JOC Article

# Mild α-Halogenation Reactions of 1,3-Dicarbonyl Compounds Catalyzed by Lewis Acids

Dan Yang,* Yi-Long Yan, and Bob Lui

*Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China*

*yangdan@hku.hk*

*Received June 7, 2002*

Lewis acid $Mg(ClO_4)_2$, combined with NBS, in $CH_3CN$ or EtOAc provided mild and fast bromination of 1,3-dicarbonyl compounds. In particular, this protocol could be applied to the α-monobromination of α-unsubstituted *β*-keto esters. Similar Lewis acid catalysis was also extended to the α-chlorination and iodination of 1,3-dicarbonyl compounds with NCS and NIS, respectively.

## Introduction

α-Bromination of 1,3-dicarbonyl compounds is an important transformation,[1] as the resulting α-brominated products are highly versatile intermediates in organic synthesis.[2] The most commonly used reagents for this transformation include bromine,[3] *N*-bromosuccinimide (NBS),[4] and cupric bromide.[5] The reaction conditions of these methods are in general highly acidic or basic. In terms of availability and ease of handling, *N*-bromosuccinimide is a superior brominating reagent. However, in our investigation of Lewis acid-catalyzed atom-transfer radical cyclization reactions,[6] we found some olefinic α-bromo *β*-keto esters, especially α-monobromo *β*-keto esters from α-unsubstituted substrates, could not be conveniently prepared by bromination of *β*-keto esters with NBS following literature procedures.[4] This led us to search for a new α-bromination method. It is known that the chelation of Lewis acids to the two carbonyl groups of a *β*-keto ester substrate promotes the enol formation and thus changes the electronic property of the α-carbon.[7] Recently, Togni et al used Ti−TADDOLate to catalyze enantioselective α-halogenation of α-substituted *β*-keto esters.[8] We thus investigated the use of Lewis acids in α-bromination of *β*-keto esters. Here we report that NBS combined with the Lewis acid $Mg(ClO_4)_2$ can afford mild and fast α-bromination of a wide range of functionalized 1,3-dicarbonyl compounds. In addition, this method can be applied to the α-chlorination and α-iodination of 1,3-dicarbonyl compounds,[9,10] thereby providing useful building blocks for organic synthesis.[11,12]

## Results and Discussion

**I. Lewis Acid-Catalyzed α-Bromination of α-Substituted *β*-Keto Esters.** α-Bromination reactions of α-monosubstituted *β*-keto esters **1a**−**1f** were conducted

(1) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH Publishers Inc.: New York, 1999; pp 715−719.

(2) For examples of α-bromo 1,3-dicarbonyl compounds in organic transformations, see: (a) Misra, A. P.; Raj, K.; Bhaduri; A. P. *Synth. Commun*. **1999**, *29*, 3227−3236. (b) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett*. **1995**, *36*, 7735−7738. (c) Endo, M.; Droghini, R. *Can. J. Chem*. **1988**, *66*, 1400−1404. (d) Hlavka, J.; Bitha, P.; Lin, Y.; Strohmeyer, T. *J. Heterocycl. Chem*. **1985**, *22*, 1317−1322. (e) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *Tetrahedron Lett*. **1984**, *25*, 2817−2820. (f) Kaye, P. T.; Meakins, G. D.; Smith, A. K.; Tirel, M. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1677−1680.

(3) (a) Bigelow, L. A.; Hanslick, R. S. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, p 244. (b) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035−2044. (c) Ogilvie, W.; Rank, W. *Can. J. Chem*. **1987**, *65*, 166−169. (d) Dowd, P.; Kaufman, C.; Kaufman, P. *J. Org. Chem*. **1985**, *50*, 882−885.

(4) (a) NBS or $Br_2$/NaH: Boyd, R. E.; Rasmussen, C. R.; Press: J. B. *Synth. Commun*. **1995,** *25*, 1045−1051. (b) NBS/$NEt_3$: Karimi, S.; Grohmann, K. G. *J. Org. Chem*. **1995**, *60*, 554−559. (c) NBS/NaH: Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem*. **1989**, *54*, 1826−1831. (d) NBS/KH: Curran, D. P.; Chang, C. T. *J. Org. Chem*. **1989**, *54*, 3140−3157.

(5) (a) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett*. **1995**, *36*, 7735−7738. (b) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171−3175. (c) Shi, X.; Dai, L. *J. Org. Chem*. **1993**, *58*, 4596−4598.

(6) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc*. **2001**, *123*, 8612−8613.

(7) For examples of Lewis acid-catalyzed transformations of *β*-keto esters, see: (a) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc*. **2000**, *122*, 1658−1663. (b) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc*. **1999**, *121*, 5579−5580. (c) Tateiwa, J.-I.; Hosomi, A. *Eur. J. Org. Chem*. **2001**, 1445−1448. (d) Keller, E.; Feringa, B. L. *Tetrahedron Lett*. **1996**, *37*, 1879−1882. (e) Colombo, M. I.; Signorella, S.; Mischne, M. P. *Tetrahedron* **1990**, *46*, 4149−4154. (f) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc*. **1995**, *117*, 6194−6198. (g) Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett*. **1996**, *37*, 5561−5564.

(8) (a) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425−2435. (b) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 4359−4362. (c) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed*. **2002**, *41*, 979−982.

(9) Chlorination with NCS: (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941−3949. (b) Tanaka, K.; Chen, X.; Yoneda, F. *Tetrahedron* **1988**, *44*, 3241−3249.

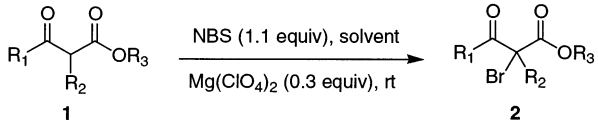
(10) Iodination with NIS: (a) Cossy, J.; Thellend, A. *Tetrahedron Lett*. **1990**, *31*, 1427−1428. (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc*. **1991**, *113*, 6607−6617.

(11) For examples of α-chloro 1,3-dicarbonyl compounds in organic transformations, see: (a) Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; Kiso, Y. *J. Org. Chem*. **2000**, *65*, 8402−8405. (b) Guerin, D.; Carlier, R.; Lorcy, D. *J. Org. Chem*. **2000**, *65*, 6069−6072. (c) Vasudevan, A.; Mavandadi, F.; Chen, L.; Gangjee, A. *J. Org. Chem*. **1999**, *64*, 634−638. (d) Hayes, T.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc*. **1988**, *110*, 5533−5543. (e) Blount, J. F.; Coffen, D. L.; Katonak, D. A. *J. Org. Chem*. **1978**, *43*, 3821−3824.

(12) For examples of α-iodo 1,3-dicarbonyl compounds in organic transformations, see: (a) Kang, J.; Lee, J. H.; Noh, S. B.; Oh, C. S.; Kim, H. Y.; Chung, B. Y. *Synlett* **1990**, 153−154. (b) Curran, D. P.; Chen, M. S.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc*. **1989**, *111*, 8872−8878. (c) Reference 4c.

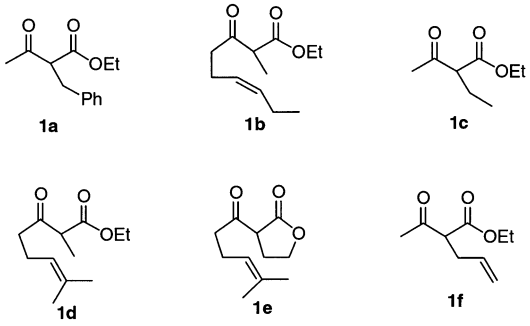
10.1021/jo026025t CCC: $22.00 
Published on Web 09/26/2002

**TABLE 1. Lewis Acid-Catalyzed α-Bromination of α-Substituted *β*-Keto Ester[a]**




1 2

Substrates:



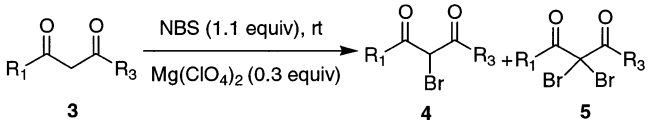

| entry | substrate | solvent | time | conversion (%)[b] | isolated yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | $Et_2O$ | 3.5 h | 100 (26) | 81 (17) |
| 2 | **1a** | $CH_3CN$ | 1 h | 100 (25) | 98 (20) |
| 3 | **1a** | EtOAc | 4.5 h | 100 (14) | 90 (10) |
| 4[c] | **1b** | $Et_2O$ | 1 h | 95 (58) | 76 (14) |
| 5 | **1b** | $CH_3CN$ | 1 h | 100 (100) | 76 (6) |
| 6 | **1c** | $CH_3CN$ | 40 min | 100 (3) | 86 (3) |
| 7 | **1d** | $CH_3CN$ | 1 h | 100 (100) | 65 (17) |
| 8 | **1d** | EtOAc | 1 h | 100 (59) | 80 (24) |
| 9 | **1e** | $CH_3CN$ | 1 h | 100 (78) | 80 (25) |
| 10 | **1f** | EtOAc | 40 min | 100 (24) | 86 (10) |

[a] Unless otherwise indicated, all reactions were carried out with 0.5 mmol of substrate in 10 mL of solvent in the presence of $Mg(ClO_4)_2$ (0.3 equiv). [b] The numbers in parentheses represent the results obtained in the absence of $Mg(ClO_4)_2$. [c] $Mg(ClO_4)_2$ (1.0 equiv) was added.

in the presence or absence of Lewis acids in various solvents at room temperature (Table 1). Substrates **1a** and **1b** were first examined in order to find an optimal condition. It was found that while Lewis acids $Mg(ClO_4)_2$, $Yb(OTf)_3$, and $LiClO_4$ all catalyzed the bromination reaction in $Et_2O$, $Mg(ClO_4)_2$ turned out to be the best catalyst for both **1a** and **1b** in term of yields and reaction rates (entries 1 and 4). With $Mg(ClO_4)_2$ as the Lewis acid, it was found that solvents such as $CH_3CN$ and EtOAc gave higher yields than $Et_2O$ (entries 2, 3 vs 1). In the presence of 0.3 equiv of $Mg(ClO_4)_2$, α-bromination of **1a** conducted in $CH_3CN$ was completed within 1 h, and product **2a** was isolated in 98% yield (entry 2). Therefore, $Mg(ClO_4)_2/CH_3CN$ or EtOAc was employed as the catalytic system for the α-bromination of other substrates **1c**−**1f** (entries 6−10). It was interesting to find that, although the starting materials **1c**−**1f** could be consumed within 1−2 h without Lewis acids in $CH_3CN$, the isolated yields of the expected α-bromo products were low and complicated side products were formed. With the catalysis of $Mg(ClO_4)_2$, the yields of bromination products increased dramatically from 6−25% to 65−86%. This indicated that Lewis acid not only accelerated the α-bromination reactions but also reduced the side reactions.

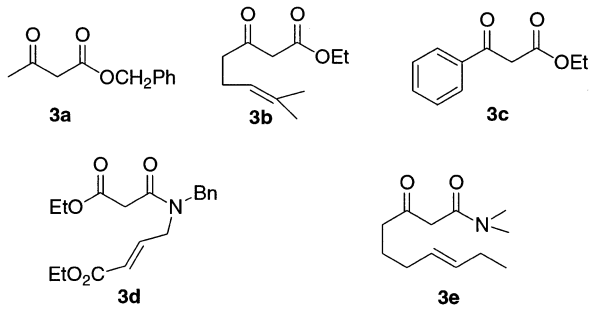
**II. Lewis Acid-Catalyzed α-Monobromination of α-Unsubstituted *β*-Keto Esters and Amides.** α-Monobromination of *β*-keto esters without α-substituents has been a challenging problem, since some α-monobrominated *β*-keto esters were reported to be unstable upon storage and readily disproportionated to dibrominated and debrominated products. [5c,13,14] Hoffman et al. have investigated the reaction conditions in order to improve the yields and ratios of monobrominated products of *β*-keto esters without α-substituents. [13] We found that, by using NBS combined with a catalytic amount of $Mg(ClO_4)_2$ in $CH_3CN$ or EtOAc, the yields of α-monobrominated products of α-unsubstituted *β*-keto esters could be dramatically increased (Table 2). For substrates **3a** and **3b**, the ratios of mono- to dibrominated products increased from around 1:1 in the absence of Lewis acid to more than 10:1 in the presence of Lewis acid, and yields of monobrominated products **4a** and **4b** also increased from 13−40% to about 80% (entries 1−3), although the change was less significant for *β*-keto ester **3c** (entry 4). The advantage of this mild bromination system was also evident in the α-bromination of some substrates such as **3d**. **3d** could not be brominated with bromine or other reagents under highly basic conditions, because it contains an α,*β*-unsaturated ester group, which is prone to intramolecular Michael addition reaction. In contrast, **3d** could be brominated with the aid of a Lewis acid in high yields (entry 5). In general, the effect of Lewis acids was less significant for *β*-keto amides **3d** and **3e**, because the

**TABLE 2. Lewis Acid-Catalyzed α-Monobromination of 1,3-Dicarbonyl Compounds[a]**




3 4 5

Substrates:

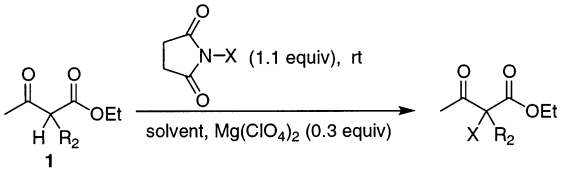



| entry | substrate | solvent | time | yield of **4** (%)[b] | ratio of **4**:**5**[b] |
|---|---|---|---|---|---|
| 1 | **3a** | $CH_3CN$ | 1 h | 75 (22)[c] | 10.3:1 (0.6:1)[c] |
| 2 | **3a** | EtOAc | 1 h | 85 (45)[c] | 14.8:1 (1.5:1)[c] |
| 3 | **3b** | $CH_3CN$ | 40 min | 80 (13)[d] | 11.9:1 (0.8:1)[d] |
| 4 | **3c** | $CH_3CN$ | 40 min | 96 (69)[d] | *e* |
| 5 | **3d** | $CH_3CN$ | 1 h | 87 (81)[d] | *e* |
| 6 | **3e** | $CH_3CN$ | 30 min | 91 (89)[d] | *e* |

[a] All reactions were carried out with 0.5 mmol of substrate in 10 mL of solvent in the presence of $Mg(ClO_4)_2$ (0.3 equiv). [b] The numbers in parentheses represent the results obtained in the absence of $Mg(ClO_4)_2$. [c] Determined by using NMR. [d] Determined by isolation. [e] Only product **4** was isolated.

(13) Hoffman, R. V.; Weiner, W. S.; Maslouh, N. *J. Org. Chem.* **2001**, *66*, 5790−5795.
(14) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Izawa, K. *Org. Lett.* **2002**, *4*, 447−449.

**TABLE 3. Lewis Acid-Catalyzed α-Chlorination and Iodination of *β*-Keto Esters**[a]




| entry | substrate | X | solvent | time | conversion (%)[b] | isolated yield **6** or **7** (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | Cl | $CH_3CN$ | 1.5 h | 100 (17) | 99 (16) |
| 2 | **1a** | Cl | EtOAc | 4.5 h | 100 (11) | 96 (10) |
| 3 | **1a** | I | $CH_3CN$ | 7.0 h | 100 (26) | 85 (20) |
| 4 | **1a** | I | EtOAc | 5.5 h | 100 (44) | 84 (34) |
| 5 | **1c** | Cl | $CH_3CN$ | 2 h | 100 (11) | 86 (9) |
| 6 | **1c** | I | $CH_3CN$ | 15 min | 100 (17) | 86 (14) |

[a] All reactions were carried out with 0.5 mmol of substrate in 10 mL of solvent in the presence of $Mg(ClO_4)_2$ (0.3 equiv). [b] The numbers in parentheses represent the results obtained in the absence of $Mg(ClO_4)_2$.

corresponding bromination reactions with NBS in $CH_3CN$ was complete within a short period of time in good yields, even without any Lewis acid (entries 5 and 6).

We found that some α-monobrominated *β*-keto esters disproportionated during column purification on silica gel. Among **4a**−**c**, **4a** was the easiest one to disproportionate, but **4c** would not. α-Monobrominated *β*-keto amides **4d** and **4e** were also stable during column purification.

**III. Lewis Acid-Catalyzed α-Chlorination and Iodination of *β*-Keto Esters.** We also tested the possibility of using Lewis acids to catalyze α-chlorination and α-iodination of *β*-keto esters with NCS and NIS, respectively. Substrates **1a** and **1c** were thus halogenated with NCS or NIS under the catalysis of $Mg(ClO_4)_2$ in $CH_3CN$ or EtOAc (Table 3). Compared to those without Lewis acid, the α-halogenation reactions in the presence of $Mg(ClO_4)_2$ were much faster and the isolated yields were also much higher. Within the same reaction time, the yields increased from 9−34% to 84−99% with Lewis acid catalysis.

## Conclusion

In summary, we have developed a general method for mild α-halogenation of 1,3-dicarbonyl compounds using the Lewis acid $Mg(ClO_4)_2$ combined with *N*-halosuccinimide. This method is very chemoselective, as it can tolerate an olefinic C=C bond and other sensitive functional groups. Thus, it allows convenient access to a variety of α-halogenated 1,3-dicarbonyl compounds, which are important intermediates in organic transformations. It will be interesting to extend this Lewis acid catalysis to the catalytic enantioselective α-halogenation reactions when proper chiral ligands are employed. [8,15]

## Experimental Section

**Preparation of Substrates.** Substrates **1b**, **1d**−**1f**, **3b**, and **3e** were prepared according to literature procedures.[16]

**Typical Procedure for the Lewis Acid-Catalyzed α-Bromination of 1,3-Dicarbonyl Compounds.** To a stirred solution of substrate **1d** (106 mg, 0.5 mmol) in EtOAc (10 mL) was added Lewis acid $Mg(ClO_4)_2$ (34 mg, 0.15 mmol) at room temperature. Solid NBS (98 mg, 0.55 mmol) was added to the above mixture 5 min later. When the reaction was finished, the reaction mixture was diluted with $Et_2O$, washed with water, and then dried over $MgSO_4$. After concentration, the crude product was purified by flash column chromatography using EtOAc/*n*-hexane as eluents to give **2d** (116 mg, 80%) as a colorless oil: analytical TLC (silic gel 60), 10% EtOAc in *n*-hexane, $R_f = 0.50$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.09 (dd, $J$ = 4.1, 9.6 Hz, 1H), 4.28 (q, $J$ = 7.1 Hz, 2H), 2.87 (m, 1H), 2.71 (m, 1H), 2.32 (q, $J$ = 7.3 Hz, 2H), 1.99 (s, 3H), 1.69 (s, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$; DEPT) $\delta$ 200.7 (C), 168.6 (C), 133.4 (C), 122.6 (C), 63.3 ($CH_2$), 63.3 (C), 38.5 ($CH_2$), 25.9 (C), 25.7 (C), 23.6 ($CH_2$), 17.9, 14.1; IR ($CHCl_3$) 2987, 1749, 1724, 1264 cm$^{-1}$; LRMS (EI, 20 eV) *m*/*z* 291 ($M^+$ − H, 14), 289 ($M^+$ − H, 15), 211 (7), 153 (100); HRMS (EI) for $C_{12}H_{18}BrO_3$ ($M^+$ − H) calcd 289.0439, found 289.0415.

**Acknowledgment.** This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. Y.-L.Y. is a recipient of Hui Pun Hing Scholarship for Postgraduate Research. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship Award.

**Supporting Information Available:** Characterization data of compounds **2b**, **2e**, **4b**, **4d**, **4e**, **5b**, **7a**, and **7c**. $^1$H NMR and $^{13}$C NMR spectra of compounds **2b**, **2d**, **2e**, **4b**, **4d**, **4e**, **5b**, **7a**, and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026025T

(15) For more examples of asymmetric α-halogenation, see: (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531−1532. (b) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049−2051. (c) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728−10729.

(16) (a) Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, 4067−4070. (b) Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1475−1480.