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Boric acid catalyzed thia-Michael reactions in water or alcohols

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Abstract

Boric acid acts as an efficient catalyst for the conjugate addition of aliphatic thiols, dithiols and aromatic thiols to α,β-unsaturated nitriles, esters, ketones and aldehydes with very good yields in water at room temperature. The reactions are faster in MeOH or EtOH. The use of boric acid, being a safe chemical, as the catalyst and water as the reaction medium are important attributes in the present protocol.

Keywords: Michael addition; Thiols; α,β-Unsaturated olefins; Boric acid

1. Introduction

The conjugate addition of thiols to electron deficient olefins leading to the formation of C–S bonds is a key reaction in the synthesis of organosulfur compounds as well as in biosynthesis [1]. Organosulfur compounds have multiple applications [2] in the synthesis of biologically active molecules, including calcium antagonist dilthiazem [3], thereby providing additional impetus to the study of thia-Michael reactions. Consequently, there has been sustained interest in the development of improved methods for the construction of C–S bonds. Strategically, the success of the addition of marcaptans to conjugated alkenes lie in the activation [4] of either the acceptor olefins with acids or the thiols by a base. However, the use of very strong acids or bases has limitations, especially leading to undesired side reactions. In order to overcome such difficulties as well as to reduce the chances of polymerization and hydrolysis, the Michael reaction has undergone metamorphosis over the years using a variety of reagents and catalysts, namely, inorganic salts [5], tetrabutylammonium halides [6], ionic liquids [7], and combination of ionic liquids and water [8]. Many of these methods have limited utility because of producing hazardous wastes [5,6] requiring longer reaction times [5] and high temperatures [6], using halogenated solvents [5] and toxic chemicals [7,8]. In addition, the chances of poisoning of metal-based catalysts by sulfur cannot be ruled out. Of late, polyethylene glycol [9], cyclodextrin in water [10], micellar solution of sodium dodecyl sulfate [11], azaphosphtrane nitrate [12], and $HClO_4/SiO_2$ [13] in dichloromethane or MeOH have been used for the thia-Michael reactions, although some of these are neither commonly used chemicals nor are they cost effective to be applied in higher scale operations. Thus, there is still need for a simpler, cost effective, commercially viable and environmentally acceptable protocol for this type of reaction that might be of interest to a wide range of organic chemists. In view of this and considering the capability of boric acid to produce H^+ in water to activate the acceptor olefins, it was thought worthwhile to investigate if it would catalyse thia-Michael reactions. Significantly boric acid has been shown in some recent papers by Houston et al. [14] and Yamamoto and co-workers [15] to be an efficient, cost effective and environmentally benign catalyst for the esterification of α-hydroxycarboxylic acids with alcohols at ambient temperature. In this paper, we report the results of boric acid catalyzed conjugate addition of a variety of thiols to α,β-unsaturated nitriles, esters, ketones and aldehydes in water [16]. The same reactions are capable of being conducted in MeOH or EtOH with greater ease.

2. Results and discussion

An easy availability, cost effectiveness and environmental compatibility in addition to weak acidity and ability to produce H^+ from its reaction with water or alcohol, $B(OH)_3 + H_2O \rightarrow B(OH)_4^- + H^+$ or $B(OH)_3 + ROH \rightarrow B(OH)_3(OR)^- + H^+$, are some of the most important reasons for selecting boric acid as the catalyst. The additional advantages of $B(OH)_3$ based

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Table 1
Reaction of thiophenol with cyclohexenone using various catalysts and solvents

Entry	Catalyst[a]	Solvent	Time (h)	Yield (%)	Ref.
1	$InBr_3$	CH_2Cl_2	24	80	[4a]
2	$RuCl_3$	PEG	12	89	[5h]
3	$Bi(NO)_3$	CH_2Cl_2	2–4	65	[5b]
4	Bu_4NBr	Bu_4NBr (100–105 °C)	0.5	92	[6]
5	$NaHCO_3$	H_2O	10	40–50	[11]
6	$B(OH)_3$	H_2O	4	88	Present work
		CH_3OH	3	92	
		C_2H_5OH	4	89	
7	HCl	H_2O	3	23	
8	H_2SO_4	H_2O	3	15	
9	TsOH	H_2O	3	22	
10	CH_3COOH	H_2O	3	11	

[a] Cost of the catalyst follow the order: 2 > 1 > 3 > 4 ≫ 5 > 6.

catalysis [14,15,17], over many other, are the use of safer solvents like water, MeOH or EtOH at room temperature, relatively facile reactions and very high yields. It is evident from the results summarized in Table 1 that $B(OH)_3$–H_2O, MeOH and EtOH systems work better than many other catalytic systems. Further, a comparison of the results of catalysis using HCl, H_2SO_4, TsOH and CH_3COOH each in water, with all other conditions being maintained the same as that of $B(OH)_3$–H_2O, shows that $B(OH)_3$ is much more effective. With these acids the yields were not only low but also some side reactions seemed to have occurred. The one property that is common to all these acids is their higher acidity compared to that of $B(OH)_3$. This may be the reason for their less effectiveness. Thus, because of the ease in handling and operation, its weak acidity leading to the desired reactions, no side reactions and efficacy, $B(OH)_3$ appears to be superior to the other acids studied herein. Accordingly, water, MeOH or EtOH became the solvent of choice with 10–20% of the chosen catalyst (Table 2).

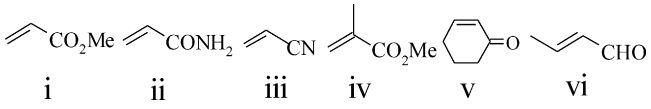
The reaction strategies worked well and a variety of structurally diverse α,β-unsaturated compounds such as methyl acrylate, acrylonitrile, crotonaldehyde, acrylamide, cyclohexenone and methyl methacrylate underwent 1,4-addition with a wide range of thiols in the presence of 10–20 mol% of boric acid at room temperature to give the corresponding β-sulfido compounds in good to very good yields (Table 3). It is notable that the reaction can be performed on a relatively larger scale

Table 2
Reaction of thiophenol with methyl acrylate in different solvents with varying mol% of $B(OH)_3$

Run	$B(OH)_3$ (mol%)	Solvent	Time (h)	Yield (%)
1	1	MeOH	8	55
2	20	MeOH	2	92
3	10	MeOH	3	90
4	10	H_2O	4	89
5	20	H_2O	3	90
6	10	EtOH	4	85
7	20	EtOH	3	85
8	10	CH_3CN	8	64

Table 3
$B(OH)_3$ (10 mol%) catalyzed conjugate addition of thiols to α,β-unsaturated compounds in water at room temperature

Entry	Thiols	α,β-Enone	Time (h)	Yield (%)[a]	Ref.
a	PhSH	i	4, 3[b]	89, 92[c] 90[b] 85[d]	[6]
b	*p*-MeOPhSH	i	4	82	[5i]
c	*p*-NO_2PhSH	i	5	79[e]	
d	C_2H_5SH	i	3	87, 91[d]	
e	$C_{12}H_{25}SH$	i	12	90	
f	PhSH	ii	5	78[e]	[13]
g	C_4H_9SH	ii	6	70[e]	
h	PhSH	iii	3.5, 3[b]	92, 91[b]	[6]
I	C_4H_9SH	iii	3	87	[6]
j	$C_{12}H_{25}SH$	iii	12, 8[d]	78, 82[d]	
k	PhSH	iv	5	85	[6]
l	C_2H_5SH	iv	4, 3[b]	82, 81[d]	[6]
m	C_4H_9SH	iv	5	79	[6]
n	PhSH	v	4, 3[b]	88, 92[b] 89[d]	[4a]
o	*p*-MeOPhSH	v	3, 2[d]	90, 85[d]	[5i]
p	*p*-NO_2PhSH	v	4	88	
q	$C_{12}H_{25}SH$	v	12	90	
r	C_2H_5SH	v	3, 2[b]	90,78[b] 85[d]	[7]
s	PhSH	vi	4	(80, 83[d])[e]	[5i]

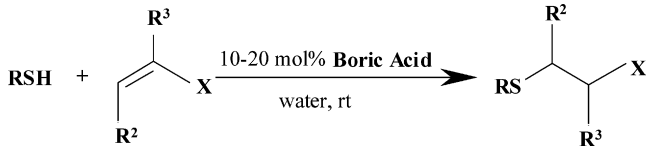


[a] Isolated yields.
[b] Reaction in MeOH.
[c] Yield on a 5 g scale.
[d] Reaction in EtOH.
[e] 20 mol% catalyst used.

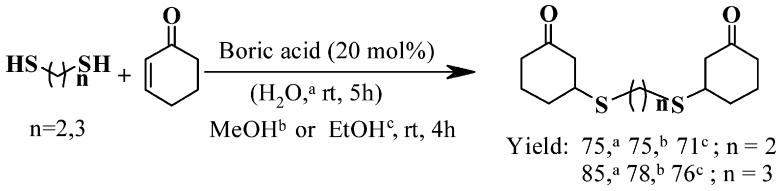
(5 g) to give good yields (entry a, Table 3), showing its potential for large-scale preparations (Scheme 1).

Under similar experimental conditions, dithiols underwent Michael addition giving bis-adducts in good yields (Scheme 2). These reactions were nearly as facile as the monothiols. Incidentally, the Michael reactions involving dithiols appear to be quite scarce [11]. Such reactions may be highly useful in the designed synthesis of organosulfur polymers, supramolecular architectures and macromolecules.

To extend scope of this protocol, α- and β-substituted Michael acceptors were tested under the present conditions. It was found that with Me groups at either the α- or β-positions, the procedure gave good yields (entries k–m and s, Table 3), whereas with a Ph group at the β-position it failed. In view of the synthetic importance of the present results, it may be mentioned that prolonging the reaction time can increase yields further. The



Scheme 1.



Scheme 2.

reaction works relatively better in MeOH or EtOH. The reactions in alcohols are faster than in water. However, considering the cost factor and need for avoidance of organic solvents, one might prefer water as the reaction medium. Finally, upon completion of the reaction, recyclability of the catalyst was examined through a series of reactions with thiophenol and cyclohexenone using the aqueous phase containing boric acid. The reaction continued giving good results from the second to the fourth cycles with the yields being 89, 86 and 85%, respectively. However, the yield dropped to 80% at the fifth cycle. This is explained by attrition and leaching of the catalyst.

3. Conclusion

It is thus evident that thia-Michael reactiions, for both mono and dithiols, can be very easily carried out in water, MeOH or EtOH using $B(OH)_3$ as the catalyst, and scaled up, if desired. The main advantages of the method are the use of very cheap, recyclable, nontoxic and safe catalyst without any polymerization of the products or other side reactions. The reaction is capable of being performed neatly in the chosen solvents at ambient temperature without catalyst poisoning. To our knowledge, $B(OH)_3$ catalyst is possibly environmentally the most enduring for such reactions.

4. Experimental

Reagents and solvents were used as purchased. All reactions were monitored by TLC on silica gel 60 F_{254} (0.25 mm), visualization being effected with UV and/or by developing in iodine. Chromatography refers to open column chromatography on silica gel (60–120 mesh). Organic extracts were dried over Na_2SO_4 (anhydrous). Solvents were removed in a rotary evaporator under reduced pressure. Crystalline boric acid was used for the reaction. Melting points were recorded with a Buchi B-545 melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Varian 400 MHz spectrometer. Chemical shifts are reported in (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded in KBr or neat with a Nicolet Impact 410 spectrophotometer. Elemental analyses were carried out on a Perkin-Elmer 2400 automatic carbon, hydrogen, nitrogen and sulfur analyzer.

4.1. General experimental procedure

Boric acid (0.2 mmol, 0.012 g) was dissolved in water, MeOH or EtOH (1 mL) followed by the addition of the thiol (2 mmol) or dithiol (1 mmol) and α,β-unsaturated compounds (2.2 mmol) and the whole were stirred at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 5 mL), dried over Na_2SO_4 and the resulting product was purified (in the case of MeOH or EtOH the reaction mixture was concentrated, adsorbed on silica gel and directly loaded) on silica gel and eluted with ethyl acetate and *n*-hexene (1:9) as eluent to afford the pure β-sulfido adduct. A precipitate was formed for the reactions of amide with thiols. The precipitate was fitered and washed with water followed by recrystalization from MeOH. The products were identified by comparing their physical and spectral data (IR and ^{1}H NMR, ^{13}C NMR) with the literature values. The physical and spectral data of the heretofore-unreported products are given below.

4.2. Analytical and spectral data

3-(4-*Nitrophenylsulfanyl*)*propionic acid methyl ester* (*entry c*): light yellow solid (m.p. 56–57 °C), IR (KBr) $\tilde{\nu}$ = 1340 and 1511 (NO_2), 1733 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.71(t, J = 7.6 Hz, 2H), 3.30(t, J = 7.2 Hz, 2H), 3.71(s, 3H), 7.34(d, J = 8.8 Hz, 2H), 8.12(d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.39, 33.73, 52.37, 124.20(2C), 126.76(2C), 145.21, 146.27, 171.89; $C_{10}H_{11}NO_4S$ (241.27): calcd. C 49.78, H 4.60, N 5.81, S 13.29, found C 49.62, H 4.65, N 5.85, S 13.25.

3-*Ehtylsufanylpropionic acid methyl ester* (*entry d*): pale yellow liquid, IR (neat) $\tilde{\nu}$ = 1744 (C=O) cm^{-1}; ^{1}H NMR (400 MHz,$CDCl_3$) δ = 1.24(t, J = 7.2 Hz, 3H), 2.54(q, J = 7.2 Hz, 2H), 2.59(t, J = 7.6 Hz, 2H), 2.77(t, J = 7.6 Hz, 2H), 3.67(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.87, 26.11, 26.67, 34.83, 51.84, 172.24; $C_6H_{12}O_2S$ (148.23): calcd: C 48.62 H 8.16, S 21.63, found C 48.47, H 8.20, S 21.55.

3-*Dodecylsulfanylpropionic acid methyl ester* (*entry e*): colorless oil, IR (neat) $\tilde{\nu}$ = 1747 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.87(t, J = 6.4 Hz, 3H), 1.25–1.59(m, 20H), 2.51(t, J = 7.6 Hz, 2H), 2.60(t, J = 7.2 Hz, 2H), 2.77(t, J = 7.2 Hz, 2H), 3.69(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.80, 23.36, 27.66, 29.53, 29.88, 29.99(2C), 30.18(2C), 30.25(2C), 32.56, 32.86, 35.40, 52.37, 172.38; $C_{16}H_{32}O_2S$ (288.50): calcd. C 66.61, H 11.18, S 11.11, found C 66.52, H 11.25, S 11.07.

3-*Butylsulfnylpropionamide* (*entry g*): white solid: (m.p. 78 °C) IR (KBr) $\tilde{\nu}$ = 1657 (C=O), 3197 and 3374 (NH_2) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.91(t, J = 7.6 Hz, 3H), 1.41(sext., J = 7.6 Hz, 2H), 1.57(quin, J = 7.6 Hz, 2H), 2.48–2.56(m, 4H), 2.79(t, J = 7.2 Hz, 2H), 6.02(bs, NH), 6.16(bs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.95, 22.21, 27.71, 31.85, 32.24, 36.23, 174.14; $C_7H_{15}NOS$ (161.27): calcd. C 54.14, H 9.38, N 8.69, S 19.88, found C 52.09, H 9.39, N 8.72, S 19.79.

3-*Dodecylsulfanylpropionitrile* (*entry j*): colorless oil, IR (neat) $\tilde{\nu} = 2340\,cm^{-1}$ (CN); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 0.87$(t, $J = 6.8$ Hz,3H), 1.25–1.60(m, 20H), 2.58(t, $J = 8$ Hz, 2H), 2.62(t, $J = 7.2$ Hz, 2H), 2.77(t, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 14.24$, 19.05, 22.79, 27.76, 28.87, 29.28, 29.43, 29.57(2C), 29.72(3C), 32.00, 32.44, 118.25; $C_{15}H_{29}NS$ (255.47): calcd. C 70.52, H 11.44, N 5.48, S 12.55, found C 70.32, H 11.49, N 5.49, S 12.48.

3-(4-*Nitrophenylsulfanyl*)-*cyclohexanone* (*entry p*): yellow solid: (m.p. 70 °C); IR (KBr) $\tilde{\nu} = 1340$ and 1508 (NO_2), 1717 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 1.81$–1.89(m, 2H), 2.15–2.26(m, 2H), 2.39–2.49(m, 3H), 2.76–2.80(dd, $J_1 = 4.4$ Hz, $J_2 = 14$ Hz, 1H), 3.68–3.75(m, 1H), 7.40(d, $J = 8.4$ Hz, 2H), 8.12(d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 24.25$, 31.22, 41.09, 44.73, 47.50, 124.22(2C), 129.21(2C), 144.28, 146.04, 207.27; $C_{12}H_{13}NO_3S$ (251.31): calcd. C 57.35, H 5.21, N 5.57, S 12.76, found C 57.17, H 5.27, N 5.60, S 12.73.

3-*Dodecylsulfanyl-cyclohexanone* (*entry q*): colorless oil, IR (neat) $\tilde{\nu} = 1717$ (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 0.87$(t, $J = 6.4$ Hz, 3H), 1.25–1.59(m, 20H), 1.67–1.73(m, 2H), 2.10–2.15(m, 2H), 2.32–2.39(m, 3H), 2.53(t, $J = 7.6$ Hz, 2H), 2.67–2.72(m, 1H) 3.10–3.11(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 14.80$, 23.35, 24.96, 29.61, 29.86, 29.99, 30.15, 30.27(2C), 30.39(2C), 31.24, 32.36, 32.55, 41.59, 43.41, 48.89, 209.22; $C_{18}H_{34}OS$ (298.54): calcd. C 72.42, H 11.48, S 10.74, found C 72.20, H 11.54, S 10.71.

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