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Epoxidation of α,β-Unsaturated Ketones Using Dialkylzinc-Oxygen Reagents

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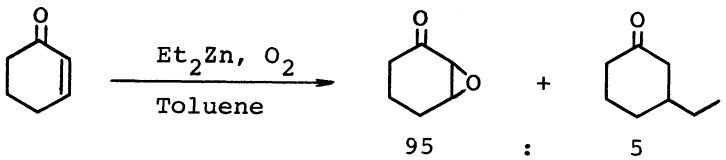
The autoxidation of the dialkylzinc well precedes the conjugate addition of this reagent to α,β-unsaturated ketones, which undergo nucleophilic epoxidation with the resulting alkylperoxozinc species.

There has been recent progress in enantioselective addition of dialkylzincs to an aldehyde in the presence of a catalytic amount of chiral aminoalcohols owing to the low nucleophilic reactivity of dialkylzincs themselves.[1] Also, the selective conjugate addition of lithium trialkylzincates to α,β-unsaturated ketones[2] has found their synthetic usefulness in the asymmetric reactions reported by us.[3]

We wish to report that the autoxidation of dialkylzincs takes place readily prior to attack of the latter on the α,β-unsaturated ketones present and that the resulting alkylperoxozinc species acts as an efficient epoxidizing reagent. It is well known that organomagnesiums or aluminums, as well as dialkylzincs, are easily oxidized at low temperature with oxygen (or dry air) to form the corresponding alkylperoxometal intermediate. These intermediates, however, rapidly undergo disproportionation to form eventually alkoxymetal compounds[4] and hence there seem to be few reports on the utilization of these alkylperoxo intermediates for the synthetic purposes.

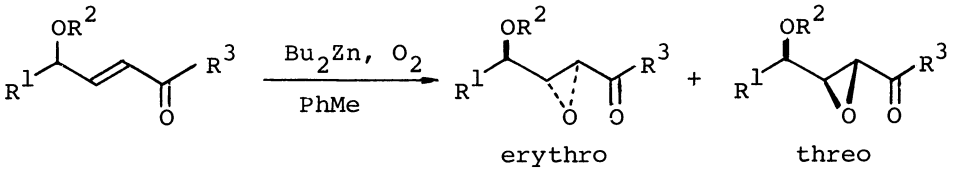
A solution of 2-cyclohexenone (96.1 mg, 1.0 mmol) and diethylzinc (1 mol·dm^{-3} in toluene, 1.2 ml) in dry toluene (5 ml) was stirred and treated with oxygen in a balloon at room temperature. Tlc monitoring revealed that the enone disappeared completely in 1 h, forming two new components. Glc analysis (Silicone DC-550 at 130 °C, 3 m) indicated two components in a ratio 5 : 95. The reaction mixture was quenched with aqueous NH_4Cl and brine, and the organic layer was dried ($MgSO_4$). The filtered solution was subjected to chromatography (Silica gel, ether-hexane) to separate 3-ethylcyclohexanone[5] and 2,3-epoxycyclohexanone, respectively, both of which were identified by ^1H NMR (Eq. 1). In exactly the same manner as above, the epoxidation was carried out in dry ether (5 ml). The reaction proceeded much slower than in toluene, being completed in 5 h at room temperature. In addition, the contamination of the minor component, 3-ethylcyclohexanone, increased.



(1)

The novel epoxidation was applied to certain γ-alkoxy-α,β-unsaturated ketones in order to look at the diastereoselectivity. Thus, (E)-4-benzyloxy-1-phenyl-2-alkenones and analogs were prepared and subjected to epoxidation in essentially the same manner as described above. It was found that (E)-4-benzyloxy-1-phenyl-2-pentenone (**1a**) afforded erythro- (**2a**)[6] and threo-4-benzyloxy-1-phenyl-2,3-epoxy-pentanone (**2a'**)[6] in a ratio 83:17, whereas (E)-4-benzyloxy-5-methyl-1-phenyl-2-hexenone (**1b**) gave almost exclusively the erythro isomer (**2b**).[7] In every case the epoxidation proceeded smoothly at room temperature in a few hours. All results for the present diastereoselective epoxidation of γ-alkoxy-α,β-unsaturated ketones are given in Table 1.

Table 1. Epoxidation of γ-Alkoxy-α,β-unsaturated Ketones with Dialkylzinc/oxygen



erythro threo

Entry[a]	R^1	R^2	R^3	Time/h	Yield/%[b]	erythro : threo[c]	
1	Me	Bn	Ph (**1a**)	3	78	83	17
2	i-Pr	Bn	Ph (**1b**)	2	87	>99	1
3[d]	i-Pr	Bn	Ph (**1b**)	4.5	77	>99	1
4	i-Pr	MOM	Ph	1	74	>99	1
5	i-Pr	Bn	Me (**3**)	18	69	>99	1
6	i-Pr	MOM	Me (**4**)	24	34	>99	1
7[e]	i-Pr	MOM	Me	14	58	>99	1

a) Reaction using a substrate (0.35 mmol) and Bu_2Zn (0.64 mol·dm^{-3} in PhMe, 0.45 mmol) under oxygen. b) Isolated yield. c) Determined by HPLC (SI-60-5). d) Et_2Zn was used. e) Bu_2Zn (3 equiv.) was used.

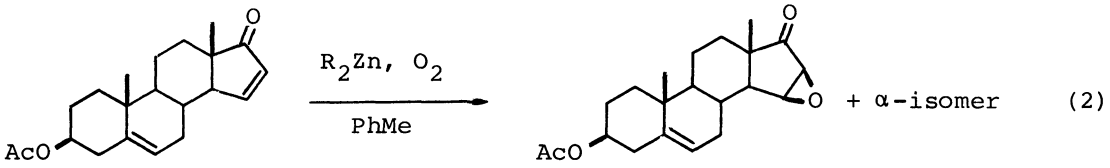
It is evident that the steric requirement of R^1 (Me or i-Pr) plays a crucial role to direct an erythro-selective attack of the nucleophilic reagent (Entries 1 and 2). Both (E)-5-benzyloxy-6-methyl-3-hepten-2-one (**3**) and (E)-5-methoxymethoxy analogue (**4**) reacted very slowly but with excellent diastereoselectivity to give the erythro epoxidation product in moderate yields(Entries 5-7). Dibutylzinc and diethylzinc were equally useful for the present epoxidation (Entries 2 and 3).

It is well documented that α,β-unsaturated ketones can be epoxidized using nucleophilic reagents such as the sodium salts of hydrogen peroxide or t-butyl-hydroperoxide.[8] In order to estimate a plausible reactive species of the dialkylzinc-oxygen system, three different and related experiments were carried out: (i) Reaction of Bu_2Zn with an equivalent amount of anhydrous t-BuO_2H took place at 0 °C to give t-BuO_2ZnBu, which was, in turn, allowed to react with enone **1b** under an argon atmosphere at room temperature to give **2b** in 81% yield. (cf. entry 2 in Table 1) (ii) When **1b** was treated with half an equivalent amount of Bu_2Zn under an oxygen atmosphere, **2b** was obtained in 35% yield along with

unreacted **1b** in 54% recovery. (iii) According to the reported procedure,[9] $(EtO_2)_2Zn$ was prepared *in situ* by treating Et_2Zn with oxygen at room temperature overnight and reacted with **1a**. After 5 h of reaction, there were obtained **2a** and **2a'** in only 5% combined yield and 93% of the starting **1a** was recovered unchanged. Therefore, it is most probable that the nucleophilic epoxidation of enones under the present conditions proceeds with ROOZnR but neither with ROOZnOR which must be produced by the second autoxidation of the primary product, ROZnR, nor with $(ROO)_2Zn$ which may be generated, if any, prior to the epoxidation of enones.

It should be noted that the epoxidation with dialkylzinc/oxygen system is very chemoselective in carrying out only for enones. Attempted epoxidation of α,β-unsaturated esters such as dimethyl benzylidenemalonate and ethyl (*E*)-4-benzyloxy-2-pentenoate recovered starting materials intact.

Synthetic application of the epoxidation using dialkylzinc/oxygen may be found in the following example: 3β-acetoxy-5,15-androstadien-17-one (0.7 mmol) was as readily epoxidized as 2-cyclohexenone with use of Et_2Zn (0.84 mmol) in toluene (5 ml) under oxygen in 4 h to yield 3β-acetoxy-15,16β-epoxy-5-androsten-17-one[10] and its α-isomer[10] in a 50:50 ratio in 76% combined yield. When Bu_2Zn was used, the isomer ratio of the products (88% combined yield) changed signifi-



+ α-isomer (2)

R=Et (76%)	50	:	50
R=Bu (88%)	64	:	36

cantly to 64:36 (Eq. 2). It was previously found that the 3β-(*t*-butyldimethylsilyl)oxy analog was epoxidized using *t*-BuO_2H/KH in THF to give exclusively the 15,16β-epoxy derivative.[11]

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References

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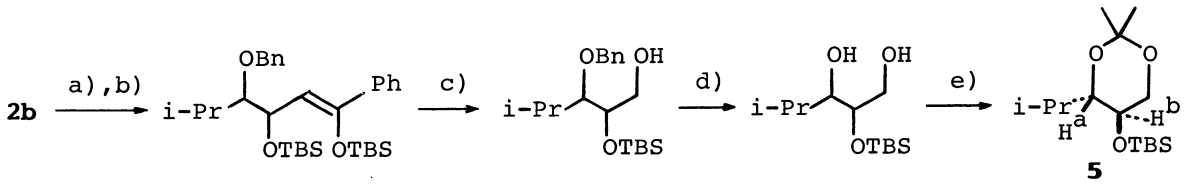
5) Boron trifluoride-mediated conjugate addition of dialkylzincs to α,β-unsaturated ketones was found to be useful and will be reported elsewhere.

6) **2a**: ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 1.36(d, J=6.4 Hz, 3H), 3.20(dd, J=2.2, 4.2 Hz, 1H), 3.74(dq, J=4.2, 6.4 Hz, 1H), 4.30(d, J=2.2 Hz, 1H), 4.64(d, J=2 Hz,

1H), 7.34(s, 5H), and 7.3-8.1(m, 5H). ^{13} NMR (22.5 MHz) δ 17.6, 55.1, 61.9, 71.9, 72.7, 127.7, 128.7, 133.8, 135.5, 138.2, and 194.2.

2a': ^{1}H NMR 1.36(d, J=6.4 Hz, 3H), 3.29(dd, J=2.2, 6.4 Hz, 1H), 3.57(dq, J=6.4, 1H), 4.09(d, J=2 Hz, 1H), 4.69(d, J=12.1 Hz, 1H), 4.76(d, J=12.1 Hz, 1H), 7.35(s, 5H), and 7.3-8.1(m, 5H). Diastereomeric identification of **2a** and **2a'** was carried out as follows: a mixture of these products was treated with a slight excess of Me_2CuLi in ether at -70 °C followed by aqueous workup to give the corresponding aldol products. The NMR spectral data of the minor component arising from **2a'** was identical with those of the threo isomer which was obtained from the reaction of α-benzyloxypropionaldehyde with an acetophenone enolate: C. H. Heathcock, S. K. Davidson, K. T. Hug, and L. A. Flippin, J. Org. Chem., 51, 3027 (1986); J. R. Bull and H. H. Lachmann, Tetrahedron Lett., 1973, 3055.

7) **2b**: ^{1}H NMR 1.02(d, J=6.8 Hz, 6H), 1.94(d of septet, J=5.2, 6.8 Hz, 1H), 3.27(dd, J=2, 3.8 Hz, 1H), 3.42(ddd, J=0.5, 3.2, 5.2 Hz, 1H), 4.35(d, J=2 Hz, 1H), 4.59(d, J=11.8 Hz, 1H), 4.69(d, J=11.8 Hz, 1H), 7.33(s, 5H), and 7.3-8.1(m, 5H). ^{13}C NMR 18.0, 18.6, 31.5, 54.8, 60.3, 73.8, 81.3, 127.9, 128.5, 128.9, 133.9, 135.8, 138.5, and 194.6. The exclusive product **2b** was converted into 2,2-dimethyl-4-isopropyl-5-(t-butyldimethylsilyl)oxy-1,3-dioxolane (5) in the following sequence of reactions:



a) Me_2CuLi/Et_2O; b) TBSOTf; c) O_3/CH_2Cl_2, $NaBH_4$; d) Na/liq.NH_3; e) CH_2=CMeOMe/cat. $POCl_3$. (TBS=t-butyldimethylsilyl)

Configurational assignment of the erythro-**2b** was made on the basis of the vicinal coupling, $J_{H^aH^b}$ = 9 Hz, of **5**.

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10) β-Epoxy isomer: ^{1}H NMR 1.08(s, 3H), 1.17(s, 3H), 1.64(s, 3H), 3.30(d, J=2.9 Hz, 1H), 3.82(br d, J=2.9 Hz, 1H), 4.2-4.8(m, 1H), 5.3-5.4(m, 1H), and 0.9-2.6(m, 15H).
^{13}C NMR 19.0, 19.2, 20.0, 21.3, 27.7, 28.7, 30.3, 32.9, 36.9, 37.1, 38.2, 42.0, 51.2, 53.2, 53.4, 55.6, 73.6, 121.2, 140.7, 167.4, and 170.4.
α-Epoxy isomer: ^{1}H NMR 1.05(s, 3H), 1.56(s, 3H), 2.04(s, 3H), 3.4-3.8(m, 2H), 4.2-4.8(m, 1H), 5.3-5.5(m, 1H), and 0.7-2.6(m, 15H).
^{13}C NMR 19.1, 21.3, 22.1, 24.1, 27.6, 31.2, 31.9, 36.7, 36.8, 37.8, 39.2, 40.7, 48.1, 49.1, 49.5, 53.3, 73.4, 120.7, 140.3, 168.1, and 170.4.

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