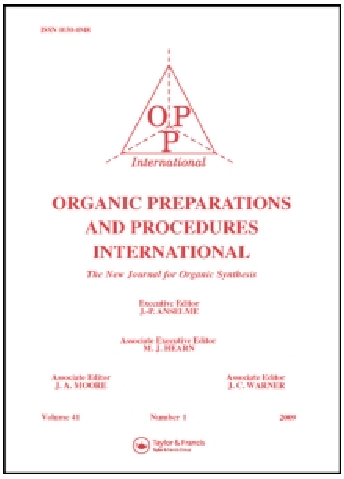

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SIMPLE AND EFFICIENT METHOD FOR THE EPOXIDATION OF α, β-UNSATURATED ALDEHYDES AND KETONES USING AQUEOUS HYDROGEN PEROXIDE-SODIUM ETHOXIDE

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To cite this Article Patra, A. , Bandyopadhyay, M. , Ghorai, S. K. and Mal, D.(2003) 'A SIMPLE AND EFFICIENT METHOD FOR THE EPOXIDATION OF α, β-UNSATURATED ALDEHYDES AND KETONES USING AQUEOUS HYDROGEN PEROXIDE-SODIUM ETHOXIDE', Organic Preparations and Procedures International, 35: 5, 515 — 520
To link to this Article: DOI: 10.1080/00304940309355863
URL: http://dx.doi.org/10.1080/00304940309355863

ORGANIC PREPARATIONS AND PROCEDURES INT., 35 (5), 515-525 (2003)

OPPI BRIEFS

A SIMPLE AND EFFICIENT METHOD FOR THE EPOXIDATION OF α, β-UNSATURATED ALDEHYDES AND KETONES USING AQUEOUS HYDROGEN PEROXIDE-SODIUM ETHOXIDE

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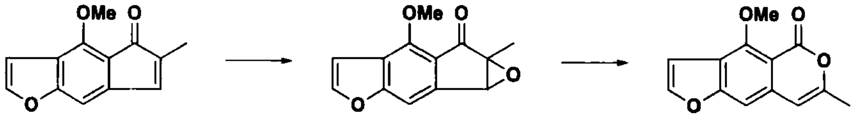
Epoxidation of carbon-carbon double bonds conjugated to carbonyl groups is a process of great synthetic utility.[1] There exist in the literature a large number of procedures[2] for the preparation of epoxides from the corresponding α,β-unsaturated carbonyl compounds. Most commonly, aqueous hydrogen peroxide in combination with inorganic bases (*e.g.*, NaOH, LiOH[3a], Na_2CO_3[3b], hydrotalcite[3c], etc.) is utilized. *tert*-Butyl hydroperoxide in the presence of different bases (Bu_4F, KF-Al_2O_3, NaOH, Triton B, KH, KO^{t}Bu, BuLi, etc.)[2] is also employed. Alternatively, anhydrous *tert*-butyl hydroperoxide[4] in the presence of an organic base, namely, DBU and cyclic guanidines[5] is recommended for the transformation where use of hydrogen peroxide fails. Occasionally, sodium hypochlorite[6] in the presence of hexamethylguanidinium chloride has also been used for such purposes. In recent years, development of H_2O_2-based heterogeneous catalytic systems[7] has been an active area of research. While the existing methods serve well the need of synthetic organic chemistry, the yields of the reactions vary widely for different substrates and on many occasions they are abysmally low for multi-step reaction sequences. The work of Wipf *et al.*[8] on the epoxidation of naphthoquinone spiroketals clearly demonstrates that the existing methods based on hydrogen peroxide may lead to decomposition of products and there is a need for further development in this area. Recently, we reported a total synthesis[9] of coriandrin (**3**) by a new route in which one of the key steps was a thermal rearrangement of epoxide **2** to isocoumarin **3**. Though the synthesis was concise, it was plagued by low yields of the epoxide **2**.

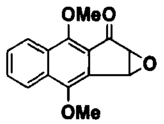
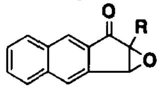
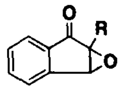
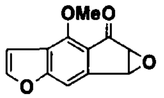
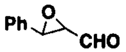
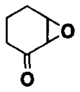
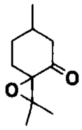
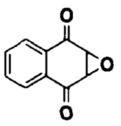
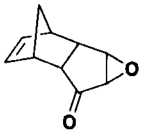


1 2 3

Similar problems are well documented in the literature. For instance, the epoxidation[10] of 1-indenone using *tert*-butyl hydroperoxide in the presence of catalytic amounts of Triton-B results in the formation of polymeric material along with a minor amount of the desired 2,3-epoxyindanone. This result is consistent with the sensitivity of indenones towards alkali. Similarly, epoxidation of 4,9-dimethoxy-*1H*-benz[*f*]inden-1-one was problematic.[11] Several known methods based on the use of hydrogen peroxide were examined. In most cases, an intractable mixture of products resulted. With H_2O_2-NaOH in a methanol-dichloromethane solvent system, the product arising out of conjugate addition of methanol was isolated as the sole product.[11] An attempt to epoxidize *1H*-benz[*f*]inden-1-one using H_2O_2-Na_2CO_3 in acetone provided a complex mixture of products. Work-up of an incomplete reaction followed by NMR analysis of the crude product indicated the presence of only two compounds: starting enone and the desired epoxide **5a**. This led us to conclude that the epoxide decomposes only on prolonged reaction time. To shorten the reaction time, we were guided by the recent finding[12] of Choudary *et al.* who demonstrated that doping of hydrotalcite clay with a strong base such as *tert*-butoxide results in an enormous increase in the rate of hydrogen peroxide assisted epoxidation of α,β-unsaturated ketones. Now we disclose a simple and efficient protocol for the epoxidation of α,β-unsaturated carbonyl compounds based on the use of 30% hydrogen peroxide in the presence of sodium ethoxide. The results are summarized in the table. The initial optimization experiments were conducted with *1H*-benz[*f*]inden-1-one (**2a**) as a substrate.

To a stirred solution of the indenone in acetone at 0° was added a solution of 30% hydrogen peroxide followed by one equivalent of sodium ethoxide in ethanol. Upon disappearance of the enone (monitored by tlc), the reaction mixture was quenched by dilution with water. Work-up provided the epoxide in sufficiently pure state for further use. Chromatographic purification of the crude material followed by recrystallization yielded epoxide **5a** in 84% yield. Similarly, epoxidation of furanoindenone (*entry* 4), worked well with H_2O_2-NaOEt. This method was then extended to other simpler enones (*entries* 5-9). The yields are either comparable to or better than the reported methods. It is difficult to propose a non-arguable explanation for the role of NaOEt base. However, it may be speculated that use of a strong base such as NaOEt produces a high concentration of $^{-}$OOH, which in turn, speeds up its conjugate addition to the β-olefinic carbon atom of the α,β-unsaturated ketone, followed by ring closure to give the corresponding epoxyketone.

Table 1. Yields and Physical Constants of Epoxycarbonyl Compounds

Entry	Epoxide		Yield (%)	mp (°C)	*lit.* mp/(bp) (°C)
1	 **4**		73	105-106	
2	 **5**	a) R = H	84	168-169	
		b) R = CH_3	71	178-179	
		c) R = C_2H_5	74	122-123	
		d) R = $CH_2CH{=}CH_2$	75	121-122	
3	 **6**	a) R = H	75	96-97	97
		b) R = CH_3	71	88-89	(64-66/0.06 mm)[13]
4	 **7**		56	150-151	
5	 **8**		60	Oil	(66-68/0.2 mm)[14]
6	 **9**		92	Oil	(56/0.2 mm)[15]
7	 **10**		94	46-47	43[16]
8	 **11**		74	132-133	133[17]
9	 **12**		95	Oil	soft solid[18]

In summary, we have shown that the combination of hydrogen peroxide and sodium ethoxide is an effective system for the epoxidation of a variety of α,β-unsaturated carbonyl compounds under mild reaction conditions and has been successfully applied to the synthesis of a number of base-sensitive 2,3-epoxyindanones. The yields are good to excellent and the procedure is convenient.

Table 2. Spectral Data and Combustion Analysis of Epoxycarbonyl Compounds

Cmpd	^{1}H NMR(δ) (CDCl$_3$)	^{13}C NMR(δ) (CDCl$_3$)	IR(cm^{-1})	MS (m/e)	Elemental Analysis (Found) C	H
4	8.33 (d, 1 H, J = 8.5), 8.11 (d, 1 H, J = 8.5), 7.69 - 7.54 (m, 2 H), 4.78 (d, 1 H, J = 2.8), 4.18 (s, 3 H), 4.15 (s, 3 H), 3.98 (d, 1 H, J = 2.8)	193.62, 154.25, 149.05, 132.15, 129.92, 129.63, 127.23, 125.01, 122.35, 122.11, 117.93, 63.24, 63.04, 56.71, 51.34	1720, 1352, 1068, 1021, 701, 616		70.31 (70.12)	4.69 (4.81)
5a	8.26 (s, 1 H), 7.98 (s, 1 H), 7.95 - 7.87 (m, 2 H), 7.64 - 7.55 (m, 2 H), 4.60 (d, 1 H, J = 2.4), 4.04 (d, 1 H, J = 2.4)	195.77, 140.11, 136.08, 133.37, 131.70, 130.49, 129.21, 128.35, 127.37, 127.01, 125.17, 56.28, 54.08	1719, 1627, 1183, 784, 691	196 (M$^+$), 168, 139 (100%), 113, 86, 57	79.59 (79.86)	4.08 (4.18)
5b	8.26 (s, 1 H), 7.93 (d, 1 H, J = 8.0), 7.92 (s, 1 H), 7.87 (d, 1 H, J = 8.0), 7.62 (t, 1 H, J = 7.6), 7.54 (t, 1 H, J = 7.6), 4.46 (s, 1 H), 2.29 (s, 3 H)	197.47, 140.39, 136.49, 133.66, 132.62, 130.86, 129.48, 128.72, 127.65, 127.32, 125.11, 63.43, 60.27, 10.89	1732, 1634, 1503, 1449, 1404, 1152, 1069, 899, 761	210 (M$^+$, 100%), 181, 168, 139, 127, 69, 43	80.00 (79.82)	4.76 (5.02)
5c	8.41 (s, 1 H), 7.93 (d, 1 H, J = 8.1), 7.92 (s, 1 H), 7.86 (d, 1 H, J = 8.1), 7.61 (t, 1 H, J = 7.2), 7.54 (t, 1 H, J = 7.2), 4.47 (s, 1 H), 2.3 - 2.21 (m, 2 H), 1.12 (t, 3 H, J = 7.2)	197.61, 140.49, 136.47, 133.64, 133.18, 130.85, 129.45, 128.70, 127.62, 127.13, 125.05, 67.04, 58.67, 18.02, 8.96.	1737, 1635, 1504, 1455, 1255, 1150, 1093, 908, 878, 761	224 (M$^+$, 100 %), 209, 181, 139, 127, 69, 57	80.35 (80.21)	5.36 (5.59)
5d	8.25 (s, 1 H), 7.79-7.84 (m, 3 H) 7.63-7.51 (m, 2 H), 5.95-5.81 (m, 1 H), 5.26-5.16 (m, 2 H), 4.47 (s, 1 H), 3.07-2.82 (m, 2 H)	196.52, 139.65, 135.98, 133.14, 132.37, 130.94, 130.37, 129.05, 128.23, 127.20, 126.82, 124.77, 119.10, 64.98, 58.02, 28.66	1729, 1634, 1035, 929, 760	236 (M$^+$) 221, 208, 179, 165, 139 (100%), 89	81.35 (81.58)	5.08 (5.27)
6b	7.2 (d, 1 H, J = 7.4), 7.55-7.53 (m, 2 H), 7.44-7.41 (m,1 H), 4.33 (s, 1 H), 1.72 (s, 3 H)		1732, 1077, 923, 850, 776, 712			
7	7.61 (d, 1 H, J = 2), 7.33 (s, 1 H), 7.01 (q, 1 H, J = 0.8), 4.45 (d, 1 H, J = 2.6), 4.25 (s, 3 H), 3.94 (d, 1 H, J = 2.4).	193.4, 159.9, 154.7, 145.1, 144.5, 119.6, 116.4, 106.2, 104.3, 60.8, 56.0, 53.1	1715, 1593, 1480, 1297, 1097, 967, 787	216 (M$^+$) 188, 173 (100%), 159, 145, 138	66.66 (66.40)	3.70 (3.46)

EXPERIMENTAL SECTION

Mps are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz (Brucker) for solutions in ^{2}H chloroform. Chemical shifts are reported as δ values and coupling constants in Hz. IR spectra were obtained on a Perkin-Elmer Model-883 as a KBr pellet or neat liquid. Combustion analysis data were collected from IACS, Kolkata. All the enones except those commercially available were prepared according the procedures described in ref. 11.

Typical Procedure: To a well-stirred solution of an enone (2.0 mmol) in acetone (5.0 mL) at 0° was added 30% hydrogen peroxide (1.5 mL) followed by a solution of NaOEt (2.0 mmol) in ethanol (1.0 mL). Stirring of the reaction mixture was continued at 0° for a period of approximately 30 min or until no starting material was detected by TLC. Water (20 mL) was then added. At this point, much of the product separated from the reaction mixture as a white solid. The mixture was extracted with ethyl acetate (3 x 20 mL) and the extract was washed with brine and dried. After removal of the solvent under reduced pressure, the resulting residue was recrystallized or chromatographed on silica gel (pet ether-chloroform gradient) to isolate the product.

Acknowledgements.- This work was supported by a grant from CSIR, New Delhi. AP and MB are thankful to CSIR, New Delhi for their research fellowships.

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AN IMPROVED PREPARATION OF 4-AMINO-3-MERCAPTOBENZOIC ACID

Submitted by (04/04/03)

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4-Amino-3-mercaptobenzoic acid (**4**) is commonly used as a precursor of 6-carboxybenzothiazole[1] which is heavily utilized by materials chemists[2] and to a lesser extent by medicinal chemists.[3] Two procedures have been reported for the synthesis of **4**; the first involves reaction of sodium sulfide[3b,4] with 4-amino-3-thiocyanatobenzoic acid (**2**), and the second[1a] requires hydrolysis of 1-amino-6-carboxybenzothiazole (**3**), derived from 4-aminobenzoic acid (**1**). Although, the later procedure[1a] can be conducted on large scale and has successfully been repeated by others (*Scheme 1*),[2d,2e,3a] it requires either catalytic[3a] or stoichiometric[1a] amounts of