Highly Efficient Aza-Michael Reactions of Enones with Carbamates Using a Combination of Quaternary Ammonium Salts and $BF_3·OEt_2$ as a Catalyst

Li-Wen Xu, Lyi Li, Chun-Gu Xia,* Shao-Lin Zhou, Jing-Wei Li, Xiao-Xue Hu

State Key Laboratory of Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China
Fax +86(931)8277088; E-mail: cgxia@ns.lzb.ac.cn

Received 13 October 2003

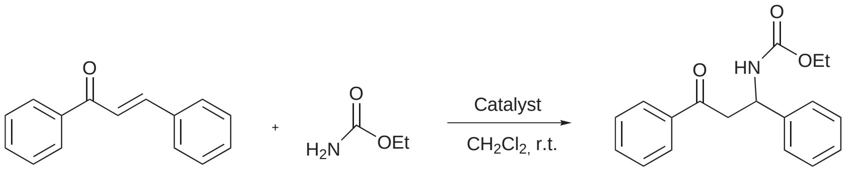
Abstract: Aza-Michael reactions of enones with carbamates took efficiently in the presence of a catalytic amount of quaternary ammonium salts and $BF_3·OEt_2$ to afford the total products in high yields. The new catalytic system was also efficient in the aza-Michael reaction of chalcone, which was difficult to react with carbamates by transition metal salts catalysts.

Key words: quaternary ammonium salts, Lewis acids, Michael reaction, carbamate, enone

The β-amino carbonyl functionality is not only a segment of biologically important natural products but also a versatile intermediate for the synthesis of nitrogen-containing compounds.[1] The development of novel synthetic methods leading to β-amino ketone, β-amino acids or their derivatives has attracted much attention in organic synthesis.[2] Among the traditional methods for generating -amino carbonyl compounds, Mannich-type reaction is one of the classical and powerful methods, the reactions of enolates either with imines are established processes for the synthesis of these moieties through carbon-carbon bond formation.[3] However, due to the harsh reaction conditions and the long reaction times, the classic Mannich reaction presents serious disadvantages.[4] Alternatively, aza-Michael additions can be used to create carbon-heteroatom bonds by reaction of α,β-unsaturated carbonyl compounds with amines. The conjugated addition of nucleophiles to α,β-unsaturated compounds usually requires strong basic conditions or acid catalysis.[5] To avoid typical disadvantages resulting from the presence of such catalyst, a large number of alternative procedures have been developed in the past few years.[6–10] However, most methods for intermolecular conjugated addition to unsaturated carbonyl compounds reported to date describe the addition of alkyl or aryl amines. Because carbamates are weakly nucleophilc, many catalysts are practically ineffective in catalyzing a similar reaction with carbamates. Recently, Spencer et al. demonstrated that $PdCl_2(MeCN)_2$ and copper-catalyzed intermolecular aza-Michael reactions of enones with benzyl carbamate as nitrogen nucleophile.[11] And Kobayashi surveyed catalytic activity of various transition metal salts in the aza-Michael reaction of enones with benzyl carbamate and demonstrated that some transition metal salts, such as platinum salts, iridium salts, gold salts, are effective for addition reactions with carbamates.[12] However, all these catalysts were not reported that could be performed in catalyzing the conjugate addition of chalcone with carbamates. Although recent advances have made this route more attractive, development of cheaper, simpler, and more efficient metal catalyst, especially which can be applied to chalcone, is highly desirable.

We are also interested in aza-Michael reactions of enones with carbamates and other nitrogen-containing reagent.[13] To the best of our knowledge, only we first reported a iron-catalyzed aza-Michael reaction of chalcone in the presence of TMSCl.[13a] Herein, we reported a new catalyst system is quite effective for the aza-Michael reactions of chalcone and other enones with carbamates.

As a special Lewis acid catalyst,[14] quaternary ammonium salt has been shown to be extraordinarily effective and useful catalysts for alkylation,[15] aldol,[16] epoxidation,[17] and Michael reaction.[18] A systematic study of the Michael addition of thiols to α,β-unsaturated ketones in the presence of quaternary ammonium salts and cinchona alkaloids as a catalyst has also been reported.[18,19] However, no reports are available on a quaternary ammonium salts-catalytic approach for the aza-Michael reaction. We try to explore the catalytic activities of quaternary ammonium salts in the aza-Michael reaction, and found that the cata-

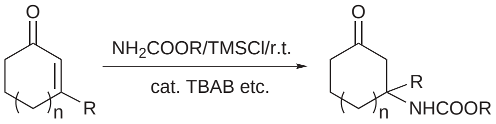


Scheme 1

SYNLETT 2003, No. 15, pp 2337–2340
Advanced online publication: 07.11.2003
DOI: 10.1055/s-2003-43333; Art ID: U21303ST.pdf

lyst was not effective in this reaction with or without a base (for example, NaOH, K_2CO_3).

It has reported that Me_3SiCl was helpful to the conjugate addition of organic-copper regeants[20] and Michael addition reactions of chiral benzylic anions.[21] Recently, we also found that $FeCl_3 \cdot 6H_2O$ was an effective catalyst for this aza-Michael reaction in the presence of TMSCl.[13a] The previous studies prompted us to address the question whether the combination of quaternary ammonium salts and $BF_3 \cdot OEt_2$ or Me_3SiCl generate the most active catalysts. At this point we decided to investigate the new system of Me_3SiCl or $BF_3 \cdot OEt_2$ and quaternary ammonium salts as a new Lewis acid catalyst in the aza-Michael reaction.



1a–d
n = 0, 1
R = H, CH_3

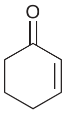
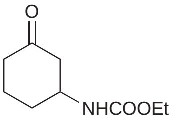
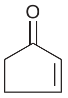
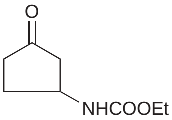
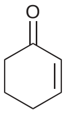
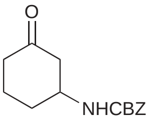
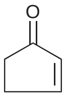
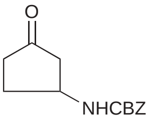
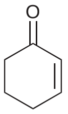
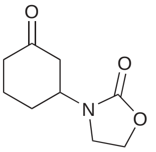
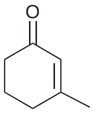
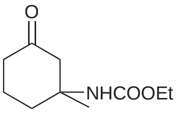
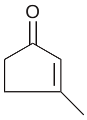
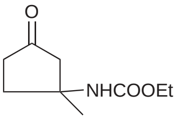
2a–d
n = 0, 1
R = H, CH_3

Scheme 2 Conjugate addition of carbamate to α,β-unsaturated cyclic enone at room temperature.

Several attempts have been performed toward achieving conjugate addition of carbamates to chalcone in the presence of Me_3SiCl or $BF_3 \cdot OEt_2$. We surveyed catalytic activity of various quaternary ammonium salts, such as TBAB, TEAB, benzyltrimethylammonium chloride, TEAC, in the aza-Michael reaction of chalcone with ethyl carbamate in CH_2Cl_2 at room temperature (Scheme 1). Interestingly, all the quaternary ammonium salts were found to be effective in the conjugate addition of chalcone with ethyl carbamate in the presence of $BF_3 \cdot OEt_2$ (40–50% isolated yields). The combination of quaternary ammonium salts and Me_3SiCl was proved to an inefficient catalyst in the aza-Michael reaction (lower yields). And the combination of TBAB–$BF_3 \cdot OEt_2$ shows the best result in this aza-Michael reaction. A control experiment was conducted in the absence of quaternary ammonium salt catalyst and no desired product was observed in the Me_3SiCl or $BF_3 \cdot OEt_2$-catalyzed aza-Michael reaction. Single quaternary ammonium salts catalyst was also not effective in the aza-Michael reaction without Me_3SiCl or $BF_3 \cdot OEt_2$. In this Letter, having established the remarkable catalytic activity of TBAB–$BF_3 \cdot OEt_2$ catalytic system in the aza-Michael reaction, we disclose the first conjugate addition of enones with carbamates.

Recently, Spencer et al reported that Brønsted acid catalyst can be superior to metal ion catalyst when weak nucleophiles are used in the hetero-Michael reaction.[22]Although this aza-Michael reaction of alkyl enones were induced by Brønsted acid, for example, aqueous HBF_4, TsOH, these Brønsted acid catalysts that are successfully employed in aza-Michael additions with alkyl enones have failed to produce b-amino ketone of chalcone derivatives. However, the combination of quaternary ammonium salts and other Lewis acid or Brønsted acid, such as, aqueous HBF_4, TsOH, CF_3COOH, was also effective in this aza-Michael reaction but have lower yields than the combination with $BF_3 \cdot OEt_2$.

Table 1 Evaluation of Quaternary Ammonium Salts as Catalysts in Aza-Michael Reaction of Cyclohexenone with Ethyl Carbamate[a]

Entry	Catalysts[b]	Enones	Products	Yield (%)[c]
1	TBAB			95
2	TEAC			88
3	THAB			90
4	–[d]			23
2	TBAB			92
3	TBAB			90
4	TBAB			86
5	TEAB			89
6	TBAB			Trace
7	TBAB			Trace

[a] All reactions were carried out using 10 mol% of quaternary ammonium salt catalyst, cyclohexenone (1 mmol), carbamate (1.2 mmol) and $BF_3 \cdot OEt_2$ (0.2 mmol) in CH_2Cl_2 at r.t. for 24 h.

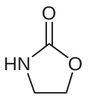
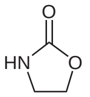
[b] TBAB = tetrabutylammonium bromide; THAB = tetrahexylammonium bromide; TEAB = tetraethylammonium bromide; TEAC = tetraethylammonium chloride.

[c] Isolated yields.

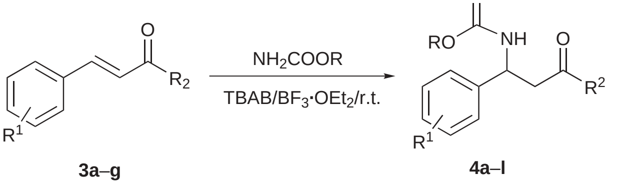
[d] No addition of quaternary ammonium salt.

With the effective catalyst system in hand (TBAB/$BF_3 \cdot OEt_2$), aza-Michael reactions of various cyclic enones with carbamates in CH_2Cl_2 at room temperature were investigated (Scheme 2 and Table 1). In this conjugate addition reaction, good to excellent yields of b-amino ketones were obtained with several cyclic enones. Benzyl carbamate, ethyl carbamate reacted smoothly with 2-cyclohexen-1-one, 2-cyclopetenone and other acyclic enones to give corresponding aza-Michael adducts in high yields.

Table 2 Aza-Michael Reactions of Various Carbamates with Chalcone Derivatives[a]

4	R^1	R^2	R	Yield (%)[b]
a	H	Ph	NH_2CBZ	50
b	*p*-Br	Ph	NH_2COOEt	41
c	*p*-CH_3	Ph	NH_2CBZ	47
d	H	CH_3	NH_2CBZ	42
e	*p*-CH_3	Ph	NH_2COOEt	50
f	H	Ph		42
g	*o*-Cl	Ph	NH_2COOEt	40
h	H	Ph	NH_2COOEt	43
i	*p*-Br	Ph	NH_2CBZ	42
k	*p*-NO_2	Ph	NH_2COOEt	29
l	*p*-CH_3	Ph		41

[a] All reactions were carried out using 10 mol% of quaternary ammonium salt (TBAB) catalyst, cyclohexenone (1 mmol), carbamate (1.2 mmol) and $BF_3{\cdot}OEt_2$ (0.2 mmol) in CH_2Cl_2 at r.t. for 24 h.
[b] Isolated yields.



Scheme 3

Aza-Michael reactions of other various chalcone derivatives with carbamates in CH_2Cl_2 at room temperature were also investigated (Scheme 3, Table 2)[23]. In contrast to previous transition metal catalysts, TBAB/$BF_3{\cdot}OEt_2$ catalytic system could also mediates aza-Michael addition of carbamates to chalcone and derivatives. Simple carbamates such as ethyl carbamate were suitable nucleophiles and moderate yields were obtained with the synthetically more useful benzyl carbamate. Although carbamates are very weakly nucleophilic, both *p*-and *o*-substituted chalcone derivatives were similarly effective substrates in the aza-Michael reaction, which allows the introduction of the amide group.

In conclusion, we have demonstrated that the conjugate addition of enones especially chalcone with a less nucleophilic carbamates can be accomplished on $BF_3{\cdot}OEt_2$/quaternary ammonium salts catalyst system under very mild conditions. Apart from experimental simplicity, the advantages of this methodology are the use of a very cheap catalyst and the insensitivity of the reaction mixture towards air. The catalyst systems based on the combination of quaternary ammonium salts and $BF_3{\cdot}OEt_2$ was found to be highly active catalyst for aza-Michael reaction of chalcone and cyclic enones with carbamates. Although the mechanism of the reaction is still unclear, asymmetric catalysis based on the catalyst might be possible. We are currently investigating the development of an enantioselective catalytic process. Further study along to this line is now in progress.

Acknowledgment

This study was supported in part by the Natural Science Founder of National for financial support of the work (29933050).

References

(1) (a) Cardill, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (c) *The Organic Chemistry of β-Lactams*; George, G. I., Ed.; VCH publishers: New York, **1993**. (d) Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983. (e) Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015.

(2) (a) Drury, W. J.; Ferraris, D.; Cox, C.; Young, B.; Leckta, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (b) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, *6*, 1. (d) Varala, R.; Alam, M. M.; Adapa, S. *Synlett* **2003**, 720. (e) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041. (f) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700. (g) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(3) (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, . (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. (d) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143. (e) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180.

(4) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1045.

(5) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, **1992**, 114. (b) Perez, M.; Pleixates, R. *Tetrahedron* **1995**, *51*, 8355. (c) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274. (d) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett* **2000**, 1257. (e) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (f) Sani, M.; Bruche, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 2060.

(6) Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.* **1994**, 827.

(7) Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975.

(8) (a) Kawatsura, M.; Hartiwig, J. F. *Organometallic* **2001**, *20*, 1960. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240. (d) Sibi, M. L.; Liu, M. *Org. Lett.* **2000**, *2*, 3393. (e) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615.

(9) Bartoli, G.; Bosco, M.; Marcantoni, E.; Pertrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052.

(10) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109.

(11) (a) Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25. (b) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891.

(12) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319.

(13) (a) Xu, L. W.; Xia, C. G.; Hu, X. X. *Chem. Commun.* **2003**, 2570. (b) Xu, L. W.; Xia, C. G.; Li, J. W.; Zhou, S. L. *Synlett* **2003**, 2246. (c) Xu, L. W.; Li, J. W.; Xia, C. G.; Zhou, S. L.; Hu, X. X. *Synlett* **2003**, in press.

(14) Selected new references: (a) Yamamoto, H. *Lewis Acids Inorganic Synthesis*; Wiley-VCH: Weinheim, **2000**. (b) Denmark, S. E.; Fan, Y. *J Am. Chem. Soc.* **2003**, *125*, 7825. (c) Labrie, P. *Synlett* **2003**, 279. (d) Szmigielski, R.; Danikiewicz, W. *Synlett* **2003**, 372. (e) Peyronneau, M.; Roques, N.; Mazieres, S.; Le Roux, C. *Synlett* **2003**, 631.

(15) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.

(16) Horikawa, M.; Busch-Peterson, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

(17) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287.

(18) Zhang, F. Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.

(19) Wynberg, H.; Hiemstra, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

(20) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.

(21) Beckwith, R. E. J.; Heron, N.; Simpkins, N. S. *J. Organomet. Chem.* **2002**, *658*, 21.

(22) (a) Wabnitz, T. C.; Yu, J. Q.; Spencer, J. B. *Synlett* **2003**, 1070. (b) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141.

(23) Representative Experimental Procedure:
TBAB (0.1 mmol) and the enones (1 mmol) were dissolved in CH_2Cl_2 (3 mL). $BF_3{\cdot}OEt_2$ (0.2 mmol) was added. Then carbamate (1.2 mmol) was added in one portion. The mixture solution was stirred at r.t. and conversion was monitored by TLC (for 24 h). After completion of the reaction, the mixture was quenched with sat. aq $NaHCO_3$ (5 mL), and the aq layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by column chromatography (eluting solvent: EtOAc–petroleum ether). All the compounds were identified by GC–MS (Agilent 6890N GC/5973N MS, HP-5MS) and usual spectral methods. Selected spectral data of new compounds. **4a**: IR(solid): 3366, 3029, 2965, 1721, 1681, 1526, 1291, 1241, 1221, 1022, 746, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.2 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.44–7.22 (m, 12 H), 5.89 (br s, 1 H), 5.33 (d, *J* = 6.0 Hz, 1 H), 5.09 (s, 2 H), 3.68 (dd, *J* = 16.7 Hz, *J* = 4.2 Hz, 1 H), 3.45 (dd, *J* = 16.7 Hz, *J* = 4.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 155.7, 141.2, 136.6, 136.3, 133.4, 128.6, 128.5, 128.1, 127.5, 126.3, 66.8, 51.8, 43.9. GC-MS: *m*/*z* = 359. **4f**: ^1H NMR: δ = 7.95 (d, *J* = 7.2 Hz, 2 H), 7.54 (t, *J* = 7.2 Hz, 1 H), 7.45–7.24 (m, 7 H), 5.36 (dd, J_1 = 6.0 Hz, J_2 = 8.6 Hz, 1 H), 4.22 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1 H), 3.57 (br s, 2 H), 3.43 (dd, J_1 = 8.0Hz, J_2 = 16.0 Hz, 1 H): ^{13}C NMR: δ = 197.2, 157.9, 138.7, 136.6, 133.7, 129.1, 129.0, 128.4, 127.5, 62.2, 54.6, 43.4, 40.6. **4g**: ^1H NMR: δ = 7.88 (d, *J* = 7.2 Hz, 2 H), 7.57 (m, 1 H), 7.41 (m, 2 H),7.24 (m, 2 H), 6.81 (m, 2 H), 5.63 (br s, 1 H), 5.22 (dd, J_1 = 6.4 Hz, J_2 = 14.0 Hz, 1 H), 4.07 (dd, J_1 = 6.8 Hz, J_2 = 14.0 Hz, 2 H), 3.64–3.74 (m, 2 H), 3.37–3.43 (m, 1 H), 1.20 (t, J_1 = 6.4 Hz, J_2 = 15.2 Hz, 3 H). ^{13}C NMR: δ = 198.2, 159.0, 156.1, 136.9, 133.7, 133.6, 128.9, 128.3, 127.8, 114.2, 61.1, 55.5, 51.5, 44.3, 14.8. **4h**: ^1H NMR: δ = 7.88 (d, *J* = 7.2 Hz, 2 H), 7.55–7.21 (m, 8 H), 5.72 (br s, 1 H), 5.28 (dd, J_1 = 6.4 Hz, J_2 = 14.0 Hz, 1 H), 3.67 (m, 2 H), 3.40–3.46 (m, 1 H), 1.21 (t, J_1 = 6.4 Hz, J_2 = 14.0 Hz, 3 H). ^{13}C NMR: δ = 198.2, 159.8, 156.2, 141.6, 136.8, 133.6, 128.9, 128.3, 127.7, 61.2, 51.9, 44.2, 14.8. **4i**: ^1H NMR: δ = 7.85 (d, *J* = 7.2 Hz, 2 H), 7.57–7.20 (m, 12 H), 6.00 (br s, 1 H), 5.26 (dd, J_1 = 6.0 Hz, J_2 = 13.2 Hz, 1 H), 4.77 (br s, 2 H), 3.65 (m, 1 H), 3.40 (dd, *J* = 5.2 Hz, *J* = 16.8 Hz, 1 H). ^{13}C NMR: δ = 197.9, 157.0, 156.0, 140.7, 136.6, 136.5, 133.9, 132.0, 129.0, 128.7, 128.5, 128.3, 127.9, 121.5, 67.1, 51.4, 43.8.