ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 4971–4974

Tetrahedron
Letters

Iodine-catalyzed Michael addition of mercaptans to α,β-unsaturated ketones under solvent-free conditions

Cheng-Ming Chu, Shijay Gao, M. N. V. Sastry and Ching-Fa Yao*

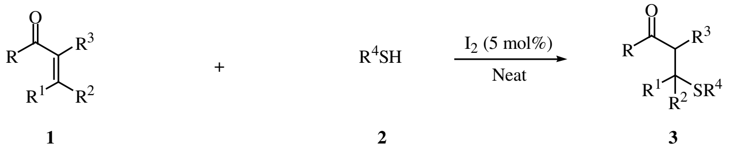
Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei, Taiwan 116, ROC

Received 6 April 2005; revised 12 May 2005; accepted 20 May 2005
Available online 13 June 2005

Abstract—A simple and efficient method for the Michael reaction between various mercaptans and α,β-unsaturated ketones using a catalytic amount of iodine (5 mol %) to generate the 1,4-adduct has been reported. The significant features of the iodine catalyzed Michael addition are (a) operational simplicity, (b) inexpensive reagents, (c) high yields of products, (d) the use of relatively low or nontoxic reagents and (e) solvent-free conditions.

The 1,4-addition of thiols to α,β-unsaturated carbonyl compounds to form carbon–sulfur bonds constitutes a key reaction in various biosynthetic processes as well as in organic synthesis.[1,2] Numerous methods have been reported in the literature regarding the 1,4-addition of thiols to electron-deficient olefins activated by different bases.[3] Alternatively, these reactions were also investigated using different Lewis acids[4,5] such as $Hf(OTf)_3$,[4a] $InBr_3$,[4b] $Bi(NO_3)_3$,[4c] $Bi(OTf)_3$,[4d] $InCl_3$[4e] and $Cu(BF_4)_2$.[4f] However, the practice of expensive and toxic metal precursors not only limits the use of these methods, but also turn out to be a serious concern under the aspects of green chemistry. In addition to the above characteristics, some of the methods also involve the use of either acidic or basic work-up procedures for the catalyst separation, recycling and disposal. Besides the drawback of using an expensive catalyst, some of the methods involve stringent and/or dry conditions, extended reaction times, complex work-up procedures and the use of stoichiometric and/or relatively expensive reagents.

Thus, the development of more efficient methods and exploring proper reagents as catalysts are still in demand to make the available procedures more convenient and simple. Over the past few years, molecular iodine (I_2) has emerged as a powerful catalyst for various organic



1a: $R + R^1 = -(CH_2)_3-$, $R^2 = R^3 = H$
1b: $R + R^1 = -(CH_2)_2-$, $R^2 = R^3 = H$
1c: $R = Me$, $R^1 = R^2 = R^3 = H$
1d: $R = Me$, $R^2 = Ph$, $R^1 = R^3 = H$
1e: $R = Ph$, $R^2 = Ph$, $R^1 = R^3 = H$
1f: $R = Ph$, $R^1 = R^2 = Me$, $R^3 = H$
1g: $R = Me$, $R^2 + R^3 = -(CH_2)_4-$, $R^1 = H$

2a: $R^4 = Ph$
2b: $R^4 = c\text{-}C_6H_{11}$
2c: $R^4 = C_6H_5CH_2$
2d: $R^4 = C_3H_7$
2e: $R^4 = CH_2{=}CHCH_2$
2f: $R^4 = ICH_2CH_2$

Scheme 1.

Keywords: Michael addition; Solvent free; Molecular iodine; Catalytic amounts; Various thiols; Unsaturated ketones; Ecofriendly.

* Corresponding author. Tel.: +886 2 2930 9092; fax: +886 2 2932 4249; e-mail: cheyaocf@scc.ntnu.edu.tw

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.05.099

Table 1. Reaction of **1** with **2a** in the presence of I_2 to prepare **3**[a]

Entry	**1**	I_2 (mol %)	Temp (°C)	Time (min)	**3** (%)[b]
1	**1a**	—	25	60	**3aa** (0)
2	**1a**	25	25	8	**3aa** (35)
3	**1a**	25	0	8	**3aa** (90)
4	**1a**	10	0	3	**3aa** (99)
5	**1a**	5	0	3	**3aa** (99)
6	**1c**	25	0	3	**3ca** (99)
7	**1c**	10	0	3	**3ca** (99)
8	**1c**	5	0	3	**3ca** (99)
9	**1d**	25	25	3	**3da** (99)
10	**1d**	10	0	8	**3da** (99)
11	**1d**	5	25	3	**3da** (99)

[a] **1**:**2a** = 1:1.1.

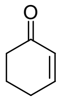
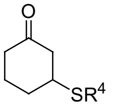
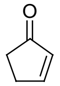
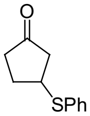
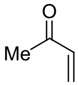
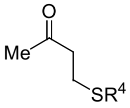
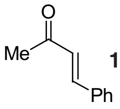
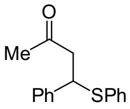
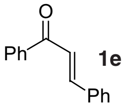
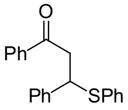
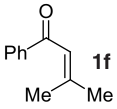
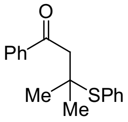
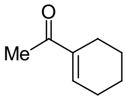
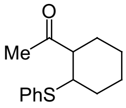
[b] Determined by GCMS and ^{1}H NMR.

transformations to afford the products in good to excellent yields.[6,7] Owing to several advantages such as inexpensive, nontoxic, eco-friendly nature, iodine has been used as a catalyst in the investigation of different organic reactions.[7] The catalytic activity of iodine in the Michael addition of indole to enones and several organic transformations has also been reported recently.[8]

In continuation of our interest on the catalytic applications of molecular iodine for various organic transformations,[10] we wish to report the novel application of inexpensive iodine as an efficient catalyst for the Michael addition of various thiols to α,β-unsaturated ketones under solvent-free conditions (Scheme 1).

In order to examine the effect of temperature as well as catalyst loading, different reactions were conducted by using α,β-unsaturated ketones **1a**, **1c** or **1d** and thiophenol **2a** in the presence of different amounts of iodine under solvent-free conditions at different temperatures. Initially, a reaction was carried out in the absence of iodine between **1a** and **2a** at 25 °C for 60 min, which resulted in the recovery of the starting materials. After the analysis of the crude mixture by NMR and GCMS it was observed with no formed product **3aa**. To check the catalytic activity of iodine, a similar reaction was carried out in the presence of 25 mol % of I_2 for the

Table 2. Iodine-catalyzed Michael addition of thiol to enone[a,d]

Entry	Enone **1**	Thiol **2**	Product **3**		Time (min)	Yield (%)[b]
1	 **1a**	**2a**: $R^4 = Ph$		**3aa**	3	97
2		**2b**: $R^4 = c\text{-}C_6H_{11}$		**3ab**	3	97
3		**2c**: $R^4 = C_6H_5CH_2$		**3ac**	3	95
4		**2d**: $R^4 = C_3H_7$		**3ad**	5	92
5		**2e**: $R^4 = CH_2{=}CHCH_2$		**3ae**	5	95
6		**2f**[c]: $R^4 = ICH_2CH_2$		**3af**	8	92
7	 **1b**	**2a**: $R^4 = Ph$		**3ba**	3	97
8	 **1c**	**2a**: $R^4 = Ph$		**3ca**	3	97
9		**2b**: $R^4 = c\text{-}C_6H_{11}$		**3cb**	3	95
10		**2c**: $R^4 = C_6H_5CH_2$		**3cc**	3	95
11		**2d**: $R^4 = C_3H_7$		**3cd**	5	95
12		**2e**: $R^4 = CH_2{=}CHCH_2$		**3ce**	5	95
13	 **1d**	**2a**: $R^4 = Ph$		**3da**	3	97
14	 **1e**	**2a**: $R^4 = Ph$		**3ea**	3	97[e]
15	 **1f**	**2a**: $R^4 = Ph$		**3fa**	5	96
16	 **1g**	**2a**: $R^4 = Ph$		**3ga**	8	93

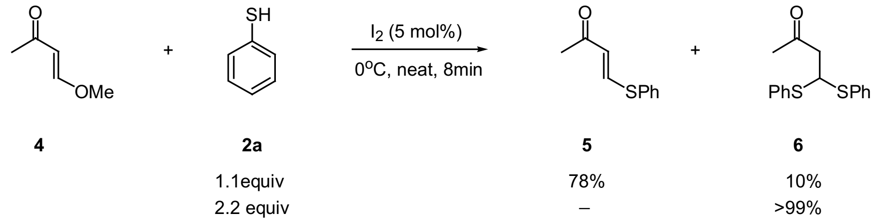
[a] 1 equiv of enone **1** was treated with 1.1 equiv of mercaptan **2** in the presence of 5 mol % of Iodine at 0 °C under solvent-free condition.

[b] Column isolated yield.

[c] For the preparation of **2f**, see Ref. 11.

[d] Reaction was carried out at room temperature.

[e] Reaction was carried out at room temperature and 1 ml CH_2Cl_2 was added.



Scheme 2.

preparation of **3**. Surprisingly, at ambient temperature within 8 min 35% of **3aa** was observed (entry 2). When the similar reaction was repeated at 0 °C for the same time, it resulted in the formation of the product **3aa** in 90% yield (entry 3). In order to confirm, the amount of iodine required for the above transformation, different experiments were carried out by varying the amount of iodine I_2. Either using 10 or 5 mol % of catalytic amounts of iodine at 0 °C, resulted in the quantitative yield of **3aa** with the same efficiency. These results clearly indicate that, the use of 5 mol % of I_2 is sufficient to catalyze the Michael addition reaction in excellent yield.[9] The reason for the lower product yield with a higher amount of iodine in case of cyclohexenone may be ascribed due to the decreased catalytic activity, which in turn leads to polymerization of the starting materials. On the other hand, the reaction temperature plays an important role with different substrates. For instance, in a reaction with thiol **2a**, the enones methlvinyl ketone **1c** and benzilideneacetone **1d** use 5 mol % of iodine, the former requires 0 °C and the later needs 25 °C. The probable reason might be the steric bulkiness of the later enone. To prove the versatility of iodine catalyzed Michael addition reactions, a variety of enones **1a**–**d** were reacted with phenyl thiol **2a** in the presence of 5 mol % of iodine to obtain the quantitative yields of the product (Table 1).

After optimizing the best condition using cyclohexenone **1a** and thiol **2a**, the generality of the iodine catalyzed reaction was examined by selecting a number of α,β-unsaturated ketones **1a**–**g** as well as thiols **2a**–**f**[11] (Table 2). As expected, excellent yields of product **3** were generated under solvent-free condition at 0 °C within 2–8 min. Both cyclic and acyclic enones were reacted with various thiols to afford the products in excellent yields. A little decrease in the product yield was observed in a reaction with **2f** using cyclohexenone. In the case of Michael acceptor such as 1-cyclohexenyl-methyl ketone, the product was formed in 96% yield using 5 mol % of iodine as catalyst. β,β-Disubstituted enone **1f** and α,β-disubstituted enone **1g** can react with thiophenol **2a** rapidly to afford Michael adducts in quantitative yield. According to these results, we found that not only the unsubstituted enone such as methyl vinyl ketone but also the β-monosubstituted enone such as **1a**, **1b**, **1d** and **1e** or the β,β-disubstituted enone **1f** or α,β-disubstituted enone **1g** can react with thiophenol **2a** rapidly. These results indicate that the I_2 catalyzed reactions were not affected by the presence of the steric hindrance between **1** and **2** and both alkyl and aryl substituted group also have no effect on the reaction yield.

Encouraged by the above results, we also examined the reaction of a different enone such as 4-methoxy-3-butene-2-one **4** with **2a** under similar conditions. In the presence of 1.1 equiv of **1a**, 78% of **5** and 10% of **6** were generated (Scheme 2). However, only quantitative yield of **6** was obtained by changing the amount of **2a** from 1.1 to 2.2 equiv. The generation of compound **5** indicates that the reaction proceeds through the substitution of the methoxy group of **4** by **2a** and the compound **6** has been generated from the addition of another equivalent of **2a** to the intermediate product **5**.

In conclusion, we have successfully demonstrated a simple and efficient methodology to prepare a wide variety of Michael adducts using iodine in catalytic amounts. The powerful catalytic activity of the iodine for these transformations can be substantiated by the less reaction times as well as high product yields. This environmentally benign process for the generation of Michael adducts represents a suitable option to the existing procedures, especially enones with different substitution.

Acknowledgements

Financial support for this work by the National Science Council of the Republic of China and National Taiwan Normal University (ORD93-C) is gratefully acknowledged.

References and notes

1. (a) Fluharty, A. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiely: New York, 1974, Part 2, p 589; (b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429; (c) Fujita, E.; Nagao, Y. J. *Bioorg. Chem.* **1977**, *6*, 287.
2. (a) Trost, B. M.; Keeley, D. E. *J. Org. Chem.* **1975**, *40*, 2013; (b) Shono, T.; Matsumura, Y.; Kashimura, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752; (c) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974.
3. (a) Hiemstra, H.; Wiberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417; (b) Suzuki, K.; Ikekawa, A.; Mukaiyama, T. *Bull. Soc. Chem. Jpn.* **1982**, *55*, 3277; (c) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363; (d) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.
4. (a) Kobyashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983; (b) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700; (c) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (d) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115; (e)

Ranu, B. C.; Dey, S. S.; Samanta, S. *ARKIVOC* **2005**, 44; (f) Garg, S. K.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 1721.

5. (a) Zahouily, M.; Abrouki, Y.; Rayadh, A. *Tetrahedron Lett.* **2002**, *43*, 7729; (b) Abrouki, Y.; Zahouily, M.; Rayadh, A.; Bahlaouan, B.; Sebti, S. *Tetrahedron Lett.* **2002**, *43*, 8951; (c) Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 6557; (d) Cheng, S.; Comer, D. D. *Tetrahedron Lett.* **2002**, *43*, 1179; (e) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Synlett* **2003**, 1070.
6. (a) Kr, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751; (b) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959; (c) Ji, S.; Wang, S.; Zhang, Y.; Loh, T. *Tetrahedron* **2004**, *60*, 2051.
7. (a) Kim, K. M.; Ryu, E. K. *Tetrahedron Lett.* **1996**, *37*, 1441; (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527; (c) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879; (d) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653; (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703; (f) Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003**, *44*, 5465; (g) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211; (h) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951; (i) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005; (j) Phukan, P. *Tetrahedron Lett.* **2004**, *45*, 4785; (k) Sun, J.; Dong, Y.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; (l) Bhosale, R. S.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 9111.
8. (a) Banik, B. K.; Bimal, K.; Fernandez; Miguel; Alvarez; Clarissa *Tetrahedron Lett.* **2005**, *46*, 2479; (b) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213; (c) Samajdar, S.; Basu, M. K.; Becker, F. F. *Synlett* **2002**, 319; (d) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425; (e) Mukhopadhyay, C.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2001**, 108; (f) Banik, B. K.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 5077; (g) Banik, B. K.; Zegrocka, O.; Manhas, M. S.; Bose, A. K. *Heterocycles* **1997**, *46*, 173; (h) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1994**, *59*, 4714.
9. Typical experimental procedure: In a typical experiment, cyclohexenone **1a** (0.198 g, 2 mmol) and thiophenol **2a** (0.249 g, 2.2 mmol) were mixed together and I_2 (0.025 g, 0.1 mmol) was added and stirred at 0 °C for 3 min (monitored through TLC). After adding the ice cold saturated sodium thiosulfate solution to the reaction mixture (to remove the traces of iodine), the solution was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over magnesium sulfate, and the crude product passed through a small plug of silica to obtain the pure product **3aa** as a colourless oil (0.400 g, 97% Y).
10. Some of our unpublished results.
11. Karjala, S. A.; McElvain, S. M. *J. Am. Chem. Soc.* **1993**, *55*, 2966.