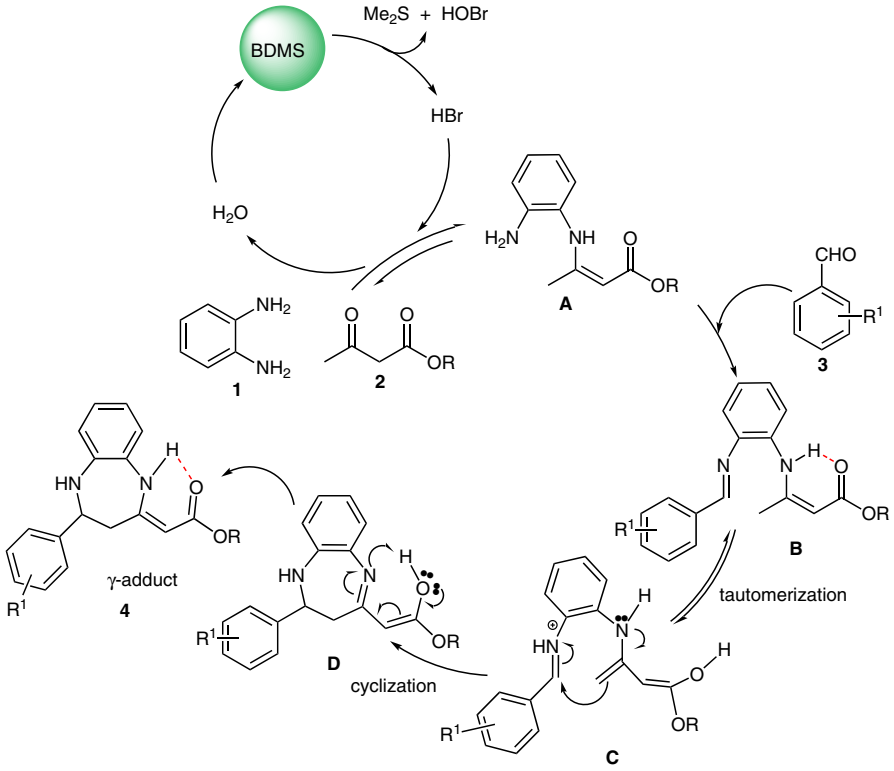


Figure 2 Scope of 1,5-benzodiazepine derivatives with substituted diamines, benzaldehyde and ethyl acetoacetate



Scheme 2 A plausible mechanism for the formation of 1,5-benzodiazepine derivatives **4**

troscopy. In the case of an *o*-phenylenediamine with a chloro substituent, we obtained a lower yield compared to that with an electron-donating substituent (Figure 2).

According, to our literature survey,[16b,e] a plausible mechanism for this conversion is depicted in Scheme 2. It is proposed that *o*-phenylenediamine (**1**) reacts with β-keto ester (**2**) to form enaminoester **A** in the presence of bromodimethylsulfonium bromide at room temperature, which is a very characteristic reaction of carbonyl compounds in the presence of an acid catalyst.

We have isolated intermediate **A**, and it was evident from the NMR spectrum of the major product isolated after 15 minutes that compound **A** was formed during the first step of this transformation. Next, intermediate **A** reacts with the aromatic aldehyde **3** under reflux conditions to form imine-enaminoester intermediate **B**. This intermediate, stabilized by an intramolecular hydrogen bonding interaction, can provide the 1,5-benzodiazepine derivative through a γ-selective C–C bond forming reaction. Thus imine-enaminoester **B** tautomerizes into intermediate **C** which undergoes cyclization to give **D**. This intermediate **D** undergoes a 1,5-H shift to form the final product **4**, the γ adduct, which is stabilized by intramolecular H-bonding.

In summary, we have devised a simple synthetic protocol for the synthesis of 1,5-benzodiazepine derivatives from *o*-phenylenediamine, β-keto esters and aromatic aldehydes catalyzed by bromodimethylsulfonium bromide, via a one-pot multi-component reaction. Bromodimethylsulfonium bromide acts as a pre-catalyst and generates hydrobromic acid in situ, which plays a vital role in the synthesis of the 1,5-benzodiazepine derivatives. The advantage of this protocol is the use of readily available starting materials without the need for an inert atmosphere.

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(18) **1,5-Benzodiazepines; General Procedure**
In an oven-dried 25 mL round-bottomed flask was added the

requisite *o*-phenylenediamine (1.0 mmol) and β-keto ester (1.0 mmol) in DCE (3 mL). Next, bromodimethylsulfonium bromide (10 mol%) was added and the mixture was stirred at r.t. After 15 min, the aromatic aldehyde (1.0 mmol) was added and the mixture was heated at 55 °C for the appropriate amount of time. Following completion (TLC), the solvent was removed on a rotary evaporator. The residue was extracted with CH_2Cl_2 (2 × 10 mL), washed with H_2O (10 mL) and dried over anhydrous Na_2SO_4. The solution was filtered, concentrated in vacuo and the residue purified by column chromatography (EtOAc–hexane, 5:95) to provide the 1,5-diazepine product.

(*Z*)-Ethyl 2-(4-Phenyl-4,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-2(3*H*)-ylidene)acetate (4a)

Yield: 0.213 g (75%); yellow solid; mp 73–77 °C. IR (KBr): 1158, 1455, 1618, 1637, 2923, 3415, 3467 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, -CH_3), 2.54 (dd, *J* = 14, 4.4 Hz, 1 H, -CH_2), 2.70 (dd, *J* = 14, 9.2 Hz, 1 H, -CH_2), 3.7 (br s, 1H, -NH), 4.1–4.2 (m, 2 H, -OCH_2), 4.61 (s, 1 H, =CH), 4.85 (dd, *J* = 9.2, 4 Hz, 1 H, -CH), 6.76–6.79 (m, 1 H, Ar-H), 6.85–6.94 (m, 1 H, Ar-H), 6.96–7.05 (m, 2 H, Ar-H), 7.28–7.32 (m, 1 H, Ar-H), 7.32–7.39 (m, 4 H, Ar-H), 10.24 (s, 1 H, -NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.75, 40.52, 59.05, 65.33, 82.42, 121.01, 121.80, 122.74, 125.19, 126.29 (2 C), 128.18, 129.03 (2 C), 130.11, 138.11, 145.07, 158.83, 170.52.HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{20}N_2O_2$: 309.1598; found: 309.1594. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.06; H, 6.59; N, 9.02.