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Tetrahedron Letters 47 (2006) 1889–1893
Tetrahedron Letters

Iodine catalyzed conjugate addition of mercaptans to α,β-unsaturated carboxylic acids under solvent-free condition

Shijay Gao, Tingkai Tzeng, M. N. V. Sastry, Cheng-Ming Chu, Ju-Tsung Liu, Chunchi Lin and Ching-Fa Yao*

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

Received 3 December 2005; revised 13 January 2006; accepted 18 January 2006
Available online 3 February 2006

Abstract—We have described herein molecular iodine catalyzed Michael addition of thiol to α,β-unsaturated carboxylic acids. This environmentally benign catalytic system (iodine) used under mild and solvent-free conditions to achieve the corresponding adducts in excellent yield.

1. Introduction

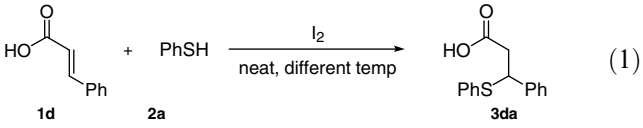
Michael addition is one of the efficient methods in organic synthesis for the formation of carbon–carbon, carbon–sulfur, and carbon–nitrogen bonds.[1] Among various nucleophilic additions, the 1,4 addition of thiols to various substrates to form a carbon–sulfur bond is of much importance, as it comprises a key reaction in the synthesis of several biologically active compounds.[2] A number of methods have been reported in the literature, regarding the conjugate addition of thiol to unsaturated carbonyl compounds such as α,β-unsaturated aldehyde, ketone, ester, and nitrile.[3] However, conjugate addition of thiol to α,β-unsaturated carboxylic acids is more difficult, due to less reactivity and the acid group itself involves or even destroys such reaction.[4] To carry out these reactions under conventional condition involves a three-step process such as protection, 1,4-addition and deprotection.[5] The alternative approach using free acid results in lower product yields.[4] The similar reaction has been reported early.[6] Thus, exploring proper reagent as catalyst and the development of simple, economic and ecofriendly procedures are essential not only for the improved and better results, but also of environmental concern. Over the past few years, molecular iodine (I_2) has been emerged as a powerful catalyst for various organic transformations to afford the corresponding products in good to excellent yields.[7,8] Additionally many advantages such as simplicity of the reagent, high yields and both economic and environmental factors make iodine as an effective catalyst for different organic reactions such as Michael additions as well as other organic transformations.[9]

2. Results and discussion

As part of our enduring efforts to explore the catalytic activity of the iodine[10], we had the opportunity to look into the Michael addition of various thiol compounds to α,β-unsaturated carboxylic acids. Herein, we wish to report the novel application of iodine as an efficient catalyst for the 1,4-conjugate addition of thiols to α,β-unsaturated carboxylic acids under solvent-free condition. Preliminary efforts were mainly focused for the catalytic evaluation of iodine by taking cinnamic acid and thiophenol as model substrates. To observe the effect of temperature, as well as the amount of iodine required, different reactions were carried out using 1 equiv (2 mmol) of *trans*-cinnamic acid **1d** and 1.5 equiv (3 mmol) of thiophenol **2a** in the presence of iodine under solvent-free condition at different temperatures (Eq. 1).

Keywords: Conjugate addition; Thiols; α,β-Unsaturated carboxylic acid; Iodine; Solvent free.
* Corresponding author. Tel./fax: +886 2 29309092; e-mail: cheyaocf@scc.ntnu.edu.tw

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.01.080



(1)

The yields of the reactions were checked by the crude ^{1}H NMR and the optimum results are provided in Table 1.

Initially, a blank reaction was conducted using the substrates **1d** and **2a** at 50 °C for 24 h resulted in the recovery of starting materials without a trace of the product **3da** (entry 1). The catalytic effect was apparently observed when the mixture was stirred in the presence of I_2. Thus, in a reaction using 10 mol % iodine afforded the product **3da** in 63% yield within 1 h. As expected, the increase in the amount of iodine (20 mol %) noticeably improved the product yield (94%). On the other hand, increase in reaction temperature (50 °C) using 10 mol % of iodine provided excellent product yield (99%). Solvents considerably influenced the product yields. In most of the solvents the reaction did not progress at all. However, nonpolar solvents such as benzene (81%) and hexane (50%) provided better yields of the product, when compared to other polar solvents. Conducting the reaction in chlorinated solvent such as dichloromethane afforded the product **3da** in 58% yield. After screening different solvents, we observed that none of the solvents gave better yields. On the other hand, solvent free condition (neat) provided maximum yield of the product (Table 2).

In order to evaluate the efficiency of the iodine catalyzed Michael additions, the generality of the reaction has been verified by taking a variety of acid substrates as well as different thiophenols. Both aromatic as well as aliphatic thiols reacted with different α,β-unsaturated carboxylic acids to provide the adducts in good to excellent yield (Table 3). Surprisingly, in case of acrylic acid (**1a**) and methylacrylic acid (**1b**) the formation of thio adducts were accompanied by a small amount of iodo adducts. Whereas in case of crotonic acid (**1c**), *trans*-cinnamic acid (**1d**) and 3,3-dimethylacrylic acid (**1e**) only thio adducts were observed. It is noteworthy to observe that when there is a β-substitution in the acid, no iodo adduct was observed. We investigated the fate of iodo adduct formed during the reaction. The iodo adduct was isolated and subjected to a reaction with thiol in the presence of I_2 (20 mol %), no reaction occurred either at room temperature or even at 50 °C (Eq. 2).

Table 1. Reaction of **1d** with **2a** under different conditions[a]

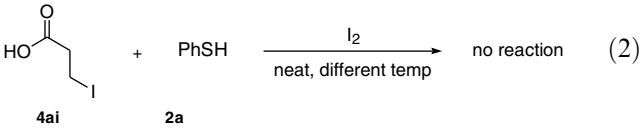
Entry	I_2 (mol %)	Temperature (°C)	Time (h)	**3da**[b] (%)	**1d**[b] (%)
1	0	50	24	0	99
2	10	rt	1	63	37
3	20	rt	1	94	6
4	10	50	1	99	0

[a] Condition: 1 equiv (2 mmol) of **1d** was treated with 1.5 equiv (3 mmol) of **2a** under a solvent-free condition.
[b] The yields were determined by the crude ^{1}H NMR.

Table 2. Effect of solvent on the reaction of **1d** with **2a** in the presence of I_2[a]

Entry	Solvent	**3da**[b] (%)	**1d**[b] (%)
1	Neat	99	0
2	Hexane	50	50
3	C_6H_6	81	19
4	CH_2Cl_2	58	42
5	THF	0	99
6	H_2O	0	99
7	EA	0	99
8	CH_3CN	0	99
9	Et_2O	0	99
10	DMF	0	99
11	DMSO	0	99
12	MeOH	0	99
13	Acetone	0	99

[a] Condition: 1 equiv (2 mmol) of **1d** was treated with 1.5 equiv (3 mmol) of **2a** in the presence 20 mol % of I_2 at room temperature for 1.5 h.
[b] The yields were determined by the crude ^{1}H NMR.

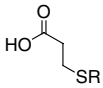
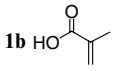
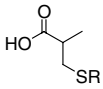
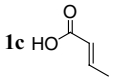
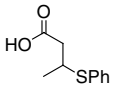
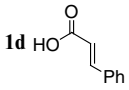
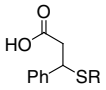
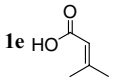
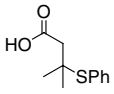


(2)

This clearly indicates that the formation of thio adduct **3aa** does not take place via the iodo adduct. We next investigated the reason for the formation of iodo adduct. In this connection, we attempted a reaction between **1a** and **2a** in the presence of molecular iodine (20 mol %) under identical reaction conditions. A detailed ^{1}H NMR study of the reaction mixture at different intervals of time revealed that there is a competition between PhS^- and I^- during the reaction (Fig. 1). A plot between the product yield versus time of the reaction mixture clearly represents that both thio adduct and iodo adducts are formed simultaneously. Owing to greater nucleophilicity of the PhS^- over I^-, more amount of thio adducts were observed in all cases. However, the reason for no iodo adduct formation in case of β-substituted acids can be explained on the basis of β-substituted steric strain, which prevents the bulky I^- nucleophile to attack β-substituted acid. Thus, the formation of iodo adduct was found to be dependent on steric effects of β-substituted acid.

Steric and electronic factors played a crucial role in case of both acid as well as thiol. In order to overcome the β,β-disubstituted steric strain, the reaction of **1e** and **2a** requires little harsh conditions (more amount of I_2 and high temperature), when compared to the corresponding counterparts. This clearly signifies the crucial role played by the steric factors. Similarly electronic factors in the thiol also affected the reaction rate as well as product yields. The reaction time of acids with aryl thiols such as thiophenol (**2a**), α-toluenethiol (**2b**), and 2-naphthalenethiol (**2e**) are less than that of alkyl thiol

Table 3. Iodine-catalyzed the Michael addition of thiol to different kind of α,β-unsaturated carboxylic acid[a]

Entry	Acid **1** thiol **2**	Temperature (°C)/time (h)	Product **3** yield (%)[b]	Product **4** yield (%)[b]
	1a 			
1	**2a**: R = Ph	rt/2	**3aa** 78	[16]**4ai** 18
2	**2b**: R = $C_6H_5CH_2$	rt/2	**3ab** 82	**4ai** 6
3	**2c**: R = *c*-C_6H_{11}	rt/7	**3ac** 87	**4ai** 9
4	**2d**: R = C_3H_7	rt/7	**3ad** 89	**4ai** 7
5	**2e**: R = 2-naphthyl	rt/4	**3ae** 78[c]	**4ai** 18
	1b 			
6	**2a**: R = Ph	50/3	**3ba** 75	[17]**4bi** 21
7	**2b**: R = $C_6H_5CH_2$	50/3	**3bb** 44	**4bi** 9
8	**2c**: R = *c*-C_6H_{11}	50/48	[12]**3bc** 64	**4bi** 22
9	**2d**: R = C_3H_7	50/16	**3bd** 84	**4bi** 12
	1c 			
10	**2a**: R = Ph	50/2.5	**3ca** 97	
	1d 			
11	**2a**: R = Ph	rt/1.5	**3da** 97	
12	**2b**: R = $C_6H_5CH_2$	50/2	**3db** 97	
13	**2c**: R = *c*-C_6H_{11}	50/4.5	[13]**3dc** 95	
14	**2d**: R = C_3H_7	50/4	[14]**3dd** 97	
15	**2e**: R = 2-naphthyl	50/2	[15]**3de** 94[c]	
	1e 			
16	**2a**: R = Ph	50/5[d]	**3ea** 95	

[a] All reactions were performed by using 1 equiv (2 mmol) of unsaturated acids **1** and 1.5 equiv (3 mmol) of thiol **2** in the presence 20 mol% of I_2 under solvent free condition.[11]

[b] Isolated yields.

[c] Reaction was carried out in 0.5 mL of CH_2CI_2.

[d] The reaction was in the presence 50 mol% of I_2.

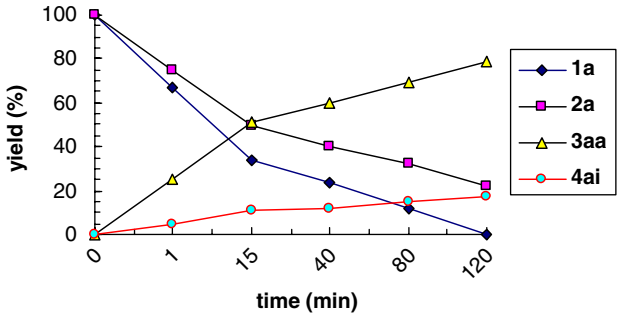


Figure 1. ^{1}H NMR study of the reaction mixture at different intervals of time.

such as cyclohexyl mercaptan (**2c**) and 1-propanethiol (**2d**). However, in most cases steric factors dominated over the electronic factors. Though the intimate mechanistic details of this reaction are not yet fully understood, a feasible pathway might involve the complex role of iodine as a Lewis acid by activating the carbonyl function of the carboxylic acid. The indirect evidence can be obtained from the slow reaction of methylacrylic acid (**1b**) with thiophenol. This may be explained on the basis of steric strain of the methyl group at α-position and coordination of iodine with carbonyl function makes the atmosphere more crowded and thus lowers the reaction rate. Further studies are in progress to understand the mechanism of iodine catalysis.

3. Conclusion

In conclusion, we have successfully developed an easy and efficient method for the Michael addition of various thiol derivatives to α,β-unsaturated carboxylic acids.

The advantages such as mild reaction conditions, simplicity of the reaction, excellent product yields, solvent-free condition and easy procedures to carry out the reaction makes the inexpensive, commercially available and relatively low or nontoxic reagent iodine as a powerful catalyst for the synthesis of a wide variety of sulfur containing carboxylic acids in excellent yields.

Acknowledgements

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

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11. **Typical experimental procedure for Michael addition**: To a mixture of *trans*-cinnamic acid **1d** (1 equiv) and thiophenol **2a** (1.5 equiv) I_2 (20 mol %) was added and the mixture was stirred at room temperature for 1.5 h. After completion of reaction (monitored by TLC), ice cold saturated sodium thiosulfate solution (15 mL) was added and extracted with dichloromethane (2×20 mL) and the combined organic extracts were dried and evaporation of the solvent under reduced pressure afforded quantitative yield of **3da** (>99% by NMR) and the pure product was obtained by passing through a small pad of silica using eluent (EtOAc–hexane, 1:10).
12. *3-Cyclohexylsulfanyl-2-methyl-propionic acid* (**3bc**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.36 (m, 8H), 1.60–1.63 (m, 1H), 1.75–1.80 (m, 2H), 1.95–1.98 (m, 2H), 2.58–2.72 (m, 3H), 2.88 (dd, 1H, $J = 6.6$, 12.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.86, 26.00, 26.27, 33.31, 33.85, 33.87, 40.69, 44.32, 181.60. HRMS (CI) *m/z* calcd for $C_{10}H_{18}O_2S$ (M^+) 202.1028, found 202.1040.
13. *3-Cyclohexylsulfanyl-2-phenyl-propionic acid* (**3dc**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10–1.38 (m, 5H), 1.48–1.56 (m, 1H), 1.59–1.75 (m, 3H), 1.92–1.96 (m, 1H), 2.38–2.45 (m, 1H), 2.81–2.91 (m, 2H), 4.32 (t, 1H, $J =$ 7.6 Hz), 7.18–7.37 (m, 5H), 10.87 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.80, 25.85, 25.99, 33.29, 33.62, 42.00, 43.21, 43.43, 127.46, 127.62, 128.65, 141.94, 177.24. HRMS (CI) *m/z* calcd for $C_{15}H_{20}O_2S$ (M^+) 264.1184, found 264.1185.
14. *3-Phenyl-3-propylsulfanyl-propionic acid* (**3dd**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J = 7.36$ Hz), 1.43–1.57 (m, 2H), 2.23–2.35 (m, 2H), 2.84–2.95 (m, 2H), 4.23 (t, 1H, $J = 7.6$ Hz), 7.20–7.34 (m, 5H), 10.40 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.59, 22.62, 33.44, 41.53, 44.85, 127.64, 127.78, 128.74, 141.43, 177.22. HRMS (CI) *m/z* calcd for $C_{12}H_{16}O_2S$ (M^+) 224.0871, found 224.0871.
15. *3-Naphthylsulfanyl-3-phenyl-propionic acid* (**3de**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95–3.06 (m, 2H), 4.72 (t, 1H, $J = 7.7$ Hz), 7.21–7.29 (m, 5H), 7.38 (dd, 1H, $J = 1.6$, 8.5 Hz), 7.44–7.48 (m, 2H), 7.71–7.73 (m, 2H), 7.77–7.79

(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.22, 40.70, 48.85, 126.68, 127.81, 127.86, 127.95, 128.68, 128.80, 130.58, 130.94, 132.84, 133.71, 140.32, 176.39. HRMS (CI) m/z calcd for $C_{19}H_{16}O_2S$ (M^+) 308.0871, found 308.0882.

16. *3-Iodo-propionic acid* (**4ai**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (t, 2H, $J = 7.1$ Hz), 3.32 (t, 2H, $J = 7.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.92, 38.57, 177.44. HRMS (CI) m/z calcd for $C_3H_5O_2I$ (M^+) 199.9334, found 199.9340.
17. *3-Iodo-2-methyl-propionic acid* (**4bi**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, 3H, $J = 7.0$ Hz), 2.84 (m, 1H), 3.28 (dd, 1H, $J = 6.16$, 9.96 Hz), 3.40 (dd, 1H, $J = 6.46$, 9.94 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.12, 18.28, 42.27, 179.53. HRMS (CI) m/z calcd for $C_4H_7O_2I$ (M^+) 213.9491, found 213.9493.