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# Oxidation of benzylic methylene compounds to ketones with *m*-chloroperoxybenzoic acid and oxygen

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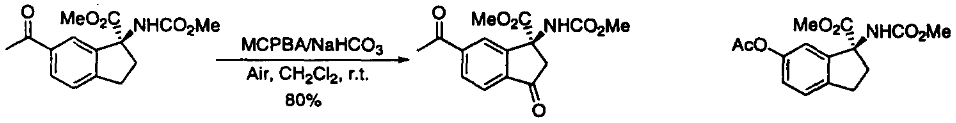
## Abstract

Suitable alkylbenzene side chains are oxidized at the benzylic position under the action of MCPBA, air and $NaHCO_3$ to provide the corresponding ketones. A possible reaction mechanism is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

As a common oxidizing reagent, *m*-chloroperoxybenzoic acid (MCPBA) has been widely used for Baeyer–Villiger oxidation of ketones,[1] epoxidation of olefins[2] and other transformations.[3–10] During studies on the synthesis of selective modulators for metabotropic glutamate receptors,[11] we needed to convert the ketone **1** into the corresponding Bayer–Villiger oxidation product **2** and the reaction shown in Scheme 1 was carried out. However, a diketone **3** but not the desired ester **2** was isolated from this reaction. The formation of **3** implied that MCPBA has the ability to oxidize benzylic methylene compounds to the corresponding ketones under certain reaction conditions. To the best of our knowledge, this behaviour of MCPBA has not been reported previously. In order to investigate the scope and limitations of this new reaction, a series of structurally and electronically different aryl compounds were subjected to the reaction conditions. The results are reported herein.



**1** **3** **2**

Scheme 1.

As illustrated in Table 1, this method worked for indane derivatives, tetralin, or simple alkyl substituted benzenes to give the corresponding ketones in good yields (entries 1–5). However, 3-ethylpyridine and 2-ethyl-1-nitrobenzene were resistant to oxidation (entries 6 and 7), which indicates that the reaction

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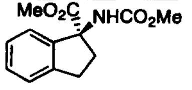
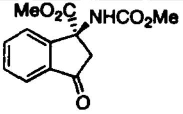
Table 1
Oxidation of benzylic methylene compounds to ketones by MCPBA and oxygen[a]

| Entry | Substrate | Product | Yield[c] |
|---|---|---|---|
| 1 |  |  | 82 |
| 2 | tetralin | tetralone | 76 |
| 3 | indane | 1-indanone | 88 |
| 4 | ethylbenzene | acetophenone | 69 |
| 5 | *n*-butylbenzene | butyrophenone | 67 |
| 6 | 3-ethylpyridine | -[b] | - |
| 7 | 2-ethyl-1-nitrobenzene | -[b] | - |
| 8 | $PhCH_2CH_2OTBDMS$ | -[b] | - |
| 9 | $PhCH_2CH_2CH_2OTBDMS$ | $PhCOCH_2CH_2OTBDMS$ | 58 |
| 10 | methyl 1-naphthylacetate | -[b] | - |
| 11 | toluene | -[b] | - |

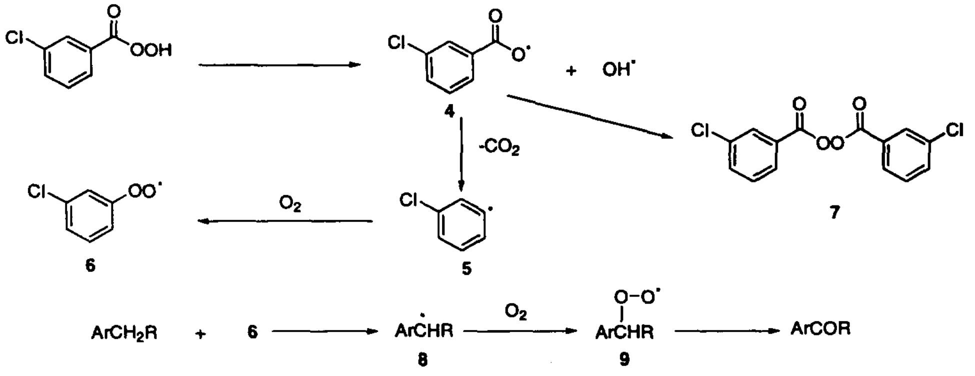
[a] Reaction conditions: substrate (1 mmol), MCPBA (2.5 mmol), $NaHCO_3$ (2.0 mmol), methylene chloride (10 mL), r.t., under air for 8-24 h. [b] No oxidized product was isolated. [c] Isolated yield.

is very sensitive to the presence of electron-withdrawing substituents. Interestingly, TBDMS protected phenethyl alcohol was not oxidized under these conditions, while TBDMS protected 3-phenyl-1-propanol could be oxidized to the desired ketone in 58% yield (compare entries 8 and 9). In addition, both methyl 1-naphthylacetate and toluene could not be oxidized under these conditions (entries 10 and 11). These results imply that both α-substituents at the benzylic position are important for the oxidation.

General procedure: To a solution of tetralin (1 mmol) in 10 mL of $CH_2Cl_2$, $NaHCO_3$ (2.0 mmol) and MCPBA (2.5 mmol) were added. The reaction mixture was stirred at room temperature under air for 12–24 h. When the reaction was completed, the mixture was diluted with 20 mL of $CH_2Cl_2$ and washed with saturated aqueous $NaHCO_3$ and brine. After being dried over anhydrous $Na_2SO_4$, tetralone was separated by flash chromatography.

Further studies indicated that this oxidation should be carried out in air because it was found that under a nitrogen atmosphere the reaction of indane with MCPBA and $NaHCO_3$ in methylene chloride did not give any indanone and the indane was recovered unchanged. This result implies that oxygen might play a key role for this oxidation reaction. It was also found that no desired oxidation product was detected by TLC in the absence of $NaHCO_3$. Chloroform was also a suitable solvent for this reaction, but the reaction time was prolonged. It should be mentioned that we also separated *m*-chlorobenzoyl peroxide **7** from the reaction mixture in about 20% yield based on the benzylic methylene compound. The structure of this side product was confirmed by X-ray analysis because of its instability to MS analysis. However, if the reaction mixture only contained $NaHCO_3$ and MCPBA, that is, if no benzylic methylene substrate was added, no *m*-chloroperbenzoic anhydride was isolated.

Based on these studies and the reports by Hirobe and co-workers[12] and Kim et al.,[13] a plausible oxidation mechanism for the present reaction is postulated as shown in Scheme 2. Initially, MCPBA may be homolysed to a hydroxyl radical and the carboxyl radical **4**, e.g. under the action of sunlight. Radical **4** may lose $CO_2$ to deliver the aryl radical **5**, which may react with oxygen to provide the arylperoxy radical **6**. After one of the hydrogen atoms of the benzylic methylene group is abstracted by the radical **6** (or the less reactive radicals **4** or **5**), the benzylic radical **8** may react with oxygen to form the peroxy radical **9**, which is convert into the isolated ketone. The *m*-chlorobenzoyl peroxide **7** may be formed by dimerization of the radical **4**.



Scheme 2.

The work described herein is characterized by the following two features: (1) it is the first example to show that MCPBA has the ability to oxidize benzylic methylene groups with the assistance of oxygen; (2) the mild conditions of the present reaction promise synthetic use for the oxidation of containing benzylic methylene groups to the corresponding carbonyl compounds.[12-14]

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## References

1. For review, see: Krow, G. R. *Org. React.* **1993**, *43*, 251.
2. For review, see: Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, p. 357.
3. Herndon, J. W.; Wu, C. *Tetrahedron Lett.* **1989**, *30*, 6461.
4. Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257.
5. Uemura, S.; Ohe, K.; Sugita, N. *J. Chem. Soc., Chem. Commun.* **1988**, 111.
6. Tamao, K.; Maeda, K. *Tetrahedron Lett.* **1986**, *27*, 65.
7. Glass, R. S.; Setzer, W. N.; Prabhu, U. S. G.; Wilson, G. S. *Tetrahedron Lett.* **1982**, *23*, 2335.
8. Yamamoto, S.; Itani, H.; Tsuji, T.; Nagata, W. *J. Am. Chem. Soc.* **1983**, *105*, 2908.
9. Srebnik, M.; Mechoulan, R. *Synthesis* **1983**, 1040.
10. Rychnovsky, S. D.; Vaidyanathan, R. *J. Org. Chem.* **1999**, *64*, 310.
11. Ma, D.; Tian, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3493. Ma, D.; Tian, H.; Sun, H.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1195. Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120.
12. Nagano, T.; Yokoohji, K.; Hirobe, M. *Tetrahedron Lett.* **1984**, *25*, 965.
13. Kim, Y. H.; Kim, K. S.; Lee, H. K. *Tetrahedron Lett.* **1989**, *30*, 6357.
14. For recent studies on the oxidation of benzylic methylene groups, see: Noureldin, N. A.; Zhao, D.; Lee, D. G. *J. Org. Chem.* **1997**, *62*, 8767, and references cited therein.