Michael addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions

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Abstract
A simple and efficient protocol has been introduced for the Michael addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions without the use of a catalyst. The significant features of this reaction are (a) mild reaction conditions, (b) operational simplicity, (c) avoiding toxic and expensive reagents, (d) short reaction times, (e) high product yields, and (f) solvent-free conditions.

Keywords: Michael addition, thiol, α,β-unsaturated carbonyl compounds, solvent-free condition

Introduction

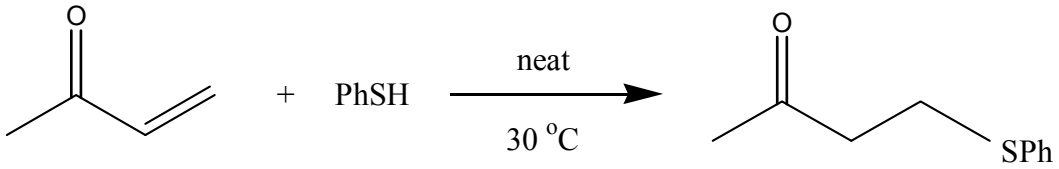
The Michael addition of nucleophiles to electron deficient alkenes is one of the most important reactions in organic chemistry.[1] Among various nucleophilic additions, the reaction of thiols to form a carbon-sulfur bond constitutes a key reaction in biosynthesis as well as in the synthesis of biologically active compounds such as the calcium antagonist diltiazem.[2] Therefore, a large number of reagents have been reported in the literature for the addition of thiols to conjugated alkenes.[1] However, to avoid the formation of undesirable side products in presence of a strong acid or a base,[3] several procedures have been introduced either based on activation of thiols by a base,[4] or activation of the acceptor olefins with either solid[5] or Lewis acids.[6] Some catalytic asymmetric Michael addition of aromatic thiols to α,β-unsaturated carbonyl compounds have also been reported.[4b,6h] Recently, ionic liquids such as *n*-Bu_4NBr,[7a] [pmim]Br,[8] and the [bmim]PF_6/H_2O solvent system[9] have been introduced as efficient catalysts for Michael addition of thiols to α,β-unsaturated carbonyl compounds. However, various disadvantages such as long reaction times,[6c-d] use of halogenated solvents,[6b-d] high temperatures,[5a,8] use of costly catalysts,[6c-d,6f,9] difficulty in recovery of high boiling solvents,[5a] moderate yields,[6b,6d] etc. encountered in the reported methodologies necessitate the development of a more efficient and convenient method.

In practice, from an ecological point of view, the best solvent is without a doubt no solvent. There are of course a great many reactions that can already be carried out in the absence of solvent. Reports on solvent-free reactions have, however, become increasingly frequent and specialized over the past few years. Areas of growth include reactions between solids,[10] between gases and solids,[11] and on supported inorganic reagents,[12] which in many cases are accelerated or even made possible through microwave irradiation.[13] There are also reactions in which at least one reactant is liquid under the conditions employed, which means that the solvent that would normally be used can simply be left out. Very recently, the catalyzed conjugated addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions have been reported.[7]

Results and Discussion

In our previous results,[14] we investigated a one-pot procedure for the reductive cleavage of disulfides and Michael addition to α,β-unsaturated carbonyl compounds mediated by the $Zn/AlCl_3$ system in aqueous media. We have now examined the conjugate addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions in the absence of any catalyst.

In a model reaction, methyl vinyl ketone was taken as a representative α,β-unsaturated carbonyl compound; this was treated with an equimolar amount of thiophenol in the absence of a catalyst under neat conditions at room temperature (~ 30 °C) (Scheme 1); after 30 min, as monitored by TLC, the isolated yield of the Michael adduct was 76%. Under the same reaction conditions, two other experiments were also carried out with molar ratios of thiophenol : methyl vinyl ketone = 1.5:1 and 2:1; at the same reaction time (30 min), the isolated yields of the product were 83 and 93% respectively. Therefore, we decided to perform our study at thiol : α,β-unsaturated carbonyl compound of 2:1. The product isolation with very high purity was easily achieved by subjecting the crude reaction mixture to preparative TLC. The reaction was also conducted, under the same reaction conditions, in various solvents affording low to good yields of the Michael adduct (Table 1).



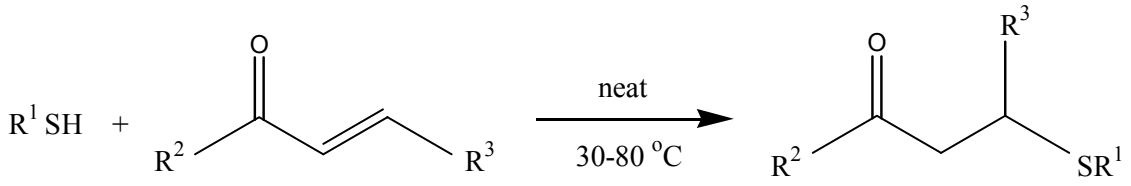
Scheme 1

Table 1. Reaction of methyl vinyl ketone with thiophenol in various solvents[a]

Entry	Solvent	Yield (%)[b]
1	H_2O	32
2	MeCN	72
3	MeOH	74
4	Me_2NCHO	61
5	$(CH_2)_4O$	65
6	Et_2O	79
7	PhMe	38
8	CH_2Cl_2	50

[a] Conditions: methyl vinyl ketone (1 equiv) was treated with thiophenol (2 equiv) at r.t. (~ 30 °C) for 30 min. [b] Isolated yield.

To establish the generality of this process, various α,β-unsaturated ketones and crotonaldehyde were treated with a range of thiols under neat conditions at 30-80 °C (Scheme 2).

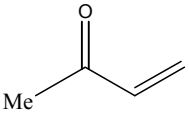
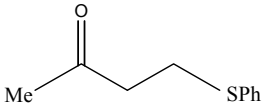
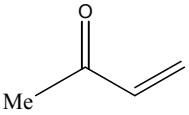
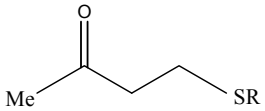
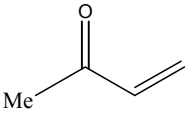
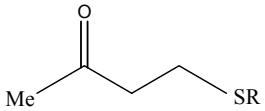
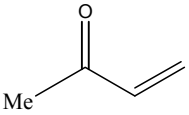
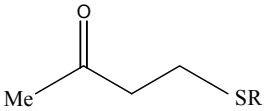
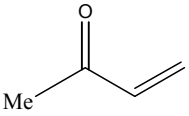
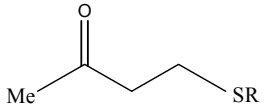
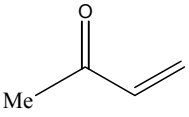
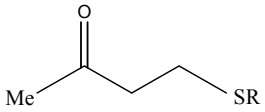
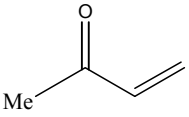
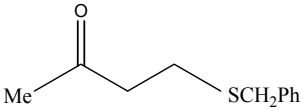
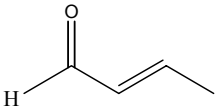
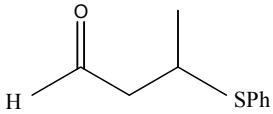
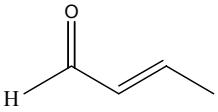
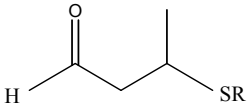
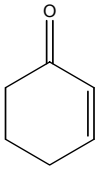
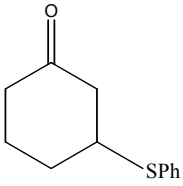


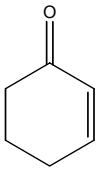
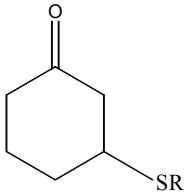
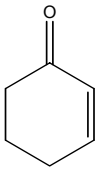
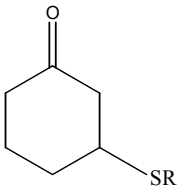
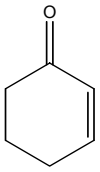
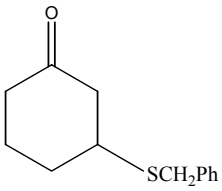
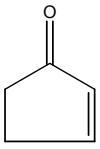
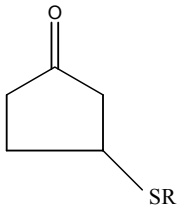
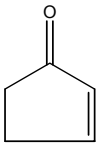
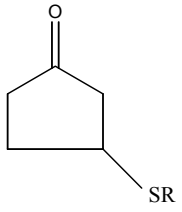
1 **2** **3**

Scheme 2

Representative results are summarized in Table 2. These reactions are in general very fast (15-105 min) and clean. In some cases higher (>30 °C) temperatures were needed to dissolve the solid thiols. The reaction was found to be general with respect to different aromatic and aliphatic thiols as evidenced by the formation of the corresponding Michael adducts in 93, 98, 85, 93, 89, 96, and 76% yields during the reaction of methyl vinyl ketone with thiophenol, 4-chlorothiophenol, 4-methylthiophenol, 4-methoxythiophenol, 2-naphthalenethiol, 4-bromothiophenol, and benzylthiol in 30, 15, 30, 30, 15, 60, and 45 min, respectively, under similar conditions (Table 2, entries 1-7). Then, thia Michael addition reaction for other α,β-unsaturated carbonyl compounds, such as crotonaldehyde, 2-cyclohexen-1-one, and 2-cyclopenten-1-one were conducted with thiols under the same reaction conditions in the absence of solvent. Very good results were obtained in each case.

Table 2. Solvent-free Michael addition of thiols to α,β-unsaturated carbonyl compounds[a]

Entry	α,β-Unsaturated carbonyl compounds	Product	Temp (°C)	Time (min)	Yield (%)[b,c]
1			30	30	93[7]
2			52	15	98[15]
3		R= 4-ClC$_6$H$_4$ 	40	30	85[6a]
4		R= 4-MeC$_6$H$_4$ 	30	30	93[6f]
5		R= 4-MeOC$_6$H$_4$ 	65	15	89[16]
6		R= 2-Naphthyl 	70	60	96[16]
7		R= 4-BrC$_6$H$_4$ 	30	45	76[6a]
8			30	50	90[7]
9			40	85	73[17]
10		R= 4-MeC$_6$H$_4$ 	30	105	76[7]

11		 R= 4-ClC_6H_4	52	30	70[4b]
12		 R= 2-Naphthyl	65	40	71[4b]
13			30	60	70[6a]
14		 R= 4-$MeOC_6H_4$	30	30	81[6f]
15		 R= 2-Naphthyl	80	30	80[6h]

[a] The reaction was carried out under solvent-free conditions using α,β-unsaturated carbonyl compounds (1 mmol) and thiols (2 mmol) at 30-80 °C. [b] Isolated yields. [c] References for known compounds.

Conclusions

In summary, we have developed a simple and efficient procedure for thia Michael addition reaction. This solvent-free reaction is very useful both from economical and environmental points of view. The present method has the advantages of (i) operational simplicity, (ii) mild reaction conditions, (iii) avoiding hazardous organic solvents, toxic and expensive reagents, (iv)

short reaction times, and (v) high product yields. This environmentally benign process represents a suitable option to existing methods.

Experimental Section

General Procedures. NMR spectra were recorded on a Bruker AQS 300 Avance instrument at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR in $CDCl_3$ solutions. IR spectra were obtained using an ABB FTLA 2000 instrument in neat for liquids and in KBr pellet for solids. Mass spectra were performed on a Hewlett-Packard spectrometer (Model 5973).

Representative experimental procedure for Michael addition (entry 4, Table 2). In a typical experiment, methyl vinyl ketone (70 mg, 1 mmol), and 4-methoxythiophenol (280 mg, 2 mmol) were mixed and stirred at 30 °C for 30 min (monitored through TLC). The mixture, after cooling, was subjected to preparative TLC (silica gel, eluent *n*-heptane : EtOAc = 4:1) to obtain pure 4-(4-methoxythiophenyl)butan-2-one (196 mg, 93%) as a yellow oil, IR (neat) 1720 cm^{-1}; ^{1}H NMR δ 2.11 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR δ 29.61, 30.11, 43.29, 55.33, 114.65, 125.52, 133.60, 159.12, 206.93. MS: *m/z* (%) 210 (100) [M$^+$], 153 (12), 139 (38), 71 (13), 43 (70).

This procedure is followed for all the reactions listed in Table 2. All products are known compounds and were identified by spectroscopic data (IR, MS, ^{1}H and ^{13}C NMR) which are in good agreement with those reported (references in Table 2).

4-Thiophenylbutan-2-one (entry 1). Colorless oil; IR 3055, 2932, 1715, 1586 cm^{-1}; ^{1}H NMR δ 2.16 (s, 3H), 2.78 (t, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 7.22-7.38 (m, 5H). MS: *m/z* (%) 180 (100) [M$^+$], 137 (28), 123 (21), 110 (40), 71 (20), 65 (12), 43 (100).

4-(4-Chlorothiophenyl)butan-2-one (entry 2). White crystal; m.p. 54-55 °C; IR 3075, 2927, 1713, 1476 cm^{-1}; ^{1}H NMR δ 2.16 (s, 3H), 2.75 (t, *J* = 7.2 Hz, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 7.27 (s, 4H); ^{13}C NMR δ 27.7, 30.1, 42.9, 129.1, 130.8, 132.3, 134.3, 206.4. MS: *m/z* (%) 216 (32) [M$^+$], 214 (100) [M$^+$], 171 (24), 144 (45), 108 (23), 71 (26), 43 (68).

4-(4-Methylthiophenyl)butan-2-one (entry 3). Colorless oil; IR 3020, 2922, 1715, 1493 cm^{-1}; ^{1}H NMR δ 2.15 (s, 3H), 2.34 (s, 3H), 2.74 (t, *J* = 7.2 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR δ 21.0, 28.2, 30.1, 43.2, 129.8, 130.5, 131.7, 136.6, 206.9. MS: *m/z* (%) 194 (100) [M$^+$], 151 (20), 137 (19), 124 (41), 91 (20), 43 (26).

4-(2-Naphthylthio)butan-2-one (entry 5). Light brown crystal; m.p. 57-58 °C (lit.[16] m.p. 57.3-58.6 °C); IR 3050, 2922, 1715, 1603, 1581 cm^{-1}; ^{1}H NMR δ 2.16 (s, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 3.26 (t, *J* = 7.2 Hz, 2H), 7.28-7.53 (m, 3H), 7.77-7.83 (m, 4H); ^{13}C NMR δ 27.2, 30.2, 43.0, 125.8, 126.7, 127.1, 127.2, 127.4, 127.8, 128.6, 131.9, 133.2, 133.7, 206.7. MS: *m/z* (%) 230 (100) [M$^+$], 173 (17), 160 (69), 128 (18), 115 (48), 43 (22).

3-Thiophenylbutanal (entry 8). Colorless oil; IR 3056, 2958, 2814, 2715, 1724, 1583 cm^{-1}; ^{1}H NMR δ 1.37 (d, *J* = 6.8 Hz, 3H), 2.60 (ddd, *J* = 17.3, 7.6, 1.6 Hz, 1H), 2.72 (ddd, *J* = 17.3, 7.6, 1.6 Hz, 1H), 3.71 (sext, *J* = 6.8 Hz, 1H), 7.27-7.37 (m, 3H), 7.43-7.46 (m, 2H), 9.76 (t, *J* = 1.6

Hz, 1H); ^{13}C NMR δ 21.1, 37.6, 50.1, 127.7, 129.1, 132.9, 133.5, 200.5. MS: *m/z* (%) 180 (40) [M^+], 137 (9), 110 (100), 65 (14), 43 (11), 39 (18), 27 (11).

3-(4-Chlorothiophenyl)cyclohexanone (entry 11). White crystal; m.p. 62-63 °C (lit.[4b] white crystalline solid); IR 3059, 2926, 1718, 1581 cm^{-1}; ^{1}H NMR δ 1.68-1.77 (m, 2H), 2.11-2.19 (m, 2H), 2.28-2.39 (m, 3H), 2.68 (dd, *J* = 13.5 Hz, 4.5 Hz, 1H), 3.39-3.42 (m, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 23.9, 31.1, 40.8, 46.3, 47.6, 129.3, 131.5, 134.1, 134.6, 208.5. MS: *m/z* (%) 242 (17) [M^+], 240 (53) [M^+], 108 (15), 97 (68), 69 (100), 55 (43), 41 (85).

3-(4-Methoxythiophenyl)cyclopentanone (entry 14). Colorless oil; IR 2952, 1746, 1597 cm^{-1}; ^{1}H NMR δ 1.96-2.04 (m, 1H), 2.15-2.34 (m, 3H), 2.41-2.58 (m, 2H), 3.69-3.77 (m, 1H), 3.82 (s, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 29.2, 36.8, 44.7, 45.1, 55.4, 114.7, 123.9, 135.7, 159.8, 216.8. MS: *m/z* (%) 222 (100) [M^+], 140 (91), 125 (21), 83 (24), 55 (89).

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