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Bromodimethylsulfonium bromide mediated Michael addition of amines to electron deficient alkenes

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Abstract—Bromodimethylsulfonium bromide has been found to be an efficient catalyst for the Michael addition of a wide variety of amines to electron deficient alkenes at room temperature. The protocol is very simple and chemoselective. Aliphatic and benzylic amines undergo conjugate addition within a very short period under solvent-free conditions and provide excellent yields of products.
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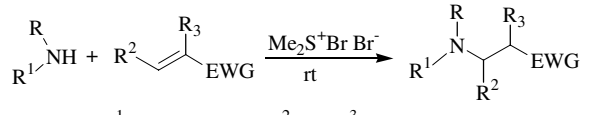
The conjugate addition of amines to electron deficient alkenes is an important and widely used transformation in organic synthesis owing to the importance of the resultant β-amino ketones, esters, nitriles or amides. It provides an easy route to β-amino acid derivatives as well as for the synthesis of heterocycles containing a β-amino carbonyl unit.[1] These β-amino carbonyl compounds are versatile synthetic intermediates for the synthesis of a variety of biologically important natural products, antibiotics and are useful in fine chemicals and pharmaceuticals.[2] The conventional method for the preparation of these compounds is via the Mannich reaction;[3] however, it has several shortcomings including long reaction times, low yields and harsh reaction conditions.

An alternative method for preparing these compounds is via Michael addition. Both from an atom economic point of view as well as simplicity of the procedure, the Michael addition is the preferred method for the preparation of β-amino carbonyl compounds. Either acid or base can be used as a promoter for this transformation. Over the years, numerous methods have been developed using a variety of reagents such as $SnCl_4$/$FeCl_3$,[4] $InCl_3$,[5] $CeCl_3{\cdot}7H_2O$–NaI,[6] $Yb(OTf)_3$,[7] $Cu(OTf)_2$,[8] CAN,[9] $Bi(NO_3)_3$,[10] $Bi(OTf)_3$,[11] $LiClO_4$,[12] KF/alumina,[13] SmI_2,[14] etc. Recently, additional methods have been reported, among them $Cu(acac)_2$/ionic liquid,[15] ionic liquid/quaternary ammonium salt in water,[16] boric acid in water,[17] β-cyclodextrin,[18] $ZrOCl_2{\cdot}8H_2O$,[19] borax,[20] etc., are notable. Although these methods are quite useful, many suffer from limitations such as the requirement for a large excess of reagents, long reaction times, harsh reaction conditions and also involvement of toxic solvents such as acetonitrile or 1,2-dichloroethane. Hence, there is a need to develop a convenient, environmentally friendly method for conjugate addition of amines to electron deficient alkenes.

Bromodimethylsulfonium bromide (BDMS) is a readily accessible, cheap and highly effective reagent[21] as well as a catalyst for various organic transformations.[22] In continuation of our work on the development of new synthetic methodologies, we have observed that



R= H/ alkyl; R^1= alkyl/benzyl; R^2= H; R^3= H/Me; EWG = CN, COMe, COEt, $CONH_2$

Scheme 1.

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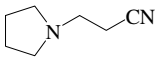
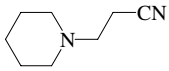
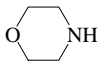
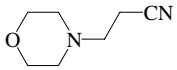
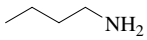
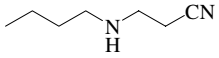
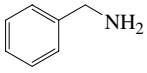
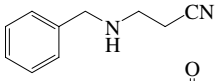
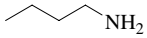
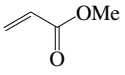
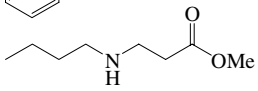
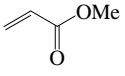
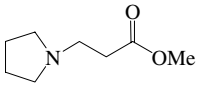
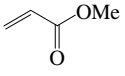
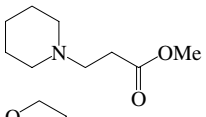
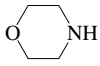
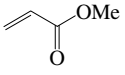
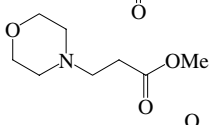
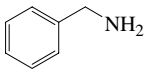
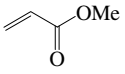
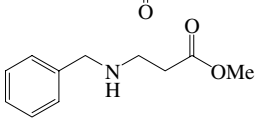
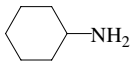
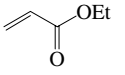
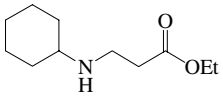
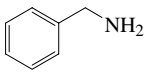
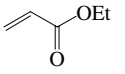
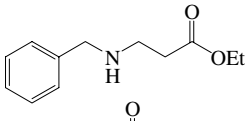
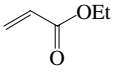
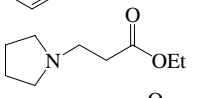
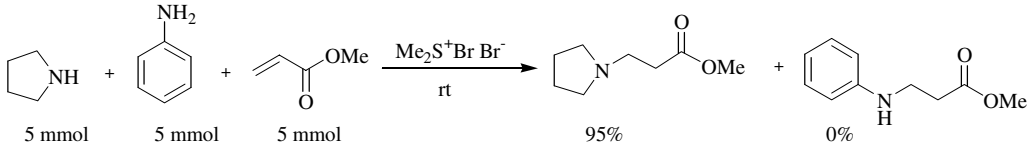
bromodimethylsulfonium bromide efficiently catalyzes the conjugate addition of various amines to electron deficient alkenes at room temperature (Scheme 1).

In a preliminary experiment pyrolidine (5 mmol) was treated with acrylonitrile (5 mmol) in the presence of bromodimethylsulfonium bromide (0.25 mmol) under

Table 1. Bromodimethylsulfonium bromide mediated Michael addition of amines to conjugated alkenes under solvent-free conditions

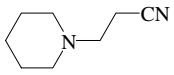
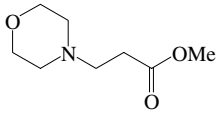
Entry	Amine **a**	Unsaturated alkene **b**	Time (min)	Product[a] **c**	Yield[b] (%)
1			5		98
2			5		99
3			5		93
4			10		92
5			15		91
6			15		85
7			5		97
8			5		96
9			5		97
10			15		84
11			10		85
12			20		89
13			5		94
14			20		88
15			15		83
16			5		91
17			15		89
18			120		0

[a] All the products were fully characterized by recording IR, ^{1}H, ^{13}C NMR and elemental analyses.
[b] Isolated yields.



Scheme 2. Chemoselective conjugate addition of aliphatic amines in the presence of aromatic amines.

Table 2. Comparison of the present protocol with reported methods

Product	Catalyst[a] (mol %)	Reaction conditions/solvent	Time min/[h]	Yield[b] (%)
	$LiClO_4$ (100)[12]	rt/solvent-free	[1]	80
	$ZrClO_4{\cdot}8H_2O$/montmorillonite (0.075 g/mmol)[19]	rt/solvent-free	15	94
	CAN (10)[9]	Ultrasonication/THF	20	96
	H_3BO_3 (10)[17]	rt/H_2O	[1.5]	95
	Borax (10)[20]	rt/H_2O	[2]	90
	β-Cyclodextrin (100)[18]	rt/H_2O	[6]	84
	BDMS (5)	rt/solvent-free	5	99
	$ZrClO_4{\cdot}8H_2O$/montmorillonite (0.075 g/mmol)[19]	rt/solvent-free	35	76
	H_3BO_3 (10)[17]	rt/H_2O	[3]	85
	Borax (10)[20]	rt/H_2O	[3]	92
	BDMS (5)	Solvent-free	5	97

[a] Corresponding reference.
[b] Isolated yield.

solvent-free conditions at room temperature, providing the corresponding Michael adduct, exclusively, within 5 min in 98% yield (Table 1, entry 1). Product **1c** was characterized by ^1H and ^{13}C NMR spectroscopy as well as by comparison with authentic data.[23] Interestingly, the crude product obtained after aqueous work-up was found to be pure as there was no detectable amount of impurities or starting material in the ^1H NMR of the crude product. Encouraged by this, other secondary amines such as piperidine and morpholine (entries 2 and 3) were treated with the same Michael acceptor under the same experimental conditions[24] and the corresponding Michael adducts were isolated in excellent yields within a short time. Similarly, the primary amines *n*-butylamine and benzylamine (entries 4 and 5) underwent Michael addition smoothly providing good yields of the desired adducts. The present protocol represents an improvement over some of the recently reported methods in terms of reaction time as well as % yields obtained. Similarly, the α,β-unsaturated esters methyl acrylate and ethyl acrylate reacted with a wide variety of amines under the same conditions to afford very good yields of the corresponding Michael adducts (entries 6–13). Methyl methacrylate and methyl *trans*-cinnamate also underwent Michael addition with morpholine and pyrrolidine, respectively, without any difficulty (entries 14 and 15).

Likewise acrylamide underwent Michael addition with pyrrolidine and morpholine (entries 16 and 17) in very good yields. However, in an attempt to react an aromatic amine, the same protocol was unsuccessful and yielded only the starting material even after 2 h of stirring (entry 18). Interestingly, the present protocol could be used on a 100 mmol scale using only 2 mol % of catalyst.

Next, to exemplify the chemoselectivity of this present protocol a competitive study was carried out using a mixture of 5 mmol of pyrrolidine, 5 mmol of aniline and 5 mmol of methyl acrylate as shown in Scheme 2. The Michael adduct of pyrrolidine was obtained exclusively and clearly reflects the chemoselectivity of aliphatic amines versus aromatic amines.

The catalytic activity of bromodimethylsulfonium bromide was ascertained by the fact that in the absence of the catalyst, the reaction of pyrrolidine with acrylonitrile afforded only a 20% yield of adduct even after 6 h of stirring at room temperature. The efficacy and generality of the present protocol can be realized by comparing some of the results presented here with recently reported methods as shown in Table 2, which compares reaction time, % yields and reaction conditions.

In summary we have developed a simple and efficient methodology[24] for the conjugate addition of amines to electron deficient alkenes using bromodimethylsulfonium bromide as an inexpensive and efficient catalyst. This method demonstrates the potential of BDMS as an efficient promoter.

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References and notes

1. (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 30–41; (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117–128; (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7791–8035.
2. (a) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207–5210; (b) Graul, A.; Castaner, J. *Drugs Future* **1997**, *22*, 956–968.
3. Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180–8186.
4. Wen, L.; Li, L.; Xia, C.-G. *Helv. Chim. Acta* **2004**, *87*, 1522–1526.
5. Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975–976.
6. (a) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massimo, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169–175; (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Pertrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052–9055.
7. (a) Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233–236; (b) Matsubara, S.; Yoshiyoka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827–830.
8. (a) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891–3894; (b) Xu, L.-W.; Li, J.-W.; Xia, C.-G.; Zhou, S.-L.; Hu, X.-X. *Synlett* **2003**, 2425–2427.
9. Duan, Z.; Xuan, X.; Li, T.; Yang, C.; Wu, Y. *Tetrahedron Lett.* **2006**, *47*, 5433–5436.
10. Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114.
11. Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 720–722.
12. Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383–387.
13. Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2005**, *46*, 3279–3282.
14. Reboule, I.; Gil, R.; Collin, J. *Tetrahedron Lett.* **2005**, *46*, 7761–7764.
15. Kantam, M. L.; Neeraja, V.; Kavita, B.; Neelima, B.; Chaudhuri, M. K.; Hussain, S. *Adv. Synth. Catal.* **2005**, *347*, 763–766.
16. Xu, L.-W.; Li, J.-W.; Zhou, S.-L.; Xia, C.-G. *New J. Chem.* **2004**, *28*, 183–184.
17. Chaudhuri, M. K.; Hussain, S.; Kantam, M. L.; Neelima, B. *Tetrahedron Lett.* **2005**, *46*, 8329–8331.
18. Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2125–2127.
19. Hashemi, M. M.; Eftekhari-Sis, B.; Abdollahifar, Amir; Khalili, B. *Tetrahedron* **2006**, *62*, 672–677.
20. Hussain, S.; Bharadwaj, S. K.; Chaudhuri, M. K.; Kalita, H. *Eur. J. Org. Chem.* **2007**, 374–378.
21. (a) Choudhury, L. H. *Synlett* **2006**, 1619–1620; (b) Khan, A. T.; Ali, A.; Goswami, P.; Choudhury, L. H. *J. Org. Chem.* **2006**, *71*, 8961–8963; (c) Das, B.; Krishnaiah, M.; Katta, V. *Tetrahedron Lett.* **2006**, *47*, 4457–4460.
22. (a) Khan, A. T.; Mondal, E.; Borah, B. M.; Ghosh, S. *Eur. J. Org. Chem.* **2003**, 4113–4117; (b) Khan, A. T.; Islam, S.; Majee, A.; Chattopadhyay, T.; Ghosh, S. *J. Mol. Catal. A: Chem.* **2005**, *239*, 158–165; (c) Khan, A. T.; Sahu, P. R.; Majee, A. *J. Mol. Catal. A: Chem.* **2005**, *226*, 207–212; (d) Khan, A. T.; Mondal, E.; Ghosh, S.; Islam, S. *Eur. J. Org. Chem.* **2004**, 2002–2009; (e) Das, B.; Holla, H.; Srinivas, Y. *Tetrahedron Lett.* **2007**, *48*, 61–64.
23. Ranu, B. C.; Dey, S. S.; Hajra, A. *ARKIVOC* **2002**, *vii*, 76–81.
24. *Representative experimental procedure for the Michael reaction* (**1c**): To a mixture of acrylonitrile (265 mg, 5 mmol) and pyrrolidine (355 mg, 5 mmol), bromodimethylsulfonium bromide (56 mg, 0.5 mmol) was added and the reaction mixture stirred at room temperature. The reaction was complete within 5 min as indicated by TLC. The reaction mixture was extracted with ethyl acetate (2×20 mL) and the combined extract was dried over Na_2SO_4 and evaporated to leave a crude product, which was sufficiently pure as ascertained by ^1H NMR of the crude product. The Michael adduct (Table 1, entry 1) was characterized by recording IR, ^1H and ^{13}C NMR spectra as well as by comparison with reported data.[23]