JOC Article

Effects of Substituents in the β-Position of 1,3-Dicarbonyl Compounds in Bromodimethylsulfonium Bromide-Catalyzed Multicomponent Reactions: A Facile Access to Functionalized Piperidines

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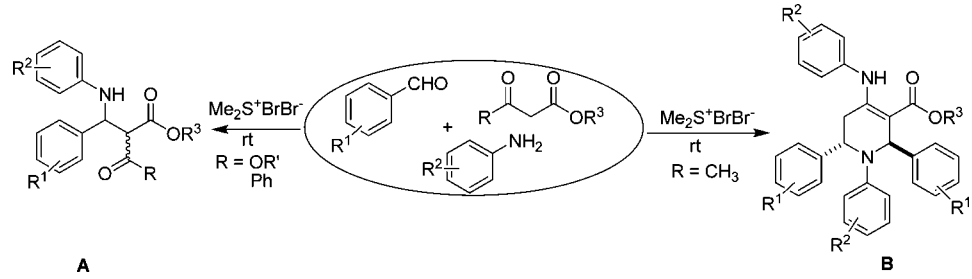

1,3-Dicarbonyl compounds can be converted to Mannich-type products **A** or highly functionalized piperidines **B** in the presence of a catalytic amount of bromodimethylsulfonium bromide (BDMS). The combination of aromatic aldehyde, amine, and 1,3-dicarbonyl compounds in the presence of a catalytic amount of BDMS leads to the formation of Mannich-type product **A** when R is a non-enolizable carbon or an alkoxy group, whereas in cases when R = CH_3, the same combination yielded highly functionalized piperidines **B**. A synthetic study and mechanistic proposal are presented.

Introduction

Multicomponent reactions (MCRs) involving domino processes, with at least three different substrates reacting in a well-defined manner to form a single compound, have emerged as a powerful tool in organic synthesis.[1] In recent years MCRs have received considerable attention from the organic community due to their advantages over conventional multistep synthesis.[2] These reactions constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. In addition, MCRs are more environmentally benign and atom economic as they avoid time-consuming and costly purification processes, as well as protection−deprotection steps.[3] The synthesis of heterocycles with use of multicomponent reactions often involves classical carbonyl condensation chemistry. Among carbonyl compounds, 1,3-dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a variety of synthetic transformations.[4] The high synthetic potential of these easily accessible reagents has found numerous applications, especially for the synthesis of complex heterocyclic structures.[5]

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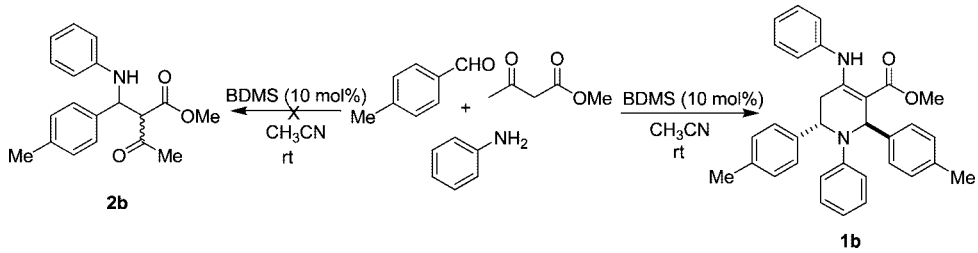
SCHEME 1. Preferential Formation of Functionalized Piperidines 1b over the Mannich-Type Product 2b



Bromodimethylsulfonium bromide (BDMS) has proven to be a very useful reagent in organic synthesis.[6] Due to its versatile activity both as a brominating agent[6b,7] and as a catalyst, it has recently been used in a wide variety of synthetic transformations.[8] As part of our ongoing research program to develop new methodologies, we have been engaged in an exploration of the virtues of BDMS for organic synthesis,[9] and envisaged that BDMS might act as an efficient catalyst for a diverse range of multicomponent reactions. Herein we report interesting MCRs of 1,3-dicarbonyl compounds that lead to different products, depending upon the substituent in the β-position.

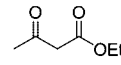
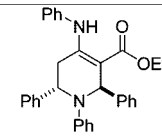
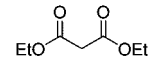
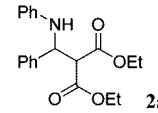
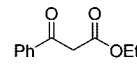
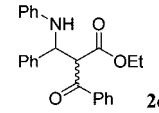
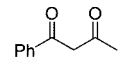
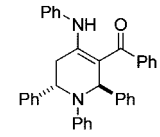
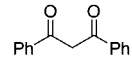
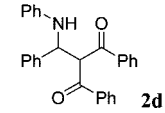
Results and Discussion

Bromodimethylsulfonium bromide was prepared from dimethyl sulfide and molecular bromine by using the reported procedure.[6e] In our initial study to assess the utility of bromodimethylsulfonium bromide in multicomponent reactions, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (2 mmol) in acetonitrile (5 mL) was stirred in the presence of 10 mol % of BDMS. At the outset we were expecting a Mannich-type reaction leading to product **2b**. Interestingly, instead we isolated a highly functionalized piperidine **1b** in a moderate yield of 39% (Scheme 1).

It is noteworthy that we have recently reported a three-component reaction involving aromatic aldehyde, aniline, and enolizable carbonyl compounds for the synthesis of corresponding Mannich-type product using bromodimethylsulfonium bromide.[9e] We therefore sought to use the same strategy for the synthesis of β-amino acid derivative **2b**. Generally, β-keto esters react with electrophiles at the α-position.[10] Only a few cases of α-alkylated β-keto esters/amides reacting with aldehyde electrophiles at the γ-position have appeared in the literature.[11] Fujioka and Kita et al. have reported a multicomponent reaction employing the γ-position of β-keto esters to form seven-membered-ring products from the combination of aromatic aldehydes, ethylenediamine, and β-keto esters.[1c] Interestingly, the formation of **1b** is an example in which both the α- and γ-positions of a β-keto ester are involved in C−C bond formation.

This unexpected result encouraged us to investigate the scope of this multicomponent reaction through a systematic study. A variety of 1,3-dicarbonyl compounds were treated with benzaldehyde and aniline in the presence of a catalytic amount of bromodimethylsulfonium bromide and the results are summarized in Table 1. As with methyl acetoacetate, ethyl acetoacetate provides the corresponding piperidine derivative in

TABLE 1. Results for the Reaction of Benzaldehyde, Aniline, and Different 1,3-Dicarbonyl Compounds in the Presence of a Catalytic Amount of BDMS[a]

Entry	1,3-dicarbonyl compounds	Time /h	Product	% Yield[b]
1.		6	 **1m**	38[c]
2.		6	 **2a**	92
3.		8	 **2c**	40
4.		12	 **1s**	20[d]
5.		12	 **2d**	0[e]

[a] Reactions were performed in a ratio of 1:1:1 (benzaldehyde: aniline:1,3-dicarbonyl compounds) in the presence of 10 mol % BDMS at room temperature. [b] Yield of pure product after crystallization. [c] For optimized yield see Table 2. [d] Optimized yield was 35%. [e] Starting material dibenzoyl acetone was recovered along with aldimine.

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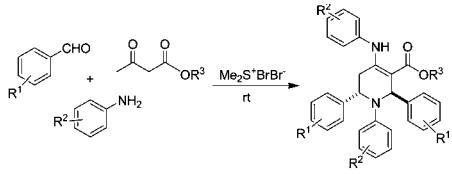
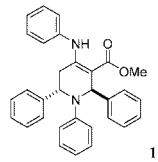
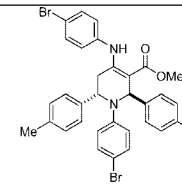
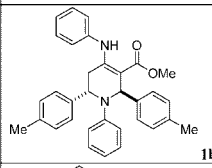
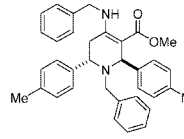
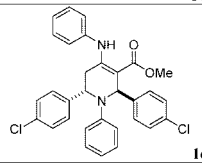
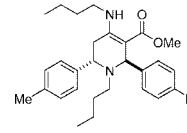
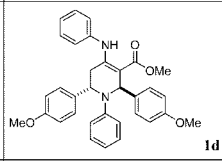
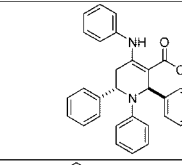
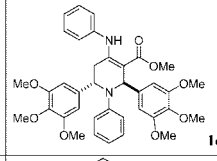
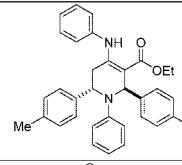
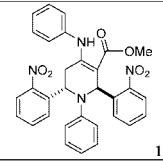
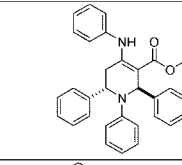
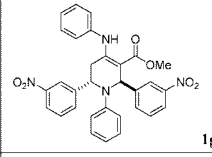
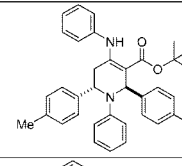
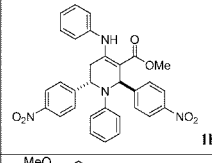
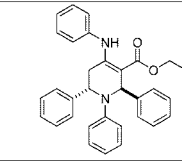
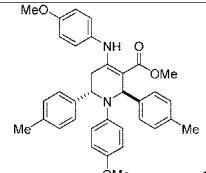
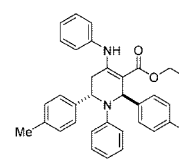
TABLE 2. Results for the Reaction of Aldehydes, Anilines, and β-Keto Esters in the Presence of Bromodimethylsulfonium Bromide in Acetonitrile[a]



Entry	Product	% Yield[b]	Entry	Product	% Yield[b]
1.	 **1a**	75	10.	 **1j**	68
2.	 **1b**	80	11.	 **1k**	48
3.	 **1c**	76	12.	 **1l**	63
4.	 **1d**	77	13.	 **1m**	76
5.	 **1e**	62	14.	 **1n**	79
6.	 **1f**	50	15.	 **1o**	60
7.	 **1g**	40	16.	 **1p**	65
8.	 **1h**	32	17.	 **1q**	70
9.	 **1i**	77	18.	 **1r**	77

[a] Aldehyde, amine, and β-keto esters were taken in (2:2:1) ratio in presence of 10 mol % of BDMS. [b] Yield of pure product after crystallization from the reaction mixture.

moderate yield (Table 1, entry 1). This suggests that the alkoxy moiety of these β-keto esters does not have any significant role in determining the course of the reaction. However, in the case of diethyl malonate (Table 1, entry 2), the corresponding Mannich-type product **2a** was obtained in good yield, as there is no other option due to the lack of an enolizable position. Likewise, ethyl benzoylacetate (Table 1, entry 3) gave Mannich-type product **2c** as a mixture of diastereomers, with the trans isomer predominating. However, in the case of benzoyl acetone (Table 1, entry 4) the corresponding piperidine was obtained in moderate yield.

In the case of dibenzoyl acetone (Table 1, entry 5) only the imine formed between benzaldehyde and aniline was obtained in addition to unreacted dibenzoyl acetone. From these results it is clear that diethyl malonate is acting as a better nucleophile in this Mannich-type reaction than the other 1,3-dicarbonyl compounds in the presence of bromodimethylsulfonium bromide (Table 1). We believe that the bulkiness of the phenyl group may have an effect on the nucleophilicity of ethyl benzoyl acetate and dibenzoyl acetone. From these studies it is apparent that substituents on the 1,3-dicarbonyl component play a vital role in determining the reactivity of substrates and the course of reactions.

A γ-substituted β-keto ester ethyl butyrylacetate was next treated with aniline and benzaldehyde under similar experimental conditions. Piperidine **1t** was not observed in the crude ^{1}H NMR after 24 h (Scheme 2). This suggests that the presence of methyl group in the β-position of β-keto esters is necessary for the successful formation of highly functionalized piperidines using these multicomponent reactions.

Functionalized piperidine rings are present in many natural products[12] and are important building blocks in pharmaceuticals. Recently, considerable attention has been paid to the synthesis of functionalized piperidines,[13,14] while, in general, the development of new synthetic methods for the efficient preparation of nitrogen heterocycles is an interesting challenge.[16] Thus we turned our attention to the optimization of this multicomponent approach to piperidines.

The influences of the catalyst, solvent, and the ratio of the components were investigated by using the combination of *p*-methylbenzaldehyde, aniline, and methylacetoacetate as a model reaction. The stoichiometric ratio 2:2:1 (aldehyde:aniline: methyl acetoacetate) in the presence of 10 mol % of bromodimethylsulfonium bromide at room temperature was found to be the most suitable condition for obtaining functionalized piperidines. Under these standard reaction conditions, the product **1b** was synthesized in good yield (80%) after a short time (3 h). A range of solvents were screened to find out the best solvent for this transformation. Among dichloromethane, acetonitrile,

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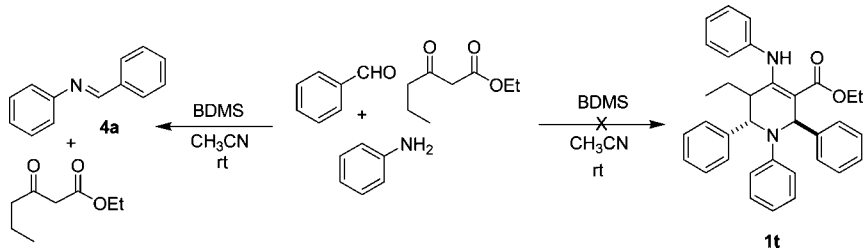
SCHEME 2. Reaction of Ethyl Butyrylacetate with Aniline and Benzaldehyde



ethanol, and water, the use of acetonitrile was found to give superior yields. However, ethanol can also be used for this transformation. The neat reaction, without any solvent, resulted in a moderate yield (40%) that may be due to the lack of effective interaction of the reactants under solvent-free reaction conditions. In the absence of BDMS, the same combination of reactants failed to provide **1b** under identical reaction conditions even after 24 h of stirring. This illustrates the efficacy of BDMS as a catalyst. Using a catalytic amount of aqueous 48% HBr instead of BDMS gave lower yields (45%). This result indicates that the generation of the protic acid HBr may not be the only factor responsible for the catalytic activity of BDMS. It is possible that the positive sulfonium moiety also has some role in facilitating the process.

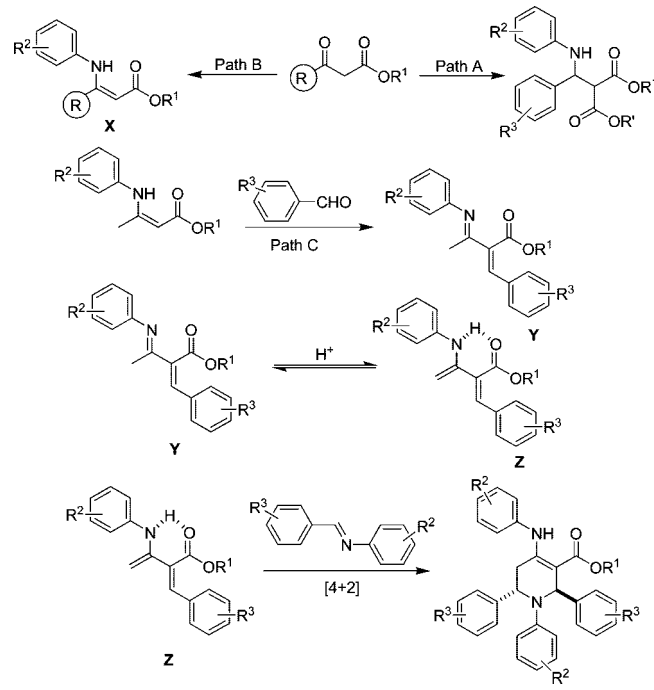
To explore the generality and scope of this multicomponent reaction a variety of aldehydes, β-keto esters, and aniline derivatives were tested and the results are summarized in Table 2. Aromatic aldehydes bearing substituents such as Cl, Me, and OMe as well as NO_2 were treated with aniline and methyl acetoacetate under the standard reaction conditions and the corresponding products (**1a**−**h**) were obtained in good to moderate yields. In the case of nitro aldehydes (Table 2, entries 6−8) the yields were low, which may be due to steric factors as well as the electron-withdrawing effect of the nitro group.

Aniline derivatives such as 4-methoxyaniline and 4-bromoaniline were also tested in the multicomponent reaction, smoothly provding the corresponding piperidine derivatives in good yields (Table 2, entries 9 and 10). To further explore the generality and scope of this MCR, benzylamine and butylamine were also treated under the same reaction conditions. The corresponding piperidines were obtained in low to moderate yields. Other β-keto esters such as ethyl acetoacetate, *tert*-butyl acetoacetate, and allyl acetoacetate also took part in this multicomponent reaction to provide the corresponding piperidine derivatives (Table 2, entries 13−18) with good yields under the optimized conditions. Unfortunately, in the case of the aliphatic aldehyde, heptanal, the present method failed to produce the corresponding functionalized piperidines.

To confirm the structure as well as the relative stereochemistry of these highly functionalized piperidines, X-ray crystallographic analysis of **1c** and **1m** was carried out. In both cases, the relative stereochemistry at the 2- and 6-positions of the piperidines was shown to be *anti* (see the Supporting Information, Figure 1). In addition, amino groups at the 4-position and carboxyl groups at the 3-position show intramolecular hydrogen bonding.

Next, we turned our attention to gaining mechanistic insights into this transformation. From our study we have revealed that the R group of the β-keto esters plays a crucial role in this multicomponent reaction (see Table 1). A possible mechanism is illustrated in Scheme 3.

SCHEME 3. Possible Mechanistic Illustration Showing the Role of the R Group and the Formation of Functionalized Piperidines via Intermediates Z



In the case when R = alkoxy group, e.g., OEt, the combination of an aromatic amine, such as aniline, and an aromatic aldehyde, with the diester, leads to the Mannich-type products following path A via the formation of an imine followed by nucleophilic attack by the 1,3-diesters. As the carbonyl group of ester substrates is less electrophilic than that of the ketone substrates, there is no reaction with the aromatic amines at room temperature, and straightforward formation of β-amino acid derivatives (Mannich-type product) is observed. However, when R is an alkyl or aryl group then the scenario becomes different. This can be attributed to the more reactive keto functionality and the emergence of other reaction pathways. In the case of β-keto esters, where R is a methyl group, enamine **X** (path B) is formed by reaction with the amine. This enamine **X** may then react with the aromatic aldehyde to produce the Knoevenagel-type product **Y** (path C).

Next, there will be a spontaneous tendency under acidic conditions for tautomerization to give the intramolecular hydrogen bonded enamine **Z**. Presumably, this hydrogen bonding along with high conjugation is the driving force for this tautomerism. The X-ray structure of compounds **1c** and **1m** shows that the carboxyl and amino goups are on the same face of the products and show intramolecular hydrogen bonding (Figure 1) thus indirectly supporting our hypothesis. Another equivalent of amine and aldehyde react in the presence of BDMS

to provide the corresponding imine. We believe BDMS facilitates the formation of imine as well as enamine **X** in this multicomponent reaction. This imine and the intermediate **Z** undergo [4+2] aza-Diels−Alder reaction to provide the functionalized piperidine. In an attempt to prove this mechanism, we synthesized the enamine from methyl acetoacetate and aniline and the resulting enamine was treated with another equivalent of 4-methylbenzaldehyde. However, we could not isolate the intermediate **Z**, instead we found a trace amount of the corresponding piperidine **1b**. It is possible that the intermediate is highly reactive and not possible to trap. However, the exact explanation is not yet clear.

Conclusions

In summary, we have demonstrated that bromodimethylsulfonium bromide mediates a new multicomponent reaction for the synthesis of highly functionalized piperidines. In addition, we have shown that substituents on the 1,3-dicarbonyl components determine the course of the reaction. This strategy is interesting as both the α- and γ-positions of β-keto esters are involved in C−C bond formation under the mild conditions. The resultant heterocyclic systems have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity. Studies toward the further generalization of this approach and the application of this method to access other heterocyclic scaffolds are underway.

Experimental Section

General Procedure for Mannich-Type Reaction.[9e] To a solution of benzaldehyde (2 mmol), aniline (2 mmol), and 1, 3-dicarbonyl compound (2 mmol) in 5 mL of acetonitrile was added bromodimethylsulfonium bromide (0.2 mmol) then the solution was stirred at room temperature. After completion of the reaction, the crude solid was just filtered off and washed with a hexane/ethanol (80:20) mixture. The solid residue was then dissolved in hot ethanol and recrystallized to provide the pure product. The pure product was characterized by conventional spectroscopic methods.

General Procedure for the Synthesis of Highly Functionalized Piperidines. To a solution of aniline (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of acetonitrile was added bromodimethylsulfonium bromide (0.1 mmol). Subsequently 4-methylbenzaldehyde (2 mmol) was added to the mixture. The resulting mixture was stirred at room temperature. After completion of the reaction as checked by TLC, the solvent was evaporated in a rotatory evaporator and the crude product was washed with ethanol and filtered off. The pure product was characterized by conventional spectroscopic methods.

Representative data for compound 1a: light yellow solid (0.345 g, 75%); mp 169−171 °C; IR (KBr) 3241, 3058, 2948, 1655, 1594, 1500, 1257, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (1H, dd, $J = 2.4$ Hz, $J = 15.2$ Hz), 2.86 (1H, dd, $J = 5.6$ Hz, $J = 15.2$ Hz), 3.93 (3H, s), 5.13−5.14 (1H, m), 6.26−6.28 (2H, m), 6.44 (1H, s), 6.51 (2H, d, $J = 8.8$ Hz), 6.59 (1H, t, $J = 7.2$ Hz), 7.03−7.10 (5H, m), 7.16 (2H, d, $J = 8.0$ Hz), 7.20−7.22 (1H, m), 7.24−7.32 (7H, m), 10.24 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 51.2, 55.2, 58.3, 98.0, 113.0, 116.3, 125.9, 126.0, 126.5, 126.8, 127.3, 128.4, 128.8, 128.9, 129.0, 137.9, 142.9, 144.0, 147.1, 156.4, 168.7. Anal. Calcd for $C_{31}H_{28}N_2O_2$ (460.58): C, 80.84; H, 6.13; N, 6.08. Found: C, 80.71; H, 6.07; N, 6.19.

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Supporting Information Available: The general experimental methods, full characterization data for **1b**−**s**, **2a**, and **2c**, ^1H NMR,^{13}C NMR spectra of new compounds, and X-ray structure, data, and CIFs of **1c** and **1m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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