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(Bromodimethyl)sulfonium bromide mediated Michael addition of thiols to α, β-unsaturated ketones

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A mild and rapid Michael addition of mercaptans to α, β-unsaturated ketones has been achieved in excellent yields, using catalytic amount of (bromodimethyl)sulfonium bromide.

Keywords: (Bromodimethyl)sulfonium bromide; α, β-Unsaturated ketones; Michael addition; Thiols; Solvent free reactions

1. Introduction

The Michael reaction i.e., conjugate addition of nucleophile(s) to α, β-unsaturated carbonyl compounds is one of the remarkable reactions in organic synthesis. It has attracted enormous attention mainly because it is one of the most important C-C or C-S bond formation reactions [1]. The Michael addition of mercaptans to α, β-unsaturated carbonyl compounds constitutes the key step in synthetic pathway of many bioactive molecules both man made and natural [2–6]. Further, it also provides a method for protection of double bond(s) of α, β-unsaturated carbonyl compounds mainly due to the ease with which they can be regenerated [7, 8]. From a synthetic chemist's perspective, numerous fascinating reports on the thia Michael addition reactions involving heterogeneous [9–17] catalysts; conjugate additions comprising activation of thiols by bases [18–21] and Lewis acids [22–29] have appeared in literature.

Despite their extensive success, many of the methods suffer from drawbacks such as usage of exotic and stoichiometric reagents, harsh reaction conditions, cumbersome work-up procedures, low yields, etc. Since the thia-Michael addition reaction is an often-encountered synthetic step in synthesis of bioactive/medicinal compounds like diltiazem [30], a simple, efficient method would be an agreeable lead. Herein, we report an experimentally convenient, mild and solvent free conjugate addition of mercaptans to α, β-unsaturated carbonyl compounds.

Over the past few years, (bromodimethyl)sulfonium bromide emerged as a powerful catalyst [31–34] for various organic transformations especially in solvent free conditions [35, 36].

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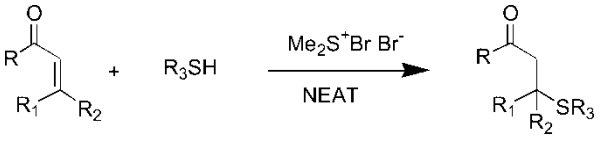


SCHEME 1

The Michael addition of thiols to α, β-unsaturated carbonyl compounds occurred almost instantaneously at room temperature in the presence of catalytic amount of (bromodimethyl)sulfonium bromide (5 mol%) to generate the 1,4- adducts in excellent yields (scheme 1). Reaction temperature plays a crucial role. Initially the reaction was carried out at 0 °C and was found to be incomplete and low yielding in spite of prolonged reaction time. However, at room temperature (24–27 °C) the conjugate addition was found to yield optimum results. Higher temperatures found to be detrimental with concomitant formation of by-product, disulfide. Similarly usage of 10 mol% of the catalyst did not significantly alter the rate of addition or the yield indicating that 5 mol% catalyst is sufficient for the conversion.

Once the reaction conditions were established, the generality of the method was examined by subjecting a variety of α, β-unsaturated carbonyl compounds to thia Michael addition by aromatic as well as aliphatic thiols in solvent free conditions (table 1). All the products were formed rapidly (3–5 min) and isolated in good yields. Unsubstituted enones, substituted enones all react with the thiols in a rapid manner. The substitutions on the phenyl rings of the α, β-unsaturated carbonyl compounds whether attached to carbonyl or to the olefinic group do not seem to significantly alter the yields of the reactions. It was also found that the addition of thiophenol was faster and better yielding when compared to ethanethiol. The reaction proceeds well with even solid α, β-unsaturated ketones. However, it was found that addition of solid thiols was not effective (as illustrated by example 9, 10; table 1).

The role of the catalyst, (bromodimethyl)sulfonium bromide, is somewhat like that of Lewis acid i.e., an electrophilic activation by co-ordination to the carbonyl oxygen of α, β-unsaturated carbonyl compound thereby rendering the β-carbon susceptible to nucleophilic attack by thiol. Instantaneous evolution of HBr was observed on addition of the catalyst to the mixture of thiol and α, β-unsaturated carbonyl compounds which indicates that the first step would be the reaction between (bromodimethyl)sulfonium bromide and the thiol leading to the formation of the species $[Me_2BrS^+]^-SR$ as shown in the scheme below. The earlier report [37] suggests formation of $[Me_2BrS^+]^-OR$ when ROH was added to the catalyst, which validates the formation of $[Me_2BrS^+]^-SR$. This might be the active species that is generated until the exhaustion of the thiol and addition of water during the work-up when dimethyl sulfoxide is generated (scheme 2).

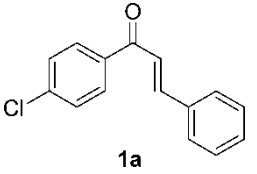
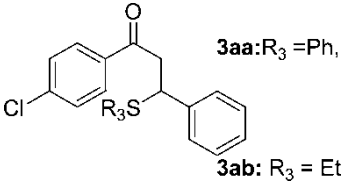
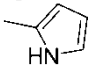
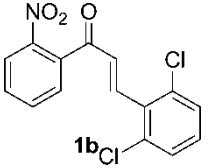
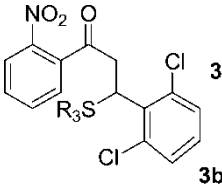
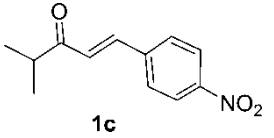
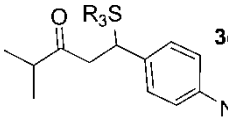
To summarize, we have been successful in developing a simple, convenient, mild, rapid and solvent free method for thia Michael addition using 5 mol% of (bromodimethyl)sulfonium bromide. This environmentally friendly protocol provides a viable alternative to the current methods.

2. Experimental

2.1 *General procedure*

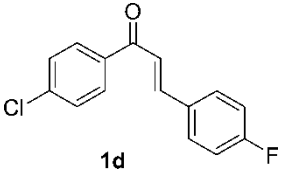
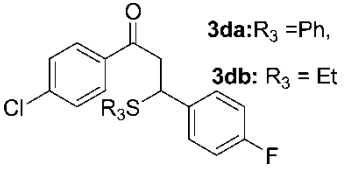
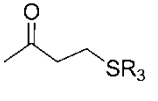
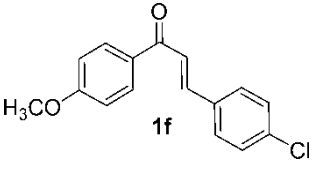
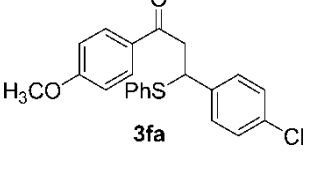
To a stirred mixture of equimolar amounts (1 mmol) of the thiol and the α, β-unsaturated ketone, (bromodimethyl)sulfonium bromide (5 mol%) (for preparation of the catalyst refer to G.A. Olah, Y.D. Vankar, M. Arvanghi, G.K. Suryaprakash *Synthesis* 720 (1979)) was added.

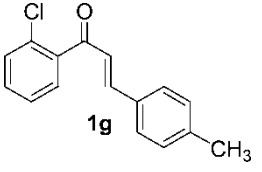
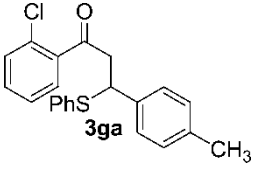
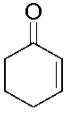
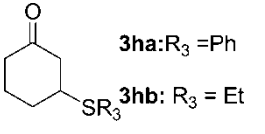
Table 1. Thiol Michael additions to α, β-unsaturated carbonyl compounds.

Entry	Unsaturated ketone	Thiol	Product	Time (min)	Yield (%)*	M.P. (°C)
1.	 **1a**	**2a**: PhSH	 **3aa**:R_3 =Ph, **3ab**: R_3 = Et	3	94[1]	–
2.		**2b**: EtSH		4	92	–
3.		**2c**: H_3CPhSH		–	–	
4.		**2d**: C_4H_4NSH	**3ac**: R_3 = H_3CPh **3ad**: R_3 = 	–	–	
5.	 **1b**	**2a**: PhSH	 **3ba**:R_3 =Ph, **3bb**: R_3 = Et	3	89	79–81
6.		**2b**: EtSH		4	80	85–86
7.	 **1c**	**2a**: PhSH	 **3ca**:R_3 =Ph, **3cb**: R_3 = Et	3	92	67–69
8.		**2b**: EtSH		4	88	68–69
9.		**2a**: PhSH		4	84	–

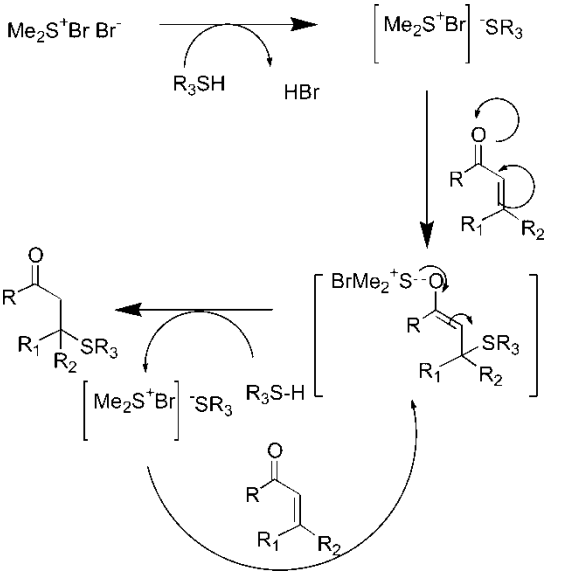
(*continued*)

Table 1. Continued.

Entry	Unsaturated ketone	Thiol	Product	Time (min)	Yield (%)*	M.P. (°C)
10.	 **1d**	**2b**: EtSH	 **3da:**R_3 =Ph, **3db:** R_3 = Et	5	84	–
11.	 **1e**	**2a**: PhSH	 **3ea:**R_3 =Ph, **3eb:** R_3 = Et **3ec:** R_3 = H_3CPh	2	85[7]	–
12.		**2b**: EtSH		3	81[7]	–
13.		**2c**: H_3CPhSH		–	–	
14.	 **1f**	**2a**: PhSH	 **3fa**	3	86	95–96

15.	 **1g**	**2a**: PhSH	 **3ga**	4	90	–
16.	 **1h**	**2a**: PhSH	 **3ha:** R_3 =Ph **3hb:** R_3 = Et	3	90[7]	–
17.		**2b**: EtSH		3	92[7]	–

*all yields are isolated.



SCHEME 2

The reaction mixture was stirred at room temperature for 3–5 min. After completion of the reaction as indicated by TLC, the reaction mixture is diluted with water and extracted with ethyl acetate. After the usual drying, the organic layers were concentrated and the product obtained purified by column chromatography (8:2-hexane: ethyl acetate).

2.2 *Compound 3ab*

IR (ν, cm^{-1}): 3015, 2883, 1640, 772, 608; ^1H NMR(δ): 7.46 (d, $J = 8$ Hz, 2H, Ar), 7.22 (d, $J = 7$ Hz, 2H, Ar), 6.20 (d, $J = 6$ Hz, 1H), 5.29 (d, $J = 6$ Hz, 1H), 2.40 (m, 2H, S-CH_2), 1.24 (t, $J = 6$ Hz, 1H), 1.08 (t, $J = 7$ Hz, 3H, CH_3); E.I. Mass: 304 (M^+); CHN Analysis: Calcd-C: 66.98, H: 5.62, S: 10.52, Found: C: 65.97, H: 5.56, S: 10.41.

2.3 *Compound 3ba*

IR (ν, cm^{-1}): 3115, 2707, 1726. ^1H NMR(δ): 8.25 (d, $J = 8$ Hz, 1H, Ar), 8.03 (d, $J = 8$ Hz, 1H, Ar), 7.45 (m, 4H, Ar), 7.20 (m, 3H, Ar), 5.68 (t, $J = 4$ Hz, 1H), 3.98 (m, 1H); E.I. Mass: 431 (M^+); CHN Analysis: Calcd-C: 53.13, H: 3.93, N: 3.64, S: 8.34; Found: C: 52.33, H: 3.89, N: 3.60, S: 8.23.

2.4 *Compound 3bb*

IR (ν, cm^{-1}): 3045, 2560, 1720; ^1H NMR(δ): 8.30 (d, $J = 8$ Hz, 1H, Ar), 8.10 (d, $J = 8$ Hz, 1H, Ar), 7.24 (m, 3H, Ar), 7.10 (d, $J = 7$ Hz, 1H, Ar), 5.40 (t, $J = 6$ Hz, 1H), 3.65 (dd, $J = 12$ Hz, 8 Hz, 1H), 2.7 (q, $J = 4$,12 Hz, 2H) 1.23 (t, $J = 8$ Hz, 3H); E.I. Mass: 383 (M^+); CHN Analysis: Calcd-C: 53.13, H: 3.93, N: 3.64, S: 8.3; Found: C: 52.59, H: 3.89, N: 3.60, S: 8.20.

2.5 *Compound 3ca*

IR (ν, cm^{-1}): 3010, 2950, 1700; ^1H NMR(δ): 8.20 (d, $J = 8$ Hz, 1H, Ar), 8.0 (d, $J = 8$ Hz, 1H, Ar), 7.63 (d, $J = 7$ Hz, 1H, Ar), 7.25 (d, $J = 8$ Hz, 1H, Ar), 7.10 (m, 5H, Ar), 4.65 (t, $J = 6$ Hz, 1H), 3.02 (d, $J = 4$ Hz, 2H), 1.2 (s, 3H, CH_3), 1.0 (s, 3H, CH_3); E.I. Mass: 329 (M^+); CHN Analysis: Calcd-C: 65.60, H: 5.81, N: 4.25, S: 9.73; Found: C: 64.68, H: 5.75, N: 4.20, S: 9.53.

2.6 *Compound 3cb*

IR (ν, cm^{-1}): 3115, 2966, 1702; ^1H NMR(δ): 8.40 (d, $J = 8$ Hz, 1H, Ar), 8.02 (d, $J = 7$ Hz, 1H, Ar), 7.31 (m, 5H, Ar), 7.13 (d, $J = 8$ Hz, 1H, Ar), 5.20 (t, $J = 6$ Hz, 1H), 4.10 (m, 1H), 3.80 (m, 1H), 2.42 (m, 2H) 1.23 (t, $J = 6$ Hz, 3H); E.I. Mass: 281 (M^+); CHN Analysis: Calcd-C: 59.76, H: 6.80, N: 4.97, S: 11.40; Found: C: 58.86, H: 6.73, N: 4.92, S: 11.25.

2.7 *Compound 3da*

IR (ν, cm^{-1}): 3038, 2881, 1726, 892, 772; ^1H NMR(δ): 7.80 (d, $J = 7$ Hz, 1H, Ar), 7.40 (s, 1H, Ar), 7.10 (d, $J = 8$ Hz, 2H, Ar), 6.95 (d, $J = 8$ Hz, 2H, Ar), 4.20 (m, 1H), 3.28 (d, $J = 4$ Hz, 2H), 2.25 (q, $J = 4$, 12 Hz, 2H), 1.10 (t, $J = 6$ Hz, 6H); E.I. Mass: 370 (M^+); CHN Analysis: Calcd-C: 68.01, H: 4.34, S: 8.64; Found: C: 66.92, H: 4.25, S: 8.55.

2.8 *Compound 3db*

IR (ν, cm^{-1}): 3035, 2973, 1713, 760; ^1H NMR(δ): 7.60 (m, 2H, Ar), 7.52 (s, 1H, Ar), 7.40–7.30 (m, 4H, Ar), 4.75 (q, $J = 4$, 12 Hz, 1H) , 3.52 (d, $J = 6$ Hz, 2H); E.I. Mass: 322 (M^+); CHN Analysis: Calcd-C: 63.25, H: 4.99, S: 9.93; Found: C: 62.30, H: 4.96, S: 8.38.

2.9 *Compound 3fa*

IR (ν, cm^{-1}): 3026, 2933, 1670; ^1H NMR(δ): 7.80 (d, $J = 8$ Hz, 2H, Ar), 7.23 (m, 2H, Ar), 6.82 (d, $J = 8$ Hz, 2H, Ar), 4.80 (t, $J = 6$ Hz, 1H), 3.80 (s, 3H, OCH_3), 3.42 (d, $J = 4$ Hz, 2H); E.I. Mass: 382 (M^+); CHN Analysis: Calcd-C: 69.01, H: 4.96, S: 8.38; Found: C: 68.04, H: 4.91, S: 8.29.

2.10 *Compound 3ga*

IR (ν, cm^{-1}): 3050, 2926, 1710, 719, 688; ^{1}HNMR(δ): 7.43 (m, 3H, Ar), 7.20 (d, $J = 8$ Hz, 2H, Ar), 7.12 (d, $J = 7$ Hz, 2H, Ar), 5.0 (t, $J = 6$ Hz, 1H, Ar), 3.60 (m, 1H), 2.25 (s, 3H, CH_3); E.I. Mass: 366 (M^+); CHN Analysis: Calcd-C: 72.01, H: 5.22, S: 8.73; Found: C: 70.92, H: 5.16, S: 8.64.

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References

[1] M. Zahouily, Y. Abrouki, A. Rayadh. *Tetrahedron Lett*., **43**, 7729 (2002) and references cited therein.
[2] E. Fujitha, Y. Nagrao. *Bioorg. Chem.,* **6**, 287 (1977).
[3] A.L. Fluharty. In *The Chemistry of Thiol Group*, part 2, S. Patai (Ed.), p. 589, Wiley Interscience, New York (1974).
[4] B.M. Trost, D.E. Keeley. *J. Org. Chem.*, **40**, 2013 (1975).
[5] A. Kumar, R.V. Salunkhe, R.A. Rane, S.Y. Dike. *J. Chem. Soc., Chem. Commun*., 485 (1991).
[6] J.H. Clark. *Chem. Rev.*, **80**, 429 (1980).
[7] S.K. Garg, R. Kumar, A.K. Chakraborti. *Tetrahedron Lett*., **46**, 1721 (2005).
[8] T. Cohen, A.J. Mura Jr, D.W. Shull, E.R. Fogel, R.J. Ruffner, J.R. Falck. *J. Org. Chem.*, **41**, 3218 (1976).
[9] U. Sharma, U. Bora, R.C. Boruah, J.S. Sandhu. *Tetrahedron Lett*., **43**, 143 (2002).
[10] D.E. Bergbreiter, J.J. Lalonde. *J. Org. Chem.*, **52**, 1601 (1987).
[11] B.C. Ranu, M. Saha, S. Bhar. *Tetrahedron Lett*., **34**, 1989 (1993).
[12] J.H. Clark, D.G. Cork, H.W. Gibs. *J. Chem. Soc., Perkin Trans. I*, 2253 (1983).
[13] P. Laszlo, M.-T. Montaufier, S.L. Randriamahefa. *Tetrahedron Lett*., **31**, 4867 (1990).
[14] B.M. Choudary, M. Lakshmi Kantam, Ch. Venkat Reddy, K. Koteswara Rao, F. Figueras. *J. Mol. Catal. A*, **146**, 279 (1999).
[15] R. Sreekumar, P. Rugmini, R. Padmakumar. *Tetrahedron Lett*., **38**, 6557 (1997).
[16] S. Sebti, A. Saber, A. Rhihil, R. Nazih, R. Tahir. *Appl. Catal. A: General*, **206**, 217 (2001).
[17] S. Sebti, R. Tahir, R. Nazih, S. Boulaajaj. *Appl. Catal. A: General*, **218**, 25 (2001).
[18] H. Hiemstra, H. Wynberg. *J. Am. Chem. Soc.*, **103**, 417 (1981).
[19] K. Suzuki, A. Ikekawa, T. Mukaiyama. *Bull. Chem. Soc. Jpn.*, **55**, 3277 (1982).
[20] H. Yamashita, T. Mukaiyama, *Chem. Lett.,* 363 (1985).
[21] E. Emori, T. Arai, H. Sasai, M. Shibasaki. *J. Am. Chem. Soc.*, **120**, 4043 (1998).
[22] S. Kobyashi, C. Ogawa, M. Kawamura, M. Sugiura. *Synlett*, 983 (2001).
[23] M. Bandini, P.G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva, A. Umani-Ronchi. *J. Org. Chem.*, **67**, 3700 (2002).
[24] N. Srivastava, B.K. Banik. *J. Org. Chem.*, **68**, 2109 (2003).
[25] M.M. Alam, R. Varala, S.R. Adapa. *Tetrahedron Lett*., **44**, 5115 (2003).
[26] B.C. Ranu, S.S. Dey, S. Samanta. *ARKIVOC*., 44 (2005).
[27] Y. Abrouki, M. Zahouily, A. Rayadh, B. Bahalouan, S. Sebti. *Tetrahedron Lett*., **43**, 8951 (2002).
[28] S. Cheng, D.D. Comer. *Tetrahedron Lett*., **43**, 1179 (2002).
[29] T.C. Wabnitz, J.-Q. Yu, J.B. Spencer. *Synlett*, 1070 (2003).
[30] R.A. Sheldon. *Chirotechnololologies, Industrial Synthesis of Optically Active Compounds*, Dekker Publishing, New York (1993).
[31] G.A. Olah, Y.D. Vankar, M. Arvanghi. *Tetrahedron Lett*., **38**, 3653 (1979).
[32] Y.L. Chow, B.H. Bakker. *Can. J. Chem*., **60**, 2268 (1982).
[33] B. Vittal Rao, K. Sucheta. *Tetrahedron Lett*., **46**, 1209 (2005).
[34] A.T. Khan, E. Mondal, S. Ghosh, S. Islam. *Eur. J. Org. Chem.,* 2002 (2004).
[35] A.R. Hajipour, A.E. Ruoho. *Sulfur Lett.*, **25**, 151 (2002).
[36] A.R. Hajipour, S.E. Mallakpour, H. Adibi. *Chem. Lett.,* 460 (2000).
[37] N. Furukawa, T. Inoue, T. Aida, S. Oae. *J. Chem. Soc., Chem. Commun*., 212 (1973).