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# Halogenation of Carbonyl Compounds by an Ionic Liquid, [AcMIm]X, and Ceric Ammonium Nitrate (CAN)

*Brindaban C. Ranu,*[A,B] *Laksmikanta Adak,*[A] *and Subhash Banerjee*[A]

[A]Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India.

[B]Corresponding author. Email: ocbcr@iacs.res.in

An ionic liquid, acetylmethylimidazolium halide ([AcMIm]X), in combination with ceric ammonium nitrate promotes halogenations of a wide variety of ketones and 1,3-keto esters at the α-position. The ionic liquid acts here as reagent as well as reaction medium, and thus the reaction does not require any organic solvent or conventional halogenating agent. The reaction is completely arrested when the radical quencher TEMPO is used. A plausible radical mechanism is also suggested.

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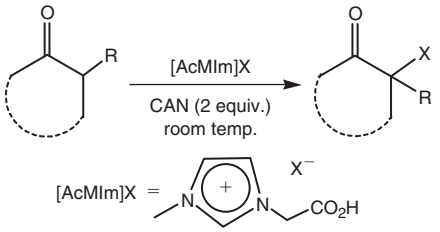
## Introduction

α-Halogenation of carbonyl compounds is an important process as the α-halogenated products are useful building blocks in organic synthesis.[1] Thus, a variety of methods have been developed for the preparation of these compounds.[2] These procedures mostly used *N*-halosuccinimides,[2a–f] molecular halogen,[2g–m] metal halides,[2n–r] and other related derivatives[2s] involving an ionic path. The molecular halogens, particularly bromine and chlorine, when used as reagents, are very hazardous. Moreover, several of these methods have disadvantages such as longer reaction times, harsh conditions, and low yields of products. Thus, a milder and more efficient methodology for this useful transformation is highly desirable.

Ionic liquids have been the subject of considerable current interest as alternative reaction media in organic syntheses.[3,4] However, we envisioned ionic liquids as having far more potential than being used as only reaction media, and various new applications of ionic liquids as efficient catalysts and reagents have been reported.[5] As a part of this continued activity we have recently introduced an ionic liquid, [AcMIm]X, for the cleavage of epoxides,[5k] and we report here another useful application of this ionic liquid in combination with ceric ammonium nitrate (CAN) for the α-halogenation of carbonyl compounds (Scheme 1).




**Scheme 1.** Use of [AcMIm]X and CAN in the α-halogenation of carbonyl compounds.

## Results and Discussion

The experimental procedure is very simple. A mixture of carbonyl compound, ionic liquid, acetylmethylimidazolium halide ([AcMIm]X), and CAN was stirred at room temperature for a period of time (TLC). The reaction mixture was quenched with water and extracted with ethyl acetate. Usual workup followed by short column chromatography produced the pure product.

A wide range of structurally diverse carbonyl compounds underwent halogenation by this procedure to produce the corresponding α-monohalogenated products. The results are summarized in Table 1. The carbonyl compounds included cyclic and acyclic α,β-unsaturated ketones and β-keto esters. All these compounds were halogenated with uniform efficiency; however, brominations and iodinations were faster than chlorinations. Brominations and chlorinations of 2- and 3-substituted cyclohexanones produced mixtures of 2- and 6-halogenated products with predominant formation of 2-halogenated isomers (entries 3, 4). The acyclic ketone where α-hydrogens are available at both positions also produced a mixture of regioisomeric products (entry 22). The α,β-unsaturated cyclic ketones, in general, furnished 2-halo enones (entries 14–16). Halogenation of β-keto esters proceeded well, leading to the corresponding α-halo products (entries 17–21).

In general, the reactions are very clean, high yielding, and fast at room temperature. The reactions did not proceed at all either in the absence of [AcMIm]X or in the absence of CAN. The ionic liquid [AcMIm]X acts here as halogenating agent as well as reaction medium, and CAN works as a one-electron oxidant. It was also observed that use of one equivalent of CAN led to only 50% halogenation, whereas with two equivalents the reaction was complete. This indicates the absolute requirement of two equivalents of CAN in this process. Further experiments showed that the presence of 2 equivalents of 2,2,6,6-tetramethylpiperidine oxide (TEMPO), a radical quencher, arrested the halogenation


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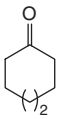
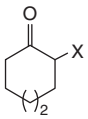
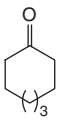
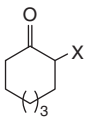
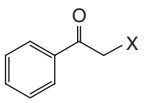
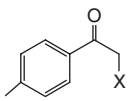
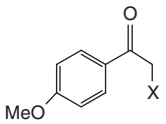
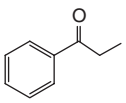
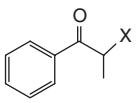
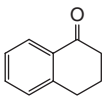
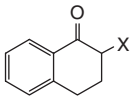
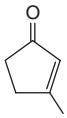
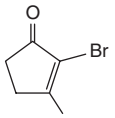
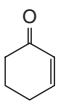
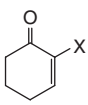
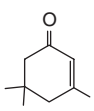
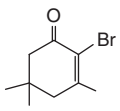
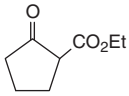
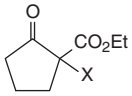
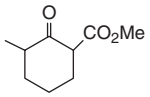
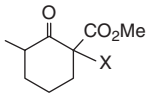
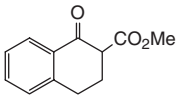
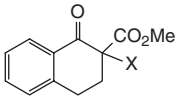
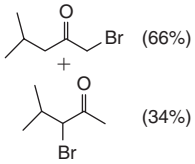
**Table 1. α-Halogenation of ketones and β-keto esters by [AcMIm]X in the presence of CAN**

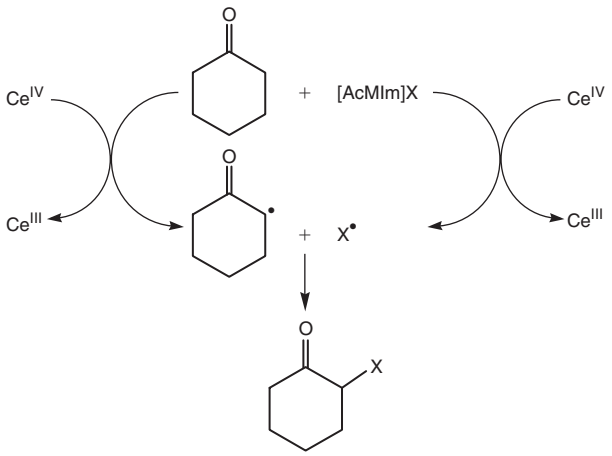
| Entry | Substrate | Product(s) | X | Time [h] | Yield[A] [%] | Ref. |
|---|---|---|---|---|---|---|
| 1 | cyclopentanone | 2-X-cyclopentanone | (a) Cl | 4.0 | 85 | [2f] |
| | | | (b) Br | 4.0 | 86 | [2f] |
| | | | (c) I | 3.0 | 80 | [2f] |
| 2 | cyclohexanone | 2-X-cyclohexanone | (a) Cl | 4.5 | 90 | [2f] |
| | | | (b) Br | 3.0 | 90 | [2f] |
| | | | (c) I | 2.5 | 82 | [2f] |
| 3 | 2-methylcyclohexanone | 2-X-2-methylcyclohexanone + | (a) Cl | 5.0 | 80 | [2f] |
| | | 6-X-2-methylcyclohexanone | (30:70) | 4.5 | 82 | [2f] |
| | | | (b) Br | | | |
| | | | (24:76) | | | |
| 4 | 3-methylcyclohexanone | 2-X-3-methylcyclohexanone + | (a) Cl | 4.5 | 82 | [6a] |
| | | 2-X-5-methylcyclohexanone | (30:70) | 4.0 | 85 | [6b] |
| | | | (b) Br | | | [7a] |
| | | | (50:50) | | | [7b] |
| 5 | 4-methylcyclohexanone | 2-X-4-methylcyclohexanone | (a) Cl | 4.0 | 84 | [2q] |
| | | | (b) Br | 3.0 | 85 | [8] |
| 6 | 4-*t*-butylcyclohexanone | 2-X-4-*t*-butylcyclohexanone | (a) Cl | 4.5 | 82 | [6a] |
| | | | (b) Br | 3.0 | 85 | [2d] |
| 7 |  |  | (a) Cl | 5.0 | 85 | [2e] |
| | | | (b) Br | 4.0 | 86 | [2e] |
| 8 |  |  | (a) Cl | 5.5 | 86 | [9a] |
| | | | (b) Br | 4.5 | 87 | [9b] |
| 9 | acetophenone |  | (a) Cl | 6.0 | 80 | [2o] |
| | | | (b) Br | 5.5 | 80 | [2d] |
| 10 | 4-methylacetophenone |  | (a) Cl | 5.5 | 82 | [2o] |
| | | | (b) Br | 5.0 | 85 | [2m] |
| 11 | 4-methoxyacetophenone |  | (a) Cl | 5.0 | 80 | [2o] |
| | | | (b) Br | 4.5 | 82 | [2m] |
| 12 |  |  | (a) Cl | 5.0 | 81 | [2q] |
| | | | (b) Br | 4.0 | 84 | [2m] |
| 13 |  |  | (a) Cl | 4.5 | 85 | [2f] |
| | | | (b) Br | 4.0 | 87 | [2f] |
| | | | (c) I | 3.0 | 85 | [2f] |
| 14 |  |  | – | 4.0 | 85 | [10b] |
| 15 |  |  | (a) Cl | 4.5 | 83 | [2p] |
| | | | (b) Br | 4.0 | 87 | [2p] |
| | | | (c) I | 3.5 | 85 | [2j] |
| 16 |  |  | – | 4.0 | 88 | [2p] |

*(Continued)*

**Table 1.** *(Continued)*

| Entry | Substrate | Product(s) | X | Time [h] | Yield[A] [%] | Ref. |
|---|---|---|---|---|---|---|
| 17 | $CH_2(CO_2Me)_2$ | $CHX(CO_2Me)_2$ | (a) Cl | 3.0 | 80 | [11] |
| | | | (b) Br | 3.0 | 82 | [11] |
| 18 | $MeOCCH_2CO_2Me$ | $MeOCCHXCO_2Me$ | (a) Cl | 3.0 | 85 | [2f] |
| | | | (b) Br | 2.5 | 87 | [2f] |
| | | | (c) I | 2.5 | 82 | [2f] |
| 19 |  |  | (a) Cl | 3.0 | 83 | [12] |
| | | | (b) Br | 2.5 | 87 | [2h] |
| | | | (c) I | 2.5 | 81 | [21] |
| 20 |  |  | (a) Cl | 3.0 | 81 | This work |
| | | | (b) Br | 2.5 | 85 | This work |
| 21 |  |  | (a) Cl | 3.5 | 82 | [2f] |
| | | | (b) Br | 3.0 | 85 | [2f] |
| 22 | $Me_2CHCH_2COMe$ |  | – | 4.5 | 89 | [2d] [2d] |

[A]Yields refer to isolated pure products.




**Scheme 2.** Plausible mechanism for the α-halogenation reaction.

process completely. It was also observed that AIBN in place of CAN failed to initiate the halogenation reaction. Obviously, CAN plays a vital role in this reaction as a one-electron oxidant. Thus, taking all these observations into consideration, the following radical mechanism has been suggested for this process (Scheme 2). The preferential halogenation in the non-substituted α-position of α-substituted ketones (entries 3, 4, 22 in Table 1) can now be explained by radical stability.

This procedure also provides improved yields and regioselectivity compared to other existing procedures. For example, bromination of ethyl acetoacetate (entry 18, Table 1) by the present procedure furnished 87% yield of product, whereas the corresponding yields using NBS/$NAHSO_4$/$SiO_2$[2d] and NBS/$NH_4OAc$[2c] were 68 and 82% respectively. On the other hand, this ionic liquid led to highly regioselective chlorination of 4-methoxyacetophenone (entry 11, Table 1) at the side chain giving only one product, whereas $NaClO_2$/$Mn(acac)_3$/alumina[2q] produced a mixture of three compounds (30:22:25) through ring as well as side-chain chlorination.

## Conclusions

In conclusion, this procedure provides a novel approach for the α-halogenation of ketones and β-keto esters using an ionic liquid, [AcMIm]X, as a halogenating agent in the presence of ceric ammonium nitrate (CAN) as a one-electron oxidant. The experimental findings indicate a radical pathway for the process. We are not aware of any previous examples of radical halogenation of carbonyl compounds using an ionic liquid as the halogenating agent. Thus, this work, besides presenting a new methodology for the halogenation of carbonyl compounds, opens up a new area for radical reactions using ionic liquids. Further applications of this radical strategy for useful transformations will be reported in due course.

## Experimental

### *General*

NMR spectra were recorded on Bruker DPX-300 instrument at 300 MHz for $^1H$ and 75 MHz for $^{13}C$ in $CDCl_3$ solutions. IR spectra were measured on a FT-8300 Shimadzu spectrometer as neat samples. All liquid substrates were distilled before use.

### *General Experimental Procedure for α-Halogenation of Carbonyl Compounds by [AcMIm]X and CAN*

#### *Representative Procedure for 2-Chlorocyclohexanone (Entry 2a, Table 1)*

Ceric ammonium nitrate (1.09 g, 2 mmol) was added to a mixture of cyclohexanone (98 mg, 1 mmol) and [AcMIm]X[5k] (168 mg, 1.2 mmol), and the whole mixture was then stirred at room temperature (25–28°C) under nitrogen for 4 h (TLC). The reaction mixture was quenched with water and extracted with ethyl acetate (2 × 10 mL). The extract was successively washed with saturated $NaHCO_3$ solution, water, brine, and dried ($Na_2SO_4$). Evaporation of solvent left the crude product, which was purified by column chromatography over silica gel to provide pure 2-chlorocyclohexanone (119 mg, 90%) as a colourless liquid. The product was easily identified by its spectroscopic data (IR, $^1$H NMR, and $^{13}$C NMR), which are in complete agreement with those reported for an authentic sample.[2f] All of the products except two are known compounds[2,6,7–12] and are easily identified by comparison of their NMR spectra with those of authentic samples (see references in Table 1). The purity of all compounds was checked by $^1$H and $^{13}$C NMR spectra and elemental analysis. The new compounds were characterized by their spectroscopic data (IR, $^1$H NMR, and $^{13}$C NMR) and elemental analysis. These values are reported below:

#### *1-Chloro-3-methyl-2-oxocyclohexanecarboxylic Acid Methyl Ester (Entry 20a, Table 1)*

Colourless liquid (one stereoisomer). $\nu_{max}$/cm$^{-1}$ 1741, 1720, 1437, 1269, 1252, 1097. $\delta_H$ 3.85 (s, 3H), 2.57–2.64 (m, 2H), 2.31–2.37 (m, 1H), 2.06–2.16 (m, 2H), 1.77–1.85 (m, 2H), 1.05 (d, *J* 6.5, 3H). $\delta_C$ 204.0, 168.5, 73.3, 53.8, 40.1, 39.1, 36.1, 20.8, 14.8. Found: C 52.8, H 6.6. Calc. for $C_9H_{13}ClO_3$: C 52.8, H 6.4%.

#### *1-Bromo-3-methyl-2-oxocyclohexanecarboxylic Acid Methyl Ester (Entry 20b, Table 1)*

Colourless liquid (one stereoisomer). $\nu_{max}$/cm$^{-1}$ 1741, 1733, 1452, 1356, 1215, 1084. $\delta_H$ 3.72 (s, 3H), 2.30–2.35 (m, 1H), 1.98–2.13 (m, 2H), 1.67–1.77 (m, 2H), 1.31–1.38 (m, 2H), 1.07 (d, *J* 6.3, 3H). $\delta_C$ 199.3, 168.3, 68.3, 53.6, 44.3, 42.1, 35.7, 24.3, 15.2. Found: C 43.3, H 5.3. Calc. for $C_9H_{13}BrO_3$: C 43.4, H 5.3%.

## Acknowledgments

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## References

[1] (a) R. C. Larock, in *Comprehensive Organic Transformations*, *2nd edn* **1999**, p. 715 (Wiley–VCH: New York, NY).
(b) C.-K. Sha, C.-T. Tseng, W.-S. Chang, *Tetrahedron Lett.* **2001**, *42*, 683. doi:10.1016/S0040-4039(00)02016-5
(c) U. Tilstam, H. Weinmann, *Org. Proc. Res. Dev.* **2002**, *6*, 384. doi:10.1021/OP010103H

[2] (a) J. Hooz, J. N. Bridson, *Can. J. Chem.* **1972**, *50*, 2387. doi:10.1139/V72-383
(b) J. C. Lee, Y. H. Bae, *Synlett* **2003**, 507. doi:10.1055/S-2003-37523
(c) K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, T. Horaguchi, *Chem. Commun.* **2004**, 470. doi:10.1039/B315340A
(d) B. Das, K. Venkateswarlu, G. Mohender, I. Mahender, *Tetrahedron Lett.* **2005**, *46*, 3041. doi:10.1016/J.TETLET.2005.03.020
(e) H. M. Meshram, P. N. Reddy, K. Sadashiv, J. S. Yadav, *Tetrahedron Lett.* **2005**, *46*, 623. doi:10.1016/J.TETLET.2004.11.140
(f) H. M. Meshram, P. N. Reddy, P. Vishnu, K. Sadashiv, J. S. Yadav, *Tetrahedron Lett.* **2006**, *47*, 991, and references therein. doi:10.1016/J.TETLET.2005.11.141
(g) C. A. Horiuchi, J. Y. Satoh, *Synthesis* **1981**, 312. doi:10.1055/S-1981-29432
(h) B. Stanovnik, M. Tisler, I. Drnovsek, *Synthesis* **1981**, 987. doi:10.1055/S-1981-29672
(i) J. Barluenga, J. M. Martinez-Gallo, C. Najera, M. Yus, *Synthesis* **1986**, 678. doi:10.1055/S-1986-31748
(j) C. R. Johnson, J. P. Adams, M.-P. Braun, C. B. W. Senanayake, *Tetrahedron Lett.* **1992**, *33*, 917. doi:10.1016/S0040-4039(00)91575-2
(k) A. Bekaert, O. Barberan, M. Gervais, J.-D. Brion, *Tetrahedron Lett.* **2000**, *41*, 2903. doi:10.1016/S0040-4039(00)00310-5
(l) M. Jereb, M. Zupan, S. Stavber, *Chem. Commun.* **2004**, 2614. doi:10.1039/B409919B
(m) M. T. Rahman, N. Kamata, H. Matsubara, I. Ryu, *Synlett* **2005**, 2664.
(n) E. M. Kosower, G.-S. Wu, *J. Org. Chem.* **1963**, *28*, 633.
(o) S. Kajigaeshi, T. Kakinami, M. Moriwaki, S. Fujisaki, K. Maeno, T. Okamoto, *Synthesis* **1988**, 545. doi:10.1055/S-1988-27633
(p) R. K. Dieter, L. E. Nice, S. E. Velu, *Tetrahedron Lett.* **1996**, *37*, 2377. doi:10.1016/0040-4039(96)00295-X
(q) S. Yakabe, M. Hirano, T. Morimoto, *Synth. Commun.* **1988**, *28*, 131.
(r) J. Barluenga, M. Marco-arias, F. Gonzalez-Bobes, A. Ballesteros, J. M. Gonzalez, *Chem. Commun.* **2004**, 2616. doi:10.1039/B411227J
(s) A. Guy, M. Lemaire, J.-P. Guette, *Synthesis* **1982**, 1018, and references therein. doi:10.1055/S-1982-30046

[3] R. P. Swatloski, J. D. Holbrey, R. D. Rogers, *Green Chem.* **2003**, *5*, 361. doi:10.1039/B304400A

[4] (a) T. Welton *Chem. Rev.* **1999**, *99*, 2071. doi:10.1021/CR980032T
(b) P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000**, *39*, 3773. doi:10.1002/1521-3773(20001103)39:21<3772::AID-ANIE3772>3.0.CO;2-5
(c) J. S. Wilkes, *Green Chem.* **2002**, *4*, 73. doi:10.1039/B110838G
(d) H. M. Zerth, N. M. Leonard, R. S. Mohan, *Org. Lett.* **2003**, *5*, 55. doi:10.1021/OL0271739
(e) A. Kumar, S. S. Pawar, *J. Org. Chem.* **2004**, *69*, 1419. doi:10.1021/JO035038J
(f) D.-G. Gu, S.-J. Ji, Z.-Q. Jiang, M.-F. Zhou, T.-P. Loh, *Synlett* **2005**, 959.

[5] (a) B. C. Ranu, A. Das, S. Samanta, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1520. doi:10.1039/B204363G
(b) B. C. Ranu, S. S. Dey, *Tetrahedron Lett.* **2003**, *44*, 2865. doi:10.1016/S0040-4039(03)00439-8
(c) B. C. Ranu, S. S. Dey, A. Hajra, *Tetrahedron* **2003**, *59*, 2417. doi:10.1016/S0040-4020(03)00289-8
(d) B. C. Ranu, S. S. Dey, *Tetrahedron* **2004**, *60*, 4183. doi:10.1016/J.TET.2004.03.052
(e) B. C. Ranu, A. Das, *Aust. J. Chem.* **2004**, *57*, 605. doi:10.1071/CH03318
(f) B. C. Ranu, R. Jana, S. S. Dey, *Chem. Lett. (Jpn.)* **2004**, *33*, 274. doi:10.1246/CL.2004.274
(g) B. C. Ranu, R. Jana, *Eur. J. Org. Chem.* **2005**, 755. doi:10.1002/EJOC.200400597
(h) B. C. Ranu, S. Banerjee, *Org. Lett.* **2005**, *7*, 3049. doi:10.1021/OL051004H
(i) B. C. Ranu, R. Jana, *Adv. Synth. Catal.* **2005**, *347*, 1811. doi:10.1002/ADSC.200505122
(j) B. C. Ranu, R. Jana, *J. Org. Chem.* **2005**, *70*, 8621. doi:10.1021/JO051373R
(k) B. C. Ranu, S. Banerjee, *J. Org. Chem.* **2005**, *70*, 4517. doi:10.1021/JO0500885
(l) B. C. Ranu, S. Banerjee, A. Das, *Tetrahedron Lett.* **2006**, *47*, 881. doi:10.1016/J.TETLET.2005.12.003
(m) B. C. Ranu, S. Banerjee, R. Jana, *Tetrahedron* **2007**, *63*, 776. doi:10.1016/J.TET.2006.10.077
(n) B. C. Ranu, K. Chattopadhyay, R. Jana, *Tetrahedron* **2007**, *63*, 155. doi:10.1016/J.TET.2006.10.035

[6] (a) W. L. Albrecht, W. D. Jones, Jr, F. W. Sweet, *J. Heterocycl. Chem.* **1978**, *15*, 209.
(b) T. Sakai, H. Tabata, A. Takeda, *J. Org. Chem.* **1983**, *48*, 4618. doi:10.1021/JO00172A035
[7] (a) G. Bellucci, G. Berti, M. Ferretti, G. Ingrosso, E. Mastrorilli, *J. Org. Chem.* **1978**, *43*, 422. doi:10.1021/JO00397A010
(b) N. L. Allinger, J. Allinger, L. R. Geller, C. Djerassi, *J. Org. Chem.* **1960**, *25*, 6. doi:10.1021/JO01071A002
[8] M. E. Garst, T. A. Spencer, *J. Org. Chem.* **1983**, *48*, 2442. doi:10.1021/JO00162A037
[9] (a) A. Kohda, K. Ueda, T. Sato, *J. Org. Chem.* **1981**, *46*, 509. doi:10.1021/JO00316A007
(b) J. Allinger, N. L. Allinger, *J. Org. Chem.* **1960**, *25*, 262. doi:10.1021/JO01072A603
[10] (a) A. A. Ponaras, O. Zaim, *J. Org. Chem.* **1987**, *52*, 5630. doi:10.1021/JO00234A025
(b) J. Righi, P. Bovicelli, A. Sperandio, *Tetrahedron Lett.* **1999**, *40*, 5889. doi:10.1016/S0040-4039(99)01213-7
[11] X.-X. Shi, L.-X. Dai, *J. Org. Chem.* **1993**, *58*, 4596. doi:10.1021/JO00069A020
[12] F. Karrenbrock, H. J. Schafer, *Tetrahedron Lett.* **1978**, *19*, 1521. doi:10.1016/S0040-4039(01)94592-7