Pergamon

Tetrahedron Letters, Vol. 37, No. 1, pp. 115-118, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02087-X

Selective Oxidation of *O*-Isopropylidene Derivatives of Diols to 2-Hydroxy Ketones Employing Dioxiranes†

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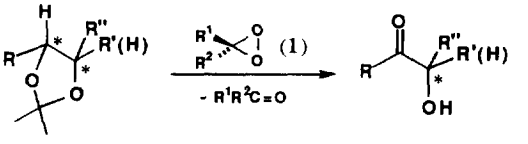
Abstract: Employing dimethyldioxirane (**1a**) or methyl(trifluoromethyl)dioxirane (**1b**), the direct conversion of *O*-isopropylidene derivatives of 1,2-diols into the corresponding 2-hydroxy ketones can be achieved in high yield and under mild conditions; optically active acetonides are transformed into homochiral 2-hydroxy ketones in high optical yield, and with preservation of configuration at the C*-OH chiral center proximal to that undergoing oxidation to carbonyl. The diacetonide of 1,4-Diphenylbutan-1,2:3,4-tetraol could be selectively converted into 1,4-diphenyl-1-oxo-2-hydroxy 3,4-acetonide, with removal of just one acetonide moiety.

In recent times, the availability of dioxiranes **1**[1] has urged the intensive utilization of these powerful (and yet selective)[1a] oxidants to carry out a great variety of synthetically useful transformations.[1] For instance, in 1993 we reported on the high-yield conversion of optically active 1,2-diols into homochiral 2-hydroxy ketones with practically no loss of optical purity.[2] This same transformation has been recently revisited and termed "desymmetrization" of diols by Mincione *et al*.[3] Protection of 1,2-diols as cyclic acetals and ketals is a practice common in organic synthesis.[4] Also, conversion of diols and polyols into the corresponding acetonides and polyacetonides is occasionally useful in separation and identification procedures.[5] However, the oxidative cleavage of *O*-isopropylidene derivatives into 2-hydroxy ketones is difficult to achieve in good yield using common oxidation reagents.

We now report that the application of dimethyldioxirane (**1a**: $R^1 = R^2 = CH_3$)[6] or of its more reactive trifluoromethyl analog (**1b**: $R^1 = CH_3$; $R^2 = CF_3$),[7] allows the *direct* transformation of *O*-isopropylidene derivatives of 1,2-diols into the corresponding 2-hydroxy ketones in high yield, as well as high retention of optical purity, whenever applicable (eq 1).



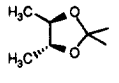
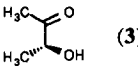
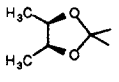
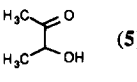
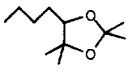
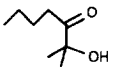
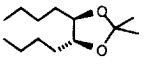
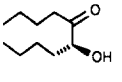
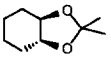
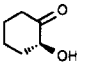
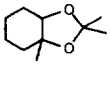
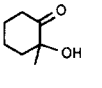
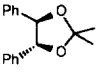
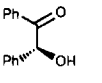
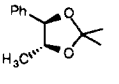
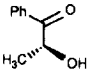
(1)

Dioxiranes **1a** and **1b** were obtained in the isolated form (as solutions in the parent ketone) by following a described general protocol.[6,7]

† Presented in part at the *12th IUPAC Conference on Physical Organic Chemistry*, Padova, Italy; Aug. 28-Sept. 2, 1994; *Abstracts* **P148**, 255.

‡ In partial fulfillment of the requirements for the Ph.D. Degree.

Table 1. Selective Oxidation of Acetonides to α-Hydroxyketones Using Dioxiranes [a]

entry	substrate: acetonide	(#) conf.	% ee [b]	dioxirane	reactn time	% conv. [c]	product: ketol	(#)	% yield [d]	$[\alpha]_D$ [e]	% ee [b] (conf)
1		(2) *R,R*-(-)	98	(1b)	40 min	> 98		(3)	> 96	- 58.6°	98 (*R*)
2		(4) *R,S*	—	(1b)	20 min	98		(5)	> 96	—	—
3		(6) —	—	(1a) (1b)	24 h 45 min	10 98		(7)	> 96 > 96	—	—
4		(8) *R,R*-(+)	97	(1b)	35 min	88		(9)	80	- 9.5°	96[f] (*R*)
5		(10) *R,R*-(-)	99	(1b)	20 min	98		(11)	98	+ 14.5°	99 (*R*)
6		(12)—	—	(1b)	15 min	99		(13)	99	—	—
7		(14) *R,R*-(+)	97	(1b)	50 min	93		(15)	99	- 111°	97 (*R*)
8		(16) *R,R*-(-)	92	(1a) (1b)	32 h 50 min	74 90		(17)	92 60[g]	—	92(*R*)[h] 92(*R*)[h]

[a] All reactions routinely run at 0 °C, with initial dioxirane to substrate molar ratio ca. 1.2 to 1; mixed solvent composition was CH_2Cl_2/TFP ca. 8:1 for oxidations with **1b**, and CH_2Cl_2/acetone ca 2:1 for oxidations with **1a**. [b] Unless noted otherwise, percentage enantiomeric excesses (ee) were estimated (±5%) upon comparison of optical rotations with literature values. [c] As determined (± 2%) by GC (SE 30, 1.5 μm film thickness, 30 m × 0.25 mm ID, or DB 1, 1.5 μm film thickness, 15 m × 0.53 mm ID/wide-bore capillary column). [d] Yields were determined by GC or GC/MS (Hewlett-Packard mod. 5970 mass selective detector and mod. 5890 gas chromatograph) and based on the amount of substrate consumed; products were identified upon comparison of their ^1H NMR spectra (Varian XL 200, Bruker AM 500 or AM 400). [e] Optical rotations (at 20 °C) of product isolated (Perkin-Elmer MC 241 spectropolarimeter). [f] As determined upon conversion of ketol **9** into its MPTA ester and GC analysis. [g] Accompanied by 1-phenyl-1,2-propanedione (ca. 35%). [h] As determined by HPLC (Hewlett- Packard mod. 1050, and UV detector mod. 35900) of the reaction mixture, employing a chiral stationary phase (DAICEL Chiralcel OD, 25 cm × 0.46 cm ID.; 2% i-PrOH /98% n-hexane, 1 mL/min).

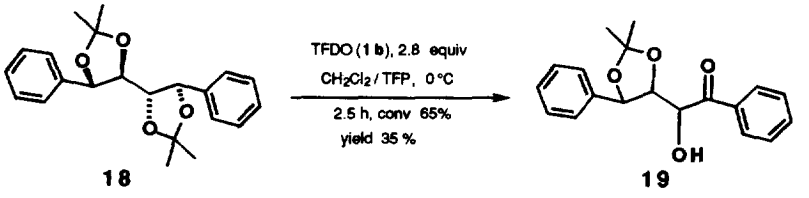
Starting with the corresponding 1,2-diols,[8] literature procedures[5] allowed to synthesize the acetonides screened as substrates, i.e.: **2**,[9] **4**,[9b] **6**,[10] **8**,[11] **10**,[12] **12**,[13] **14**,[9b] and **16**.[14]

Representative results and reaction conditions are shown in Table 1. Typically, reactions were carried out by addition of an aliquot (from 5 to 35 mL) of standardized[6,7] cold solution of ca. 0.1 M **1a** in acetone or of ca. 0.8 M **1b** in 1,1,1-trifluoro-2-propanone (TFP) to a stirred solution of the acetonide (250-500 mg) in CH_2Cl_2 (5-15 mL) at 0° C. The reactions were monitored by GC, GC/MS, and/or TLC; product isolation simply entailed removal of solvent and volatiles in vacuo. The ketol products gave fully consistent ^1H NMR and MS spectral data.[15]

Examples in Table 1 (entry 3 and 8) illustrate the fact that both dioxiranes **1a** and **1b** can be successfully applied to carry out the transformation at hand. In fact, acetonides of both *tert,sec* (entry 3 and 4) and *sec,sec* 1,2-diols could be neatly transformed into the related 2-hydroxy ketones with high conversions and yields. However, at variance with the oxidation of 1,2-diols, using dimethyldioxirane (**1a**) for oxidative cleavage of acetonides reaction times might become be inconveniently long (cf., entry 3 and 8); therefore, it is apparent that in this reaction the powerful methyl(trifluoromethyl)dioxirane (**1b**) should be the oxidant of choice. Inspection of data in Table 1 reveals that the conversion of the optically active acetonides into 2-hydroxy ketones occurs selectively and with practically complete retention of configuration at the chiral center next to the one undergoing transformation into carbonyl. In each case examined, the conservation of optical purity was excellent (cf., entry 1, 4, 5, 7, and 8). Also, regioselectivity was satisfactory in the oxidative cleavage of 1-phenylpropan-1,2-diol acetonide (**16**); here, over oxidation to the α-dicarbonyl became significant only with the powerful dioxirane **1b** (entry 8).

Similar to the dioxirane oxyfunctionalization of ethers and acetals by dioxirane **1b**,[16] it is likely that — under the conditions adopted — the oxidative cleavage of acetonides begins by way of *O*-insertion into a C-H bond of the diol moiety; this step should have no distinct *free*-radical character.[1a,17] Under our conditions, the reaction of acetonide **2** with methyl(trifluoromethyl)dioxirane (**1b**) obeys a clean second-order kinetic law up to >80% reaction; following the decay of the peroxide (iodometry),[6,7] with $[\mathbf{2}]_0 = 0.72 \times 10^{-2}$ M and $[\mathbf{1b}]_0 = 0.60 \times 10^{-2}$ M, a rate constant $k_2 = (0.54 \pm 0.02) \times 10^{-2}$ $M^{-1}s^{-1}$ was estimated in CH_2Cl_2/TFP 9.5:0.5 at 0° C (under air). Furthermore, the presence of a phenyl substituent at the putative reaction center (as in 14 and 16) seems to be of no particular advantage as for the rate of substrate conversion (e.g., cf. entries 7 and 8 with entry 1, Table 1). Also telling is the observed preservation of stereochemical integrity at the residual C*H-OH moiety in the ketol product.

Sterically encumbered 1,2-acetonides seem to be more reluctant to undergo dioxirane oxidation than the corresponding 1,2-diols; for instance (1*R*,2*R*)-*threo*-1-phenyl-1,2-propanediol is converted practically completely into ketol **17** by dioxirane **1a** during 22 h,[2] whereas acetonide **16** requires 32 h for 74% conversion (entry 8).



18 **19** (2)

This finding can be brought to proper fruition. For instance, the diacetonide **18**[18] could be transformed selectively into the 1-oxo-2-hydroxy 3,4-acetonide **19**[19] under the conditions given in eq 2.

We believe the *direct*, high-yield transformation of acetonides of 1,2-diols into 2-hydroxy ketones by dioxiranes reported herein shows promise of considerable practical value in synthesis because of its efficiency and simplicity of approach. In fact, it constitutes yet another useful entry into either structurally simple or complex 2-hydroxy ketones; the latter are important "building blocks" in the synthesis of natural products and fine chemicals.[20]

Acknowledgment. This work was supported in part by CNR - Progetto Strategico "Tecnologie Chimiche Innovative" (Rome, Italy), and the Italian Ministry of University, Scientific and Technological Research (MURST 40). We thank professor J. O. Edwards (Brown University, USA) for many helpful discussions. Thanks are also due to Peroxid-Chemie GmbH (München, Germany) for a generous gift of potassium peroxymonosulfate (Curox®).

References and Notes

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10. Hanzlick, R. P.; Leinwetter, M. *J. Org. Chem.* **1978**, *43*, 438.
11. **(+)-(*5R,6R*)-Decan-5,6-diol 5,6-Acetonide (8)**: oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.0 Hz, 6 H), 1.35 (s, 6 H), 1.29-1.49 (m, 12 H), 3.55 (m, 2 H); {^{1}H}^{13}C NMR (50 MHz, $CDCl_3$): δ 107.6 (O-*C*-O), 81.0 (-*C*-H), 32.7 (O-CH-*C*H_2), 28.3 (CH_2-*C*H-CH_2), 27.3 (O-C-*C*H_3), 22.8 (*C*H_2-CH_3), 13.9 (CH_2-*C*H_3); FT IR (neat): 2981, 2934, 1464, 1368, 1216, 1190, 1120, 1016 cm^{-1}, etc.; MS (70 eV), *m/z* (r.i.): 199 (65), 157 (21), 43 (100), etc; $[\alpha]_D$ +44.9° (*c* 1.39, MeOH); ee 97%, as determined by GC employing a chiral stationary phase (Beta-DEX™ 120, 0.25 μm film thickness, 30 m × 0.25 mm ID, capillary column).
12. Opticaly active **10** has $[\alpha]_D$ -33.4° (*c* 1.34, $CHCl_3$); ee 99%, as determined by GC employing a chiral stationary phase (Beta-DEX™ 120, 0.25 μm film thickness, 30 m × 0.25 mm ID, capillary column). For the racemic ketol, see: Pihlaja, K.; Czombos, J. *J. Prakt. Chem.* **1991**, *333*, 931.
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14. **(-)-(*1R,2R*)-1-Phenylpropan-1,2-diol 1,2-Acetonide (16)**: oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.0 Hz, 1 H), 1.52 (s, 3 H), 1.56 (s, 3 H), 3.85 (qd, *J* = 8.5 Hz, *J* = 6.0 Hz, 1 H), 4.46 (d, *J* = 8.5 Hz, 1 H), 7.28-7.39 (m, 5 H); {^{1}H}^{13}C NMR (125 MHz, $CDCl_3$): δ 137.6, 128.5, 126.4, 108.4 (O-*C*-O), 84.8 (Ph-*C*-H), 79.2 (CH_3-*C*-H), 27.4 (CH_3-C-*C*H_3), 26.9 (CH_3-C-*C*H_3), 16.2 (CH-*C*H_3); FT IR (neat): 2991, 2884, 1464, 1380, 1244, 1180, 1100, 1050 cm^{-1}, etc.; MS (70 eV), *m/z* (r.i.): 177 (6), 148 (58), 135 (21), 105 (25), 91 (30), 77 (23), 43 (100), etc; $[\alpha]_D$ -37.9° (*c* 1.98, EtOH), ee 92% as determined by HPLC (Hewlett- Packard mod. 1050, UV detector model 35900) employing a chiral stationary phase (DAICEL Chiralcel OD, 25 cm x 0.46 cm ID.; 10% i-PrOH /90% n-hexane, 0.8 mL/min).
15. (a) Ketols (**3**), (**5**), (**11**), (**15**), (**17**), see ref. 2, and literature quoted therein (b) **2-Methyl-2-hydroxyheptan-3-one (7)**: oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.3 Hz, 3 H), 1.29 (m, 2 H), 1.44 (s, 6 H, HO-C-*C*H_3), 1.58 (m, 2 H), 2.50 (t, *J* = 7.0 Hz, 2 H), 3.34 (broad s, 1 H, O*H*); {^{1}H}^{13}C NMR (100 MHz, $CDCl_3$): δ 214.6 (*C*=O), 66.1 (*C*-OH), etc.; FT IR (neat): 3460 (O-H str), 1710 (C=O str.), 1172 cm^{-1} (C-OH str.), etc.; MS (70 eV), *m/z* (r.i.): 144 (1, M$^+$), 101 (3), 111 (1), 59 (100), etc. (c) Optically active (**9**) had $[\alpha]_D$ -9.5° (*c* 1.88, MeOH); for the racemic compound, see: Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520. (d) (**13**): Tamura, Y.; Annoura, H.; Kondo, H.: Fuji, M.; Yoshida, T.; Fujioka, H. *Chem. Pharm. Bull.* **1987**, *35*, 2305.
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18. ***Meso*-1,4-Diphenylbutan-1,2:3,4-tetraol 1,2:3,4-Diacetonide (18)**: mp 54-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 3 H, C*H*$_3$), 1.59 (s, 3 H, C*H*$_3$), 3.35 (d, *J* = 8.0 Hz, 1 H, Ph-C*H*), 5.05 (d, *J* = 8.0 Hz, 1 H, Ph-CH-C*H*), 7.13-7.26 (m, 5 H); {^{1}H}^{13}C NMR (100 MHz, $CDCl_3$): δ 137-126, 109.3 (O-*C*-O), 80.2 (*C*^{1}, *C*^{4}), 79.2 (*C*^{2}, *C*^{3}), 27.4 (*C*H$_3$), 26.6 (*C*H$_3$); FT IR (KBr pellets): 2989, 2931, 1439, 1455, 1370, 1220,1164, 1061 cm^{-1} etc.; MS (70 eV), *m/z* (r.i.): 339 (4), 177 (17), 176 (60), 119 (64), 91 (100), 77 (24), 43 (39), etc.
19. **1,4-Diphenyl-2,3,4-triol-butan-1-one 3,4-Acetonide (19)**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 3 H, C*H*$_3$), 1.45 (s, 3 H, C*H*$_3$), 4.01 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1 H), 5.03 (d, *J* = 8.0 Hz, 1 H), 5.23 (d, *J* = 8.0 Hz, 1 H), 7.24-7.66 (m, 10 H); {^{1}H}^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3 (*C*=O), 137-126, 110.0 (O-*C*-O), 83.9 (Ph-*C*H), 78.0 (HO-C-*C*-O), 70.1 (*C*-OH), 26.4 (*C*H$_3$), 23.7 (*C*H$_3$); FT IR (neat): 3462 (O-H str), 3064, 3035, 2987, 2931, 1689 (C=O str.), 1450, 1064 (C-OH str.) cm^{-1}, etc.
20. For instance, see : (a) Hannessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon : New York, **1983**; Chapter 2. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(*Received in UK* 2 *October* 1995; *accepted* 3 *November* 1995)