Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 1721–1724
Tetrahedron Letters

Copper(II) tetrafluoroborate as a novel and highly efficient catalyst for Michael addition of mercaptans to α,β-unsaturated carbonyl compounds

Sanjeev K. Garg, Raj Kumar and Asit K. Chakraborti*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S. Nagar, Punjab 160 062, India

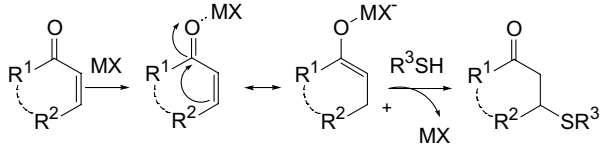
Received 15 November 2004; revised 24 December 2004; accepted 11 January 2005
Available online 28 January 2005

Dedicated to Dr. Nitya Nand on the occasion of his 80th birthday

Abstract—Copper(II) tetrafluoroborate has been found to be a new and highly efficient catalyst for Michael addition of thiols to α,β-unsaturated carbonyl compounds under solvent-free conditions and in H_2O at room temperature. The reactions are very fast and are completed in 2 min to 1 h affording high yields. The rate of thiol addition was dependent on the steric hindrance at the β-carbon of the α,β-unsaturated carbonyl substrate. In the case of chalcones, the reactions are best carried out in MeOH as solvent.

1. Introduction

The Michael addition of thiols to α,β-unsaturated carbonyl compounds constitutes a key step in biosynthesis[1] and in the synthesis of bioactive compounds.[2] The reaction gains further importance in synthetic organic chemistry as (i) it provides a means to protect the olefinic double bond of α,β-unsaturated carbonyl substrates[2b] due to the ease of regeneration by removal of the sulfur group either by copper(I)-induced elimination[3] or by oxidation followed by thermolytic elimination,[2b] and (ii) the resultant β-sulfido carbonyl compounds serve as starting materials for the generation of β-acylvinyl cation equivalents[4] and homoenolate equivalents.[5] The recent trend in the development of synthetic organic methodologies has demonstrated a great deal of interest in introducing various Lewis acid catalysts for thia Michael addition reactions. These include the use of zeolites,[6] $Hf(OTf)_3$,[7] alumina in DMF at 80 °C,[8] synthetic and natural phosphates,[9] $InBr_3$,[10] $Bi(NO_3)_3$,[11] $Bi(OTf)_3$,[12] Nafion® SAC-13[13] and $InCl_3$.[14] Recently ionic liquids have been introduced in place of metal catalysts for this purpose.[15] However, these methodologies suffer from one or more disadvantages such as long reaction times, requirements for halogenated and difficult to recover solvents, elevated temperatures, special efforts required for catalyst preparation, use of costly catalysts, moderate yields, etc. Thus, there is a need to develop better methods for this transformation.



Scheme 1. Role of the Lewis acid catalyst in the Michael addition.

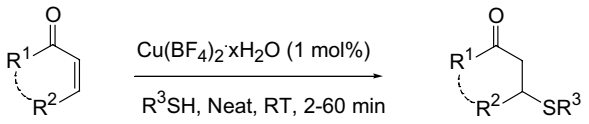
The role of a Lewis acid catalyst in the thia Michael addition reaction can be envisaged as an electrophilic activation process during which coordination of the Lewis acid with the carbonyl oxygen of the α,β-unsaturated carbonyl compound renders it more susceptible to nucleophilic attack at the β-carbon (Scheme 1).

2. Results and discussion

We have recently reported that $Cu(BF_4)_2{\cdot}xH_2O$ is an efficient electrophilic activation catalyst for heteroatom

Keywords: Michael addition; Thiol; α,β-Unsaturated carbonyl; Copper(II) tetrafluoroborate; Catalyst.
* Corresponding author. Tel.: +91 172 2214683 86/911722214682; fax: +91 172 2214692; e-mail: akchakraborti@niper.ac.in

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.051



Scheme 2. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed thia Michael addition.

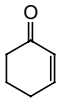
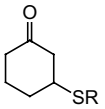
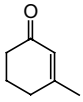
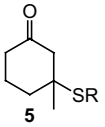
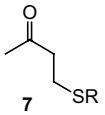
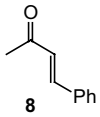
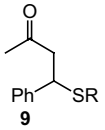
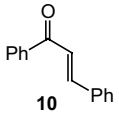
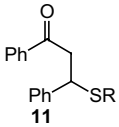
acylation[16] and aldehyde-1,1-diacetate formation.[17] Hence, we planned to use $Cu(BF_4)_2{\cdot}xH_2O$ as a catalyst for the activation of enones for Michael addition reactions with thiols (Scheme 2) and we were happy to note that treatment of 2-cyclohexen-1-one (**1**) (2.5 mmol) with PhSH (**2a**) (1.1 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) resulted in the formation 2-phenylthiocyclohexanone to 3-phenylthiocyclohexan-1-one (**3a**) in 88% yield (after purification by column chromatography) in 2 min (TLC) at room temperature (~25 °C) in the absence of solvent (Method A). 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 **3b–e** in 90%, 93%, 88% and 85% yields during the reaction of **1** with 4-methylthiophenol (**2b**), benzylthiol (**2c**), 2-furfurylthiol (**2d**) and ethanethiol (**2e**) in 5, 2, 2 and 5 min, respectively, under similar conditions (Table 1, entries 2–5). We next planned to assess the feasibility of the $Cu(BF_4)_2{\cdot}xH_2O$ catalysed thia Michael addition reaction under aqueous conditions and found that **3a** was formed in 85% yield when **1** was treated with **2a** in H_2O in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) in 5 min (Method B).

To establish the generality of the $Cu(BF_4)_2{\cdot}xH_2O$ catalysed thia Michael addition reaction for other α,β-unsaturated carbonyl compounds, various enones such as 3-methyl-2-cyclohexen-1-one (**4**), 3-buten-2-one (**6**) and *trans*-4-phenyl-3-buten-2-one (**8**) were treated with different aromatic and aliphatic thiols **2a–e** under the catalytic influence of $Cu(BF_4)_2{\cdot}xH_2O$ at room temperature in the absence of solvent (Table 1). Excellent results were obtained in each case. The reactions were, in general, fast and complete within 2 min to 1 h (TLC, IR). After the addition of the catalyst to the magnetically stirred mixture of the enone and the thiol, an exothermic reaction took place indicating product formation. The rate of the reaction was found to be dependent on the steric hindrance at the β-position of the enone. Thus, compared to the reactions of **1** with a particular thiol, the reactions of **4** took longer (Table 1, compare the results of entries 1–5 with those of entries 6–10). This is further demonstrated by comparison of the results of the reactions of **6** with those of **8** with a particular thiol (Table 1, compare entries 12 and 17, 13 and 18, 14 and 19, 15 and 20).

The superiority of $Cu(BF_4)_2{\cdot}xH_2O$ over other reported catalysts for the thia Michael addition reaction involving common reactants can be illustrated by a few representative examples. The $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) catalysed reaction afforded **3a** in 88% yield in 2 min during the reaction of **1** with **2a** in the absence of solvent (Table 1, entry 1). Compared to this, the use of $InBr_3$ (10 mol%) gave a 74% yield in dry DCM after 16–24 h.[10] The corresponding reaction afforded 65% and 72% yields in the presence of $Bi(NO_3)_3$ (15 mol%) in 2–4 h in DCM[11] and $Bi(OTf)_3$ (5 mol%) in 1.5 h in MeCN,[12] respectively. Reaction of **1** with **2e**, catalysed by $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%), afforded **3e** in 85% yield in 5 min under solvent-free conditions whereas a comparable yield was obtained when carrying out the reaction at 105 °C for 45 min in the presence of TBAB.[15b] The Michael adduct **7a** was obtained in 87% yield when **6** was treated with **2a** in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) for 5 min under solvent-free conditions (Table 1, entry 11). However, **7a** was obtained in 70%, 72% and 75% yields under the catalytic influence of $Bi(OTf)_3$ (5 mol%) in 1 h in MeCN,[12] TBAB (15 mol%) at 105 °C for 2 h[15b] and [pmim]Br (300 mg/mmol) for 45 min,[15c], respectively. The reaction of **8** with **2a** (Table 1, entry 16) resulted in an 86% yield of the Michael adduct in 5 min under the catalytic influence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) under solvent-free conditions and an 80% yield was obtained in the presence of $InCl_3$ (10 mol%) in dry MeOH for 2 h.[14] The $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) catalysed reaction of **8** with **2b** afforded **9b** in 84% yield in 75 min under solvent-free conditions (Table 1, entry 17). In comparison to this, **9b** was obtained in 78% yield in the presence of $InBr_3$ (10 mol%) in dry DCM for 16–24 h.[10] Reaction of **10** with **2a** and **b** (Table 1, entries 21 and 22), catalysed by $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%), afforded **11a** and **b** in 92% and 91% yields, respectively, in MeOH for 1 h. The corresponding products were obtained in 67% and 61% yields, respectively, under the catalytic influence of $InBr_3$ (10 mol%) in dry DCM for 16–24 h.[10]

It has been recently reported that the $InCl_3$ (10 mol%) catalysed Michael addition reaction of chalcones with thiols is dependent upon the solvent, it requires dry MeOH and does not proceed at all in other solvents such as DCM, THF and H_2O.[14] Thus we felt that the Michael addition of a thiol with a representative chalcone as substrate should reflect the advantage of $Cu(BF_4)_2{\cdot}xH_2O$ over the recently introduced $InCl_3$ as the catalyst. We chose *trans*-1,3-diphenylpropenone (**10**) as a representative chalcone and treated it with **2a** under various conditions in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%). Advantageously, we found that the $Cu(BF_4)_2{\cdot}xH_2O$ catalysed Michael addition reaction of **10** with **2a** afforded **11a** in 92% yield in non-anhydrous MeOH and was equally effective in DMF, MeCN and $MeNO_2$. However, inferior results were obtained in DCM, THF, dioxane, EtOAc, H_2O and under solvent-free conditions. The poor result obtained in H_2O was due to the immiscibility of the starting chalcone in H_2O. Similarly the inferior yield obtained under neat conditions is due to the lack of formation of a homogeneous mixture of **10** and **2a**. However, formation of a homogeneous mixture of the reactants is not the criteria for driving the Michael reaction to completion in a reasonable time. The higher rate of reaction in polar solvents such as MeOH, DMF, MeCN and $MeNO_2$ compared to those in weakly polar solvents such as DCM, THF, dioxane and EtOAc demonstrates the polar nature of the activation state and supports the postulate that the initial complexation of the carbonyl oxygen with the central

Table 1. $Cu(BF_4)_2{\cdot}xH_2O$ catalysed Michael addition of thiols to, β-unsaturated carbonyl compounds[a]

Entry	Enone	Product	Time (min)	Yield (%)[b,c,d]
	 **1**	 **3**		
1		**a**: R = C_6H_5	2	88[e]
2		**b**: R = 4-Me-C_6H_4	5	90
3		**c**: R = $C_6H_5CH_2$	2	93
4		**d**: R = 2-C_5H_5O	2	88
5		**e**: R = C_2H_5	5	85
	 **4**	 **5**		
6		**a**: R = C_6H_5	45	86
7		**b**: R = 4-Me-C_6H_4	60	83
8		**c**: R = $C_6H_5CH_2$	45	81
9		**d**: R = 2-C_5H_5O	60	82
10		**e**: R = C_2H_5	12 h	75
	 **6**	 **7**		
11		**a**: R = C_6H_5	5	87
12		**b**: R = 4-Me-C_6H_4	2	92
13		**c**: R = $C_6H_5CH_2$	2	90
14		**d**: R = 2-C_5H_5O	2	91
15		**e**: R = C_2H_5	5	81
	 **8**	 **9**		
16		**a**: R = C_6H_5	5	86
17		**b**: R = 4-Me-C_6H_4	75	84
18		**c**: R = $C_6H_5CH_2$	75	87
19		**d**: R = 2-C_5H_5O	20	88
20		**e**: R = C_2H_5	14 h	80
	 **10**	 **11**		
21		**a**: R = C_6H_5	60	92[f]
22		**b**: R = 4-Me-C_6H_4	60	91[f]
23		**c**: R = $C_6H_5CH_2$	15	89[f]
24		**d**: R = 2-C_5H_5O	10	88[f]
25		**e**: R = C_2H_5	12 h	83[f]

[a] The substrate (1 equiv) was treated with the mercaptan (1.1 equiv) in the presence of $Cu(BF_4)_2{\cdot}xH_2O$ (1 mol%) at room temperature (~25 °C) in the absence of solvent (Method A).

[b] Isolated yield of the corresponding conjugate addition product obtained after chromatographic purification.

[c] All of the products were characterised by analysis of spectral data (IR, ^1H and ^{13}C NMR and MS).

[d] All new compounds gave satisfactory elemental analysis.

[e] The product was obtained in 85% yield when carrying out the reaction in H_2O (Method B).

[f] The reaction was carried out in methanol.

metal cation of the catalyst induces carbocationic character at the β-carbon of the α,β-unsaturated carbonyl compound (Scheme 1). In the reactions of **1**, **4**, **6** and **8** carried, out under neat conditions, the electrostatic effect of the ionic aggregate of the catalyst favours the polar activation state. The reaction of **10** with other thiols such as **2b**–**e** afforded the corresponding Michael adducts **11b**–**e** in 91%, 89%, 88% and 83% yields, respectively, (Table 1, entries 22–25). The distinct advantage of the use of $Cu(BF_4)_2{\cdot}xH_2O$ as a catalyst for the thia Michael addition reaction with α,β-unsaturated carbonyl compounds is further evidenced by the fact that

the reaction of **4** with **2a** afforded **5a** in 86% yield in 45 min while the corresponding reaction did not proceed in the presence of an ionic liquid.[15c]

3. Conclusion

We have described herein a highly efficient catalyst for the thia Michael addition under solvent-free conditions and in water at room temperature. The advantages include, (i) the use of a cheap, easy to handle and commercially available catalyst, (ii) room temperature and non-anhydrous reaction conditions, (iii) short reaction times and (iv) high yields. With increasing environmental concerns[18] the solvent-free reaction conditions and the feasibility of performing the reactions in H_2O should make this methodology environmentally friendly and applicable for large scale operations.

4. Experimental

4.1. Typical procedure for the thia Michael addition

4.1.1. Method A. To a magnetically stirred mixture of **1** (0.24 g, 2.5 mmol) and **2a** (0.30 g, 2.75 mmol, 1.1 equiv) was added $Cu(BF_4)_2{\cdot}xH_2O$ (6 mg, 1 mol%). The reaction mixture was stirred at room temperature (~25 °C) for 2 min. After completion of the reaction (TLC, IR), the reaction mixture was diluted with EtOAc (2 mL), adsorbed on silica gel, charged on a column of silica gel (60–120 mesh, 5 g), eluted with hexane (to eliminate any disulfide formed) followed by 1:10 EtOAc–hexane to afford 3-phenylthiocyclohexan-1-one (**3a**) (453 mg, 88%) (Table 1, entry 1): IR (neat) cm^{-1}: 1714, ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.42–7.39 (m, 2H), 7.32–7.23 (m, 3H), 3.45–3.40 (m, 1H), 2.69–2.63 (m, 1H), 2.39–2.26 (m, 3H), 2.14–2.07 (m, 2H), 1.74–1.68 (m, 2H), ^{13}C NMR (75 MHz) δ (ppm): 208.3, 132.9, 128.8, 127.5, 47.5, 45.8, 40.6, 30.9, 23.7, MS (ESI) *m/z*: 206 (M^+) identical with an authentic sample of **3a**.[11] The remaining reactions were carried out following this general procedure and on each occasion the product was purified following the above-mentioned procedure for liquids and by crystallisation (EtOAc–hexane) in the cases of solid products.

4.1.2. Method B. To a magnetically stirred mixture of **1** (0.24 g, 2.5 mmol) and **2a** (0.30 g, 2.75 mmol, 1.1 equiv) in H_2O (2.5 mL) was added $Cu(BF_4)_2{\cdot}xH_2O$ (6 mg, 1 mol%) and the reaction mixture was stirred at room temperature until complete consumption of the starting enone (5 min, TLC). The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×10 mL). The combined EtOAc extracts were dried (Na_2SO_4), concentrated under vacuum and passed through a column of silica gel eluting with EtOAc–hexane to afford **3a** (438 mg, 85%).

References and notes

1. Fujita, E.; Nagao, Y. *Bioorg. Chem.* **1977**, *6*, 287–309.
2. (a) Fluharty, A. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley Interscience: New York, 1974; p 589, Part 2; (b) Trost, B. M.; Keeley, D. E. *J. Org. Chem.* **1975**, *40*, 2013; (c) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 485–486.
3. Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218–3219.
4. Bakuzia, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235–239.
5. Cherkauskas, J. P.; Cohen, T. J. *Org. Chem.* **1992**, *57*, 6–8.
6. Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 6557–6560.
7. Kobyashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983–985.
8. Cheng, S.; Comer, D. D. *Tetrahedron Lett.* **2002**, *43*, 1179–1181.
9. (a) Zahouily, M.; Abrouki, Y.; Rayadh, A. *Tetrahedron Lett.* **2002**, *43*, 7729–7730; (b) Abrouki, Y.; Zahouily, M.; Rayadh, A.; Bahlaouan, B.; Sebti, S. *Tetrahedron Lett.* **2002**, *43*, 8951–8953.
10. Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704.
11. Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114.
12. Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115–5119.
13. Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Synlett* **2003**, 1070–1072.
14. Ranu, B. C.; Dey, S. S.; Samanta, S. *ARKIVOC* **2005**(iii), 44–50.
15. (a) Yadav, J. S.; Reddy, B. V. S.; Baishya, G. *Org. Chem.* **2003**, *68*, 7098–7100; (b) Ranu, B. C.; Dey, S. S.; Hajra, A. *Tetrahedron* **2003**, *59*, 2417–2421; (c) Ranu, B. C.; Dey, S. S. *Tetrahedron* **2004**, *60*, 4183–4188.
16. Chakraborti, A. K.; Gulhane, R.; Shivani *Synthesis* **2004**, 111–115.
17. Chakraborti, A. K.; Thilagavathi, R.; Kumar, R. *Synthesis* **2004**, 831–833.
18. Garrett, R. L. In *Designing Safer Chemicals*; Garrett, R. L., De Vito, S. C., Eds.; American Chemical Society Symposium Series 640: Washington, DC, 1996; Chapter 1.