Oxidative Double Bond Cleavage of α-Substituted Styrenes with Molecular Oxygen

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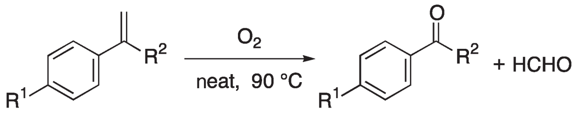
Oxidative cleavage of the carbon-carbon double bond of α-substituted styrene derivatives proceeds under an atmospheric pressure of molecular oxygen at the solventless conditions to afford the corresponding ketones in moderate yields with no requirement for transition metal catalysts or photo-activation.

Oxidation of organic compounds would ideally be achieved using molecular oxygen, because of its low cost and environmental advantage. Recently, considerable progress has been made towards realizing this goal including Mukaiyama's oxidation-reduction-hydration reaction using several transition metal catalysts,[1] Ishii's aerobic oxidation using *N*-hydroxyphthalimide,[2] and oxidation of alcohols in the presence of a catalytic amount of palladium,[3] copper,[4] or ruthenium[5] compounds. Generally molecular oxygen itself is insufficiently reactive, so it has been employed as a stoichiometric oxidant in combination with catalysts or sensitizers. It is very rare to oxidize organic compounds by the use of molecular oxygen alone with neither catalyst nor photo-activation.

On the other hand, the oxidative cleavage of alkenes to carbonyl compounds has been used as a useful synthetic tool in natural product synthesis,[6] and several procedures have been reported using molecular oxygen to achieve this transformation, and in these, transition metals[7] or sensitizers[8] have generally been employed. There are, however, a few reports in which carbon-carbon double bond is cleaved with molecular oxygen alone as shown in the following reactions: Under hash reaction conditions of high oxygen pressure ($>$20 bar of O_2) at elevated temperature,[9] several alkenes are oxidized, while very reactive *cis* β-alkoxystyrenes are converted to benzaldehyde at atmospheric pressure of oxygen at rt.[10] Though α-substituted styrenes react in chlorobenzene at 55–125 °C to afford acetophenone derivatives, yields are not satisfactory.[11]

In this paper we report that α-substituted styrene derivatives are oxidized with molecular oxygen alone, with no requirement for transition metals or photo-activation, to afford the corresponding ketone derivatives in moderate yields.

When 2-(4-methoxyphenyl)propene was treated with molecular oxygen at atmospheric pressure in CH_3CN at 90 °C for 12 h, *p*-methoxyacetophenone was found to be formed in 23% yield along with formaldehyde. First of all, solvents were screened in order to improve the yield with the results that no reaction proceeded in THF, DMF and benzene, and that the reaction proceeded only slowly in *i*-PrOH (22%). On the other hand, a much better result was obtained when the reaction was carried out without solvent (48%). The reaction temperature was also important. No reaction proceeded below 70 °C, while at higher temperature such as 110 and 130 °C, the yield decreased to 37% and 31%, respectively, with the generation of several unidentified by-products. Next, the reaction time was investigated, and it was found that the best yield of 48% was obtained after 12 h.[12]



Scheme 1.

Table 1. The oxidative cleavage of carbon-carbon double bond by molecular oxygen

Entry	Alkene	Time /h	Yield[a] /%	HOMO /kcal/mol
1	α-methylstyrene	15	41[b](41)	−208.746
2	2-(*p*-methoxyphenyl)propene	12	48(49)	−199.490
3	2-(*p*-bromophenyl)propene	15	62(69)	−211.027
4	2-(*p*-nitrophenyl)propene	115	55(87)	−227.077
5	2-(1-naphthyl)propene	15	5(50)	−198.937[c]
6	2-(2-naphthyl)propene	15	42(53)	−198.117
7	1,1-diphenylethylene	19	66(71)	−205.132
8	1,1-diphenyl-1-propene	19	31[d](32)	−203.188
9	1,1-diphenyl-2-methyl-1-propene	19	8[e](25)	−201.406

[a] Isolated yield of ketone. The figure in parentheses is the conversion yield. [b] Yield of 1-phenylethanol, which was isolated by the treatment of the reaction mixture with $NaBH_4$ instead of aq Na_2SO_3. [c] Energy of HOMO(-2), which is mostly composed of π-orbital of isopropenyl moiety, is −228.460 kcal/mol. [d] 1,1-Diphenyl-1,2-epoxypropane was obtained in 22% yield. [e] 1,1-Diphenyl-1,2-epoxy-2-methylpropane was obtained in 13% yield.

Other alkenes were examined under the same reaction conditions, the results being summarized in Table 1 along with the HOMO energy of the alkenes.[13] For α-methylstyrene, the reaction was quenched with $NaBH_4$ in order to isolate 1-phenyl-1-ethylalcohol instead of volatile acetophenone. In this case the yield was 41% (entry 1).

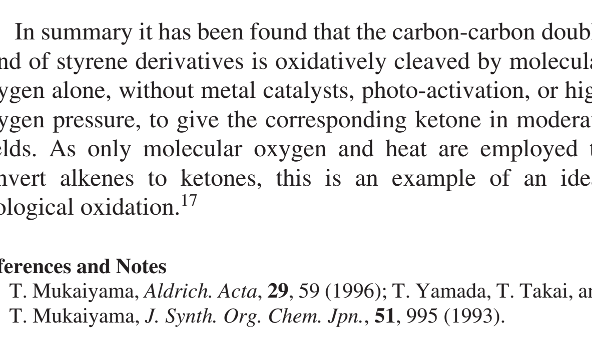
The reactivity of the alkenes is in a good correspondence with the HOMO energy of alkenes. That is, the oxidation of electron-deficient alkenes with molecular oxygen is slower, with less side reactions than that of electron-rich alkenes, making the conversion yield better. Though the reaction of 2-(4-bromophenyl)propene is slower than that of 2-(4-methoxyphenyl)propene, the conversion yield is better (69% vs 49%). For 2-(4-nitrophenyl)-propene, the reaction is much slower and the yield is 55% after 115 h with 37% recovery of the starting material, making the conversion yield 87% (entry 4).

As for naphthyl derivatives, 2-(2-naphthyl)propene reacts with molecular oxygen to afford acetonaphthone in 42% yield after 15 h (entry 6), while the reaction of the 1-naphthyl derivative is much slower and gives only a small amount of ketone with 90% recovery of the starting alkene (entry 5). The different behavior of these two naphthyl derivatives can be explained based on the difference of the energy level of π-orbital of olefinic part. That is, the highest energy of π-orbital of isopropenyl moiety of 1-naphthyl derivative (HOMO(-2),[14] −228.460 kcal/mol) is much lower than that of 2-naphthyl counterpart (HOMO, −198.117 kcal/mol).

1,1-Diphenylethylene was successfully oxidized to benzophenone in 66% yield (entry 7). In the cases of tri- and tetra-substituted alkenes, not only carbon-carbon double bond cleaved products, but also epoxides were formed. That is, benzophenone and 1,1-diphenyl-1,2-epoxypropane were obtained in 31% and 22% yields, respectively in the case of 1,1-diphenyl-1-propene, trisubstituted alkene (entry 8), while the reaction of 1,1-diphenyl-2-methyl-1-propene, tetrasubstituted alkene, was slow, affording benzophenone and 1,1-diphenyl-1,2-epoxy-2-methylpropane in 8% and 13% yields, respectively (entry 9). Low reactivity of the tetrasubstituted alkene would be attributed to the steric reason.

Styrene is not good substrate for this oxidation by molecular oxygen because several unidentified products were obtained with less than a 5% yield of benzaldehyde.

The present reaction also proceeded in the dark, indicating that it is not photochemically activated. The reaction was completely suppressed in the presence of a radical scavenger such as 2,6-di-*tert*-butyl-*p*-cresol, implying that a radical species is involved. It was also observed that electron rich alkenes are more reactive than electron poor alkenes in this reaction. Though more experiments are necessary to clarify the reaction mechanism, the results obtained so far are in good agreement with the radical chain mechanism proposed by several researchers for the oxidation of alkenes.[15] In the radical generation step would be involved a charge-transfer complex proposed by Sakuragi et al. in the oxidation of *cis* β-alkoxystyrenes.[10] That is, a charge transfer complex between an electron rich alkene and oxygen was formed, from which an electron transfer occurs to generate a radical cation. The radical thus generated reacts with the triplet ground state oxygen molecule to yield an oxygenated radical cation. As this radical cation reacts with alkene to generate a dioxetane and another radical cation, radical cation chain reaction continues.[9,16] While radical generator or photo-activation is usually employed to accelerate the initiation step, heat (90 °C) is enough for the initiation in the present reaction owing to the facile electron transfer from alkenes to oxygen because of the high HOMO level of alkenes. Neat reaction condition would be appropriate for the efficient radical chain reaction.



Scheme 2.

In summary it has been found that the carbon-carbon double bond of styrene derivatives is oxidatively cleaved by molecular oxygen alone, without metal catalysts, photo-activation, or high oxygen pressure, to give the corresponding ketone in moderate yields. As only molecular oxygen and heat are employed to convert alkenes to ketones, this is an example of an ideal ecological oxidation.[17]

References and Notes

1 T. Mukaiyama, *Aldrich. Acta*, **29**, 59 (1996); T. Yamada, T. Takai, and T. Mukaiyama, *J. Synth. Org. Chem. Jpn.*, **51**, 995 (1993).
2 Y. Ishii, S. Sakaguchi, and T. Iwahama, *J. Synth. Org. Chem. Jpn.*, **57**, 24 (1999).
3 C. Brink, I. W. C. E. Arends, and R. A. Sheldon, *Science*, **287**, 1636 (2000); T. Nishimura, T. Onoue, K. Ohe, and S. Uemura, *J. Org. Chem.*, **64**, 6750 (1999), and references cited therein.
4 I. E. Marko, P. R. Giles, M. Tsukazaki, S. M. Brown, and C. J. Urch, *Science*, **274**, 2044 (1996); I. E. Marko, A. Gautier, I. C-Regnaut, P. R. Giles, M. Tsukazaki, C. J. Urch, and S. M. Brown, *J. Org. Chem.*, **63**, 7576 (1998), and references cited therein.
5 I. E. Marko, P. R. Giles, M. Tsukazaki, I. C-Regnaut, C. J. Urch, and S. M. Brown, *J. Am. Chem. Soc.*, **119**, 12661 (1997); R. Lenz and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, **1997**, 3291.
6 Ozonization: A. H. Haines, "Methods for the Oxidation of Organic Compounds," Academic Press, London (1985). OsO_4-$NaIO_4$: R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org, Chem.*, **21**, 478 (1956). $KMnO_4$-$NaIO_4$: R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955). RuO_4-$NaIO_4$: P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
7 X. Baucherel, J. Uziel, and S. Juge, *J. Org. Chem.*, **66**, 4504 (2001); Y. H. Lin, I. D. Williams, and P. Li, *Applied Catal. A*, **150**, 221 (1997); M. T. Reetz and K. Tollner, *Tetrahedron Lett.*, **36**, 9461 (1995); K. Kaneda, S. Haruna, T. Imanaka, and K. Kawamoto, *J. Chem. Soc., Chem. Commun.*, **1990**, 1467; D. H. R. Barton, K. W. Lee, W. Mehl, N. Ozbalik, and L. Zhang, *Tetrahedron*, **46**, 3753 (1990); T. Hirao, S. Mikami, and Y. Ohshiro, *Synlett*, **1990**, 541; P. A. Ganeshpure and S. Satish, *Tetrahedron Lett.*, **29**, 6629 (1988); R. S. Drago, B. B. Corden, and C. W. Barnes, *J. Am. Chem. Soc.*, **108**, 2453 (1986), and references cited therein.
8 M. Fujita, A. Shindo, A. Ishida, T. Majima, S. Takamuku, and S. Fukuzumi, *Bull. Chem. Soc. Jpn.*, **69**, 743 (1996), and references cited therein.
9 P. E. Correa, G. Hardy, and D. P. Riley, *J. Org. Chem.*, **53**, 1695 (1988).
10 T. Kanno, M. Hisaoka, H. Sakuragi, and T. Tokumaru, *Bull. Chem. Soc. Jpn.*, **54**, 2330 (1981).
11 W. Suprun, K. Blau, and K. Reinker, *J. Prakt. Chem.*, **337**, 496 (1995); W. Suprun, *J. Prakt. Chem.*, **338**, 231 (1996); W. Suprun, *J. Prakt. Chem.*, **339**, 664 (1997); W. Suprun, *J. Prakt. Chem.*, **340**, 247 (1998); W. Suprun, *J. Prakt. Chem.*, **341**, 52 (1999).
12 The yields for other reaction times are as follows; 39% (4 h), 43% (8 h), 45% (10 h), 48% (14 h).
13 Semiempirical molecular orbital calculation at AM1 level was performed with the program package *MACSPARTANPRO* 1.0.2 of Wavefunction, Inc. (http://www.wavefun.com.). We thank Professor I. Shiina of Science University of Tokyo for the help of the calculation.
14 While HOMO of 2-(1-naphthyl)propene is composed of orbitals of naphthyl moiety, HOMO(-2) is mostly composed of π-orbital of isopropenyl moiety.
15 S. F. Nelsen, D. L. Kapp, F. Gerson, and J. Lopez, *J. Am. Chem. Soc.*, **108**, 1027 (1986); E. L. Clennan, W. Simmons, and C. W. Almgren, *J. Am. Chem. Soc.*, **103**, 2098 (1981); S. F. Nelsen and R. Akaba, *J. Am. Chem. Soc.*, **103**, 2096 (1981).
16 Epoxide would be formed according to the Mayo's mechanism proposed for oxidation of styrene and related olefins with oxygen. That is, a radical reacts with alkenes and molecular oxygen to afford copolymeric radicals, which finally either afford polymeric peroxides or undergo scission to ketone, formaldehyde and epoxide. Ratio of the formation of ketone and epoxide is dependent on the substrates. F. R. Mayo, A. A. Miller, and G. A. Russell, *J. Am. Chem. Soc.*, **80**, 2500 (1958); F. R. Mayo, *Acc. Chem. Res.*, **1**, 193 (1968).
17 Typical experimental procedure: To a glass tube of about 14 cm^3 volume was added 2-(4-methoxyphenyl)propene 93 mg and a stirring bar. The tube was filled with pure oxygen and sealed tightly, and then was deeply immersed in an oil bath at 90 °C, and the reaction mixture was stirred vigorously. After 12 h, the tube was taken out of the bath. After allowing the reaction mixture to cool to room temperature, saturated Na_2SO_3 solution was added and the organic materials were extracted 3 times with chloroform. The extracts were dried with Na_2SO_4 then evaporated, and the residue was purified by thin layer chromatography (ethyl acetate : hexane = 1 : 3) to give the ketone in 48% yield with recovery of the staring material in 3% yield.