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A simple one-pot synthesis of β-alkoxy alcohols from alkenes

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Abstract—β-Methoxy alcohols are easily obtained from the one-pot reaction of alkenes with oxone® in methanol, in the absence of any additive or catalyst. The use of other alcohols as solvents has shown that the efficiency of the process decreases with the steric hindrance of the alcohol.

β-Alkoxy alcohols constitute an important class of organic compounds,[1] and the main protocol for their synthesis is the alcoholysis of 1,2-epoxides.[2–8] For the synthesis of epoxides, oxone®[†] in the presence of transition metal complexes[9] or cyclodextrines,[10] or via the formation of dioxiranes[11] is commonly used. A few studies have reported the formation of 1,2 diols from the reaction of alkenes with oxone® in aqueous solvents.[12] That led us to envisage the one-pot synthesis of β-alkoxy alcohols from alkenes using oxone® in alcohols.

Preliminary experiments were carried out in methanol using 1-methyl-1-cyclohexene and 1 equiv of $KHSO_5$ (0.5 equiv of oxone®). A 91/9 mixture of two methoxy-methyl-cyclohexanols was obtained in 58% yield at room temperature after stirring for 24 h (Table 1, run 1), and the results were unchanged in prolonging the reaction time to 48 h (run 2). Interestingly, the use of 1 equiv of oxone® led in 24 h to an almost quantitative yield of the β-methoxy alcohols without modification of their ratio (run 3). NMR analysis of the adducts and comparison with the literature data[3] showed that the methoxy and hydroxy substituents of each isomer are in trans position, and that 2-methoxy-2-methylcyclohexanol is the main isomer. These results are in agreement with the formation of 1-methylcyclohexene oxide as an intermediate, and its alcoholysis mediated by the acidity of the solution. Indeed, the same compounds with, furthermore, similar ratios are produced from the reaction of 1-methylcyclohexene oxide with methanol in the presence of oxone, Brönstedt or Lewis acids.[4] Nevertheless, we have not been able to detect the formation of the transient epoxide in monitoring the oxidation of 1-methylcyclohexene by TLC.

Under the above experimental conditions, *trans*-2-methoxy-cycloheptan-1-ol,[5] *trans*-2-methoxy-cyclooctan-1-ol[6] and *trans*-1-methoxy-tetral-2-ol[7] have been obtained in 94–96% yields from cycloheptene, cyclooctene and 1,2-dihydronaphthalene, respectively (runs 4–6). With indene as the substrate, the oxidation led, as from 1,2-dihydronaphthalene, to the fixation of the methoxy group exclusively at the benzylic position but in contrast to 1,2-dihydronaphthalene, two diastereoisomers were produced (run 7). NMR analysis and comparison with the literature data[8b,13] showed that *trans*-1-methoxy-indan-2-ol was the main adduct. Actually, the formation of two diastereoisomers from the ring opening of indene oxide has already been observed.[14] Under our experimental conditions, a benzylic carbocation could be produced from the heterolytic cleavage of the $C^{(1)}$–O bond of the oxirane in situ formed, and its relative planar conformation would lead to the addition of the alcohol to both faces. A linear alkene, such as 1-octene was almost unreactive while styrene afforded only 21% of 2-methoxy-2-phenylethanol[4] (run 8). Elevating the temperature to 40 °C improved the yield of this β-methoxy alcohol to 47% (run 9).

Keywords: Oxone®; β-Alkoxy alcohol; β-Hydroxy ether; One-pot synthesis; Oxidation.

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[†] Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is the registered trademark from Du Pont.

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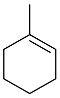
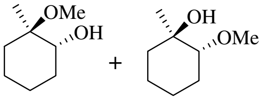
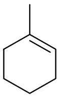
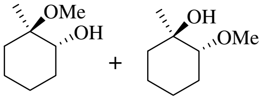
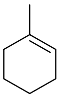
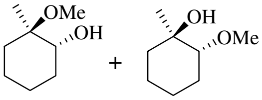
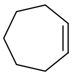
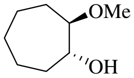
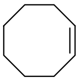
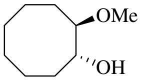
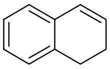
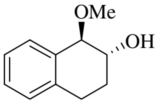
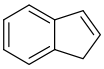
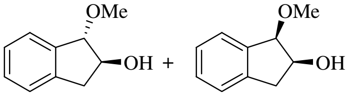
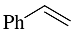
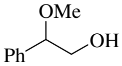
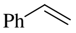
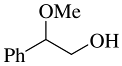
Table 1. Oxidation of alkenes with oxone® (1 equiv) in MeOH at room temperature for 24 h

Run	Alkene	Products (ratio)	Yield (%)
1[a]		 (91/9)	58
2[a,b]		 (92/8)	59
3		 (91/9)	95
4			94
5			96
6			96
7		 (57/43)	79
8			21
9[c]			47

[a] Reaction carried out with 0.5 equiv of oxone®.

[b] Reaction for 48 h.

[c] Reaction carried out at 40 °C.

The reaction was less efficient in other alcohols: 1,2-dihydronaphthalene in ethanol yielded 65% *trans*-1-ethoxy-tetral-2-ol (67% conversion) at room temperature for 24 h, while less than 10% of expected adducts were obtained in *i*-PrOH. Alcohols can provide alternative substrates for the oxidant,[12a] but the conversion observed in *t*-BuOH (⩽10%) led us to suspect that these lower efficiencies are rather due to the decrease of the solubility of oxone® in these solvents.

In conclusion, the current procedure is easy to set-up and allows the direct transformation of some alkenes to β-methoxy alcohols using oxone® and methanol as reagents, without the requirement of any additives.

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