1,3-Dioxolane Formation via Lewis Acid-Catalyzed Reaction of Ketones with Oxiranes

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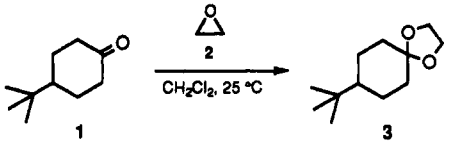
1,3-Dioxolanes are among the most widely used protecting groups for carbonyl compounds.[3] The most common methods for the synthesis of these acetals employ protic acids, aqueous conditions, or high temperatures, making them unsuitable for the protection of sensitive compounds. A gentle, low temperature method for the formation of ethylene acetals might involve the acid-catalyzed addition of an epoxide to a ketone. Bogert and Roblin[4] and later Bersin and Willfang[5] demonstrated in the 1930s that oxiranes will react with ketones and aldehydes in the presence of $SnCl_4$ to form 1,3-dioxolanes in low to moderate yields. Since that time sporadic reports of ketalizations using oxiranes in the presence of various Lewis acids have appeared.[6] To date, however, no studies on side reactions, the effect of varying reaction conditions, or the scope of this aprotic oxirane formation have been reported. Herein we wish to report an optimization of this procedure for cyclic acetal formation from carbonyl compounds and ethylene oxide catalyzed by substoichiometric amounts of $BF_3{\cdot}OEt_2$, as well as a partial survey of its scope and limitations.

Initial studies on the Lewis acid-mediated reaction of 4-*tert*-butylcyclohexanone (1) with propylene oxide showed BF_3 to be the most effective catalyst. Both $SnCl_4$ and $TiCl_4$ gave little or no acetal. Use of 4 equiv of $BF_3{\cdot}OEt_2$ led to a 1:1 mixture of the desired acetal and starting ketone. Unreacted ketone remained even in the presence of stoichiometric amounts of BF_3. Further optimization of the BF_3-mediated dioxolane formation was conducted with ketone 1 and ethylene oxide. Reactions were monitored by GC using uncorrected peak areas obtained from an FID detector. Because the mass balance for this reaction was very high (*vide infra*), internal standards were deemed unnecessary. As summarized in Table I, optimization studies led to a series of general conclusions about the BF_3-mediated acetal formation. The best yields of the desired ethylene acetal 3 were obtained using a substoichiometric amount of BF_3 (Table I, entries 1-4). An excess of epoxide is not required to obtain a high ratio of ethylene acetal to ketone (entry 5). The rate of the addition of the Lewis acid appears to play a slight role in maximizing the yield of acetal (compare entries 6 and 7). In many cases it was noted that continued reaction after the maximum ratio of ethylene acetal to ketone was obtained led to steadily declining ratios (entries 8-12). Based on these observations, all subsequent reactions were run at room temperature with the addition of ethylene oxide (1.0 M in CH_2Cl_2) over 20 min. Reactions were followed by GC and/or TLC and were quenched with triethylamine when the maximum ratio of acetal to ketone was observed.



1 3

The best results for this methodology were found for acetal formation with cyclic ketones (Table II, entries 1-3). Steric hindrance about the carbonyl strongly inhibits acetal formation (entry 4), as does the presence of carbocation stabilizing groups (*vide infra*).

Ethylene acetal formation from α,β-unsaturated ketones using ethylene glycol and protic acids typically leads to a thermodynamic mixture of α,β- and β,γ-unsaturated acetals. Thus, for example, reaction of cholest-4-en-3-one with ethylene glycol in the presence of *p*-TSA affords cholest-5-en-3-one ethylene acetal in high yield.[7-9] Traditionally, isomerization has been lowered by minimizing the amount of protic acid utilized in acetal formation,[10] or using weak protic acids.[11] More recently, Noyori *et al.*, and later Wu and Wetzel, have shown that use of

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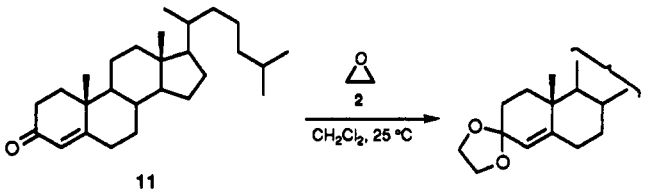
Table I. Effect of Varying Reaction Conditions on the Yield of 4-*tert*-Butylcyclohexanone Ethylene Acetal (3)[a]

entry	BF_3·OEt_2 (equiv)	ethylene oxide (equiv)	addition time (min)[b]	reaction time (min)[c]	final GC ratio acetal:ketone
1	0.1	10.0	<1	>120	26.8:1
2	1.0	10.0	<1	>120	1.8:1
3	2.0	10.0	<1	>120	1.2:1
4	4.0	10.0	<1	>120	0.3:1
5	0.1	1.3	20	120	7.7:1
6	0.1	10.0	10	60	3.0:1
7	0.1	10.0	420	60	1.1:1
8	0.1	10.0	20	15	2.6:1[d]
9	0.1	10.0	20	25	4.0:1[d]
10	0.1	10.0	20	33	4.9:1[d]
11	0.1	10.0	20	43	3.6:1[d]
12	0.1	10.0	20	50	1.2:1[d]

[a] Addition of a 1.0 M solution of ethylene oxide to a 1.0 M solution of ketone 1 and BF_3·OEt_2 at room temperature. [b] Defined as the time from the beginning of ethylene oxide addition until addition was complete. [c] Defined as the time from the completion of ethylene oxide addition until the final GC was taken. [d] Reactions run using cyclohex-2-en-1-one (9) as substrate.

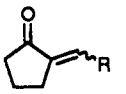
trimethylsilyl triflate to catalyze acetal formation with 1,2-bis(trimethylsilyloxy)ethane significantly decreases double-bond migration.[12] This suggests that kinetic products can be obtained on using Lewis acids, such as BF_3, for which equilibrium is slow. Thus, while the results obtained on reacting cyclohex-2-en-1-one with ethylene oxide in the presence of BF_3 (9, entry 5) were quite poor, no isomerization of the double bond was observed in the product.[12a,13,14] Cholest-4-en-3-one (11) afforded an excellent yield of the desired acetal (12, entry 6). Again, no product resulting from the migration of the Δ^4-double bond into the B ring was observed in TLC or the ^1H or ^{13}C NMR of crude reaction mixtures.



11 12

A series of attempts were made to protect heteroatom-substituted α-methylenecyclopentanones (21; R = OH, OAc, I). The oxygen-substituted systems returned starting material quantitatively. Presumably, this is due to the loss of resonance stabilization on conversion of the carbonyl carbon into an sp^3 center. Unfortunately, the iodide decomposed under the reaction conditions. In no case was more than a trace of the desired acetal observed.

The use of epoxides for acetal formation offers the advantage of being extremely gentle, operating at room temperature and under aprotic conditions. In addition, preliminary isolation of the products simply involves removal of reactants under vacuum. Also, yields do not appear to be dependent on scale of the reaction. The yield



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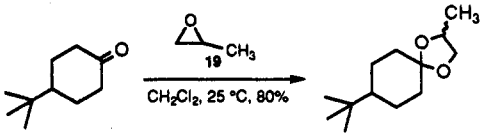
of acetal 12 remained consistently high, whether run using 1 mmol (93% yield) or 11 mmol (95% yield) of enone 11.

Protection of aldehydes and acyclic ketones proceeded in low yield, affording starting material as the only byproduct observed (entries 7–9). These results suggest the possibility of the selectiev protection of a cyclic ketone in the presence of an aldehyde or an acyclic ketone.

The Lewis acid-mediated reaction of an oxirane with a carbonyl has been reported to proceed via complexation of the acid with the epoxide oxygen, followed by nucleophilic ring-opening of the epoxide by the carbonyl oxygen and finally dioxolane ring formation.[15] Because each step of the reaction is reversible, 1,3-dioxolanes can be converted into the corresponding ketone in the presence of catalytic BF_3.[16,17] The BF_3-mediated acetal formation must suffer from a similar side reaction. Thus, acetal formation is sensitive to both structural factors such as steric hindrance which slows formation of the acetal and electronic factors which accelerate decomposition of the acetal.

In a brief examination of the use of other oxiranes in this reaction, it was found that reaction of ketone 1 with propylene oxide (19) afforded the corresponding acetal as a mixture of diastereomers in similar yield to that observed with ethylene oxide (Table II, entry 10). In contrast, oxiranes with resonance stabilizing groups (styrene oxide, *trans*-stilbene oxide) failed to give any of the desired acetal, affording returned starting ketone in quantitative yield.



1 20

In summary, BF_3 mediates the reaction of oxiranes with cyclic ketones and enones leading to a gentle method for acetal formation. The approach is applicable to both large- and small-scale reactions. The selectivity of acetal formation is currently under investigation.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent. IR spectra were obtained from neat films unless otherwise noted. MS were obtained at an ionization potential of 70 eV. Distillations were conducted using a bulb-to-bulb apparatus (Aldrich Kugelrohr); ot refers to the Kuglerohr oven temperature range over which distillation occurred. BF_3·Et_2O and CH_2Cl_2 (CaH_2) were distilled immediately prior to use. Ethylene oxide, propylene oxide, and ketones 1, 4, 6, 8, 11, 15, and 17 were obtained commercially and used without purification. Compounds 9 and 13 were distilled prior to use.

Representative Procedure. Cholest-4-en-3-one Ethylene Acetal (12, Entry 6). To a solution of cholest-4-en-3-one (11) (4.23 g, 11 mmol) and BF_3·OEt_2 (0.135 mL, 1.1 mmol) in dry

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Table II. Reaction of Carbonyl Compounds with Oxiranes in the Presence of BF_3·OEt_2[a]

entry	carbonyl compound	oxirane	acetal	reaction time (min)[b]	isolated yield of ketone (%)	isolated yield of acetal (%)
1	4-*tert*-butylcyclohexanone (1)	ethylene oxide (2)	ethylene acetal (3)	15	14	79
2	cyclopentanone (4)	2	ethylene acetal (5)	2	5	79
3	cycloheptanone (6)	2	ethylene acetal (7)	70	18	84
4	2,6-dimethylcyclohexanone (8)	2			100	0
5	cyclohex-2-en-1-one (9)	2	ethylene acetal (10)[c]	30	*d*	41
6	Δ^4-cholestenone (11)	2	ethylene acetal (12)[c]	20		95
7	3-phenylpropanal (13)	2	ethylene acetal (14)	60	*d*	52
8	2-octanone (15)	2	ethylene acetal (16)	120	*d*	47
9	acetophenone (17)	2	ethylene acetal (18)	1	43	42
10	4-*tert*-butylcyclohexanone (1)	propylene oxide (19)	methylethylene acetals (20)[e]	90	9	80

[a] Addition of a 1.0 M solution of ethylene oxide to a 1.0 M solution of carbonyl compound and BF_3·OEt_2 at room temperature. [b] Defined as the time from the completion of ethylene oxide addition until the reaction was quenched with Et_3N. [c] Carbon–carbon double bond did not isomerize during the reaction. [d] Remaining ketone was reduced with $NaBH_4$ to facilitate isolation of the acetal. [e] Isolated as a pair of diastereomers.

CH_2Cl_2 (110 mL) at rt in a flask equipped with a dry ice/acetone cooled condenser was added over 20 min a 0 °C solution of ethylene oxide (110 mL, 1.0 M in CH_2Cl_2), via cannula. The reaction was monitored by TLC and was quenched by the addition of Et_3N (1 mL) 20 min after the addition of ethylene oxide was complete. The resulting solution was concentrated under reduced pressure to give a white solid which was recrystallized from methanol to afford acetal **12** (4.47 g, 95%): mp 78–79 °C [lit.[10] mp 95–97 °C]; TLC (20% EtOAc/hexane) R_f 0.61; IR (CCl_4) 1655, 1145, 1130, 1100 cm^{-1}; ^1H NMR δ 0.67 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.03 (s, 3H), 0.92–2.25 (m, 26H), 3.65–3.67 (m, 2H), 3.68–4.02 (m, 4H), 5.22 (s, 1H); ^{13}C NMR δ 11.9, 17.6, 18.6, 21.1, 22.5, 22.8, 23.8, 24.2, 28.0, 28.2, 30.0, 32.1, 32.5, 34.9, 35.8 (2C), 36.1, 37.5, 39.5, 39.5, 39.8, 42.4, 53.9, 56.0, 64.2, 70.6, 106.2, 119.5, 151.8.

Acetals **3**, **5**, **7**, **10**, **14**, **16**, **18**, and **20** were purified using radical chromatography (SiO_2). Spectral analyses (IR, LRMS, and ^1H and ^{13}C NMR) for acetals **3**,[18] **5**,[19] **7**,[19,20] **10**,[21] **14**,[22] **16**,[23] and **18**[24] were in agreement with those previously reported. GC, TLC, ^1H and ^{13}C NMR analyses indicated that all products were >95% pure.

8-*tert*-Butyl-1,4-dioxaspiro[4.5]decane (3, entry 1): yield 0.31 g (79%); ot (bulb-to-bulb) 65–72 °C (0.2 mmHg) [lit.[18a] bp 65–67 °C (0.4 mmHg)]; IR 1125, 1100 cm^{-1}; ^1H NMR δ 0.87 (s, 9H); 1.02 (tt, J = 11.9, 3.0 Hz, 1H), 1.28 (app qd, J = 13.1, 3.9 Hz, 2H), 1.50 (td, J = 13.6, 4.6 Hz, 2H), 1.76 (br t, J = 13.7 Hz, 4H), 3.94 (s, 4H); ^{13}C NMR δ 24.8 (2C), 27.7 (3C), 32.3, 35.2 (2C), 47.2, 64.1, 64.2, 109.0; LRMS m/z (rel intensity) 198 (1.4).

Spectra of acetal **3** were identical with those of an independently prepared sample (ethylene glycol, *p*-TSA, C_6H_6; 82%).

1,4-Dioxaspiro[4.4]nonane (5, entry 2): yield 0.21 g (79%); IR 1125 cm^{-1}; ^1H NMR δ 1.65–1.73 (m, 4H), 1.75–1.81 (m, 4H), 3.91 (s, 4H); ^{13}C NMR δ 23.5 (2C), 35.9 (2C), 64.2 (2C), 118.5; LRMS m/z (rel intensity) 128 (7.5).

1,4-Dioxaspiro[4.6]undecane (7, entry 3): yield 0.27 g (84%); IR 1095 cm^{-1}; ^1H NMR δ 1.57 (br s, 8H); 1.79 (br d, J = 9.2 Hz, 4H), 3.89 (s, 4H); ^{13}C NMR δ 22.4 (2C), 29.3 (2C), 38.4 (2C), 63.9 (2C), 113.0; LRMS m/z (rel intensity) 156 (10).

1,4-Dioxaspiro[4.5]dec-6-ene (10, entry 5): reaction mixture was treated with $NaBH_4$ (1 mmol) prior to separation using SiO_2; yield 0.12 g (41%); IR 3020, 1145, 1110, 940 cm^{-1}; ^1H NMR δ 1.75–1.82 (m, 4H); 2.03–2.04 (m, 2H), 3.95–4.00 (m, 4H), 5.59 (dt, J = 10.1, 2.1 Hz, 1H), 5.97 (dt, J = 10.1, 3.7 Hz, 1H); ^{13}C NMR δ 20.7, 24.8, 33.5, 64.4, 105.6, 127.5, 132.8; LRMS m/z (rel intensity) 140 (1.3).

2-(2-Phenylethyl)-1,3-dioxolane (14, entry 7): reaction mixture was treated with $NaBH_4$ (2 mmol) prior to separation using SiO_2; yield 0.18 g (52%); ot (bulb-to-bulb) 78–85 °C (0.25 mmHg) [lit.[22] bp 115–120 °C (5 mmHg)]; ^1H NMR δ 1.95–2.04 (m, 2H), 2.73–2.78 (m, 2H), 3.84–4.02 (m, 4H), 4.89 (t, J = 4.7 Hz, 1H), 7.16–7.30 (m, 5H); ^{13}C NMR δ 30.1, 35.4, 64.8 (2C), 103.7, 125.7, 128.3 (4C), 141.5; LRMS m/z (rel intensity) 178 (3.0).

Spectra of acetal **14** were identical with those of an independently prepared sample (ethylene glycol, *p*-TSA, C_6H_6; 85%).

2-Hexyl-2-methyl-1,3-dioxolane (16, entry 8): reaction mixture was treated with $NaBH_4$ (4 mmol) prior to separation using SiO_2; yield 0.16 g (47%); at (bulb-to-bulb) 43–45 °C (0.5 mmHg) [lit.[23a] bp 83 °C (20 mmHg)]; ^1H NMR δ 0.88 (br t, J = 5.8 Hz, 3H), 1.29–1.41 (m, 6H), 1.31 (s, 3H), 1.60–1.65 (m, 2H), 3.91–3.96 (m, 4H); ^{13}C NMR δ 14.0, 22.6, 23.7, 24.0, 29.5, 31.8, 39.2, 64.6 (2C), 110.2; LRMS m/z (rel intensity) 157 (M^+ – 15, 100).

Spectra of acetal **16** were identical with those of an independently prepared sample (ethylene glycol, *p*-TSA, C_6H_6; 92%).

2-Methyl-2-phenyl-1,3-dioxolane (18, entry 9): yield 0.14 g (42%); IR (CCl_4) 3030, 3010, 1050 cm^{-1}; ^1H NMR δ 1.58 (s, 3H); 3.37–3.75 (m, 2H), 3.89–3.97 (m, 2H), 7.17–7.29 (m, 3H), 7.38–7.42 (m, 2H); ^{13}C NMR δ 28.4, 65.1 (2C), 109.5, 126.0 (2C), 128.5, 128.9 (2C), 144.2; LRMS m/z (rel intensity) 149 (M^+ – 15, 100).

4-Methyl- and 5-methyl-8-*tert*-butyl-1,4-dioxaspiro[4.5]decane (20, entry 10): yield 0.35 g (80%); TLC (10% EtOAc/hexane) R_f 0.50; ^1H NMR δ 0.87 (s, 9H), 1.26 (d, J = 6.1 Hz, 1.5H), 1.28 (d, J = 6.1 Hz, 1.5H), 1.25–1.90 (m, 9H), 3.43 (app t, J = 9.7 Hz, 1H), 4.01–4.06 (m, 1H), 4.09–4.26 (m, 1H); ^{13}C NMR δ 18.7, (C-4 + C-5 CH_3), 24.5, 24.6, 24.7, 24.8, 27.6 ($(CH_3)_3C$), 32.2-($(CH_3)_3C$), 35.1, 35.6, 36.4, 37.0, 47.0, 47.2, 70.3, 70.5, 71.4, 71.5, 109.1; LRMS m/z (rel GC retention, rel intensity) GC peak a 212 (1.00, 12), GC peak b 212 (1.02, 10).

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