

## Eliminative Ring Fission of 1,2,4-Trioxan-5-ones. A New Approach to $\alpha$ -Keto Acids

Charles W. Jefford, Jean-Claude Rossier, and John Boukouvalas

Department of Organic Chemistry, University of Geneva, CH-1211 Geneva 4, Switzerland

6-Mono-R-substituted 1,2,4-trioxan-5-ones readily undergo base-catalysed O–O bond cleavage to furnish  $\alpha$ -keto acids (RCOCOOH) in high yields even when the R-substituents are bulky.

A variety of 1,2,4-trioxanes are now available thanks to new synthetic methods based on the condensation of aldehydes and ketones with  $\beta$ -hydroperoxy cations or their equivalents.<sup>1</sup> Consequently, these oxygen heterocycles are ready for preparative exploitation. A recent and first example is provided by 1,2,4-trioxanes (**1**) monosubstituted at C-3.<sup>2</sup> The action of triethylamine on (**1**) produces the 1,2-diol monoester (**2**) by deprotonation which ruptures the peroxide link. We now report a counter-polarized variant of this process which enables  $\alpha$ -keto acids to be prepared in impressive yields. The molecules selected are 1,2,4-trioxan-5-ones (**3**) having a hydrogen atom at the C-6 position which are predisposed to undergo oxygen–oxygen bond cleavage, but in the reverse direction. Deprotonation at C-6 breaks the ring with excision of the carbonyl fragment, so liberating the  $\alpha$ -keto acid (**4**).

The reaction is illustrated by some typical 1,2,4-trioxan-5-ones (**3a–j**) which are conveniently prepared from  $\alpha$ -hydroperoxy carboxylic acids.<sup>3</sup> The conversion procedure is simple. A solution of the trioxanone (**3**) (1–5 mmol) in 10–50% Et<sub>3</sub>N–CH<sub>2</sub>Cl<sub>2</sub> (0.5–2 ml) is allowed to stand at room temperature (Table 1). The corresponding  $\alpha$ -keto acid (**4**) is obtained pure by evaporation of the volatile components. Less volatile products, such as adamantanone (entries 4, 8, and 10) are removed by extraction with CH<sub>2</sub>Cl<sub>2</sub> after treatment with saturated aqueous NaHCO<sub>3</sub>. Acidification (2 M HCl) of the aqueous phase followed by extraction with CH<sub>2</sub>Cl<sub>2</sub> furnishes the  $\alpha$ -keto acid in high purity.

Yields are high even when *t*-butyl or adamantyl substituents are attached to C-6 (entries 1–6). This behaviour contrasts with that of 1,2,4-trioxanes which react sluggishly with base when bulky groups are present at C-3. Evidently, the electronic effect of the adjacent carbonyl group in (**3e**) overrides any steric hindrance (entry 5). Even in (**3f**), where there is a steric bias towards the C-3 hydrogen, cleavage occurs only in the electronically dictated direction (entry 6). Proof that certain positions must be unsubstituted for reaction

is revealed by 3,4-dispirocyclohexyl-1,2,4-trioxan-5-one (**3k**), which is fully substituted at C-3 and C-6, and which, after exposure to neat Et<sub>3</sub>N for a month, remains unchanged (entry 11). The nature of the substituent at C-6 has no bearing on yields, except that work-up is simpler when the by-product is *not* adamantanone.

Lastly, it is important to note that the  $\alpha$ -hydroperoxy acids used for preparing the trioxanones do not themselves produce  $\alpha$ -keto acids in the presence of base. Rather, Grob fragmenta-

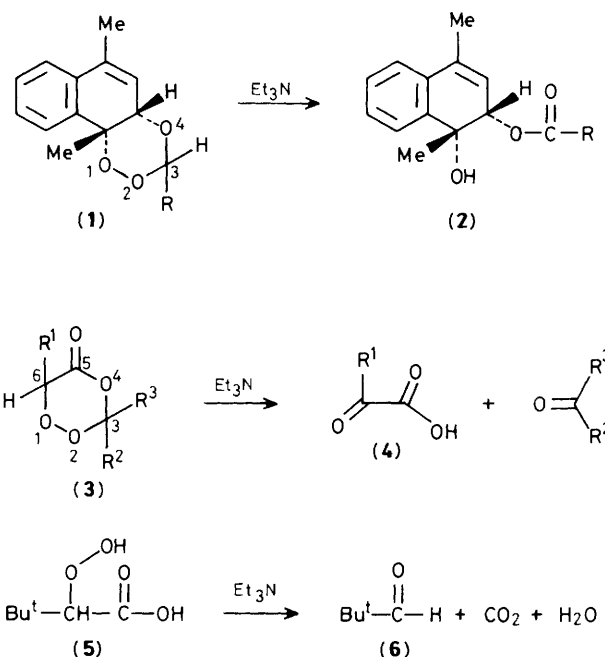


Table 1. Et<sub>3</sub>N-catalysed cleavage of some 1,2,4-trioxan-5-ones (**3**) to give  $\alpha$ -keto acids (**4**).<sup>a</sup>

Entry	1,2,4-Trioxan-5-one <sup>b</sup>	Reaction time/h	% Yield of ( <b>4</b> ) <sup>c</sup>
1	( <b>3a</b> ), R <sup>1</sup> = 1-Ad; R <sup>2</sup> –R <sup>3</sup> = –[CH <sub>2</sub> ] <sub>5</sub> –	24	100 <sup>d</sup>
2	( <b>3b</b> ), R <sup>1</sup> = 1-Ad; R <sup>2</sup> = R <sup>3</sup> = Me	16	82
3	( <b>3c</b> ), R <sup>1</sup> = Bu <sup>t</sup> ; R <sup>2</sup> –R <sup>3</sup> = –[CH <sub>2</sub> ] <sub>5</sub> –	60	79 <sup>e</sup>
4	( <b>3d</b> ), R <sup>1</sup> = Bu <sup>t</sup> ; R <sup>2</sup> –R <sup>3</sup> = 2-Ad	16	73
5	( <b>3e</b> ), R <sup>1</sup> = R <sup>3</sup> = Bu <sup>t</sup> ; R <sup>2</sup> = H	16	67
6	( <b>3f</b> ), R <sup>1</sup> = Bu <sup>t</sup> ; R <sup>2</sup> = H, R <sup>3</sup> = Me	3	87
7	( <b>3g</b> ), R <sup>1</sup> = Bu <sup>n</sup> ; R <sup>2</sup> –R <sup>3</sup> = –[CH <sub>2</sub> ] <sub>5</sub> –	16	97 <sup>f</sup>
8	( <b>3h</b> ), R <sup>1</sup> = Bu <sup>n</sup> ; R <sup>2</sup> –R <sup>3</sup> = 2-Ad	16	81
9	( <b>3i</b> ), R <sup>1</sup> = <i>n</i> -Hexyl; R <sup>2</sup> –R <sup>3</sup> = –[CH <sub>2</sub> ] <sub>5</sub> –	58	95 <sup>g</sup>
10	( <b>3j</b> ), R <sup>1</sup> = <i>n</i> -Hexyl; R <sup>2</sup> –R <sup>3</sup> = 2-Ad	62	83
11	( <b>3k</b> ), R <sup>1</sup> , C-6-H = –[CH <sub>2</sub> ] <sub>5</sub> –; R <sup>2</sup> –R <sup>3</sup> = –[CH <sub>2</sub> ] <sub>5</sub> –	30 days	0 <sup>h</sup>

<sup>a</sup> All reactions were performed at room temperature (20–25 °C). <sup>b</sup> 1-Ad = Adamantan-1-yl; 2-Ad = adamantan-2-ylidene. <sup>c</sup> Yields refer to isolated products exhibiting satisfactory spectral properties (<sup>13</sup>C and <sup>1</sup>H n.m.r.; i.r.). <sup>d</sup> 1-Adamantylglyoxylic acid, colourless crystals, m.p. 89–90 °C (from CH<sub>2</sub>Cl<sub>2</sub>–hexane, 9:1, at –30 °C, lit.<sup>4</sup> m.p. 102–104 °C; <sup>13</sup>C n.m.r. (CDCl<sub>3</sub>, 50 MHz)  $\delta$  27.5 (d), 36.3 (t), 37.1 (t), 45.1 (s), 162.9 (s), and 200.8 (s). Satisfactory elemental analyses were obtained. See also ref. 4. <sup>e</sup> Ref. 5. <sup>f</sup> Ref. 6. <sup>g</sup> Ref. 7. <sup>h</sup> (**3k**) was totally recovered.

tion<sup>8</sup> occurs as shown by 2-t-butyl-2-hydroperoxyacetic acid (5), which loses carbon dioxide to give pivalaldehyde (6).

The present method compares favourably with the others<sup>9</sup> and has merit in being short and easy to perform, enabling any  $\alpha$ -substituted acetic acid to be converted into its  $\alpha$ -keto acid via its  $\alpha$ -hydroperoxy derivative.<sup>10</sup>

We thank the Swiss National Science Foundation for support of this work.

Received, 30th July 1986; Com. 1091

## References

- 1 C. W. Jefford, D. Jaggi, J. Boukouvalas, and S. Kohmoto, *J. Am. Chem. Soc.*, 1983, **105**, 6497; C. W. Jefford, J. Boukouvalas, and S. Kohmoto, *Helv. Chim. Acta*, 1983, **66**, 2615; C. W. Jefford, S. Kohmoto, J. Boukouvalas, and U. Burger, *J. Am. Chem. Soc.*, 1983, **105**, 6498; C. W. Jefford, D. Jaggi, J. Boukouvalas, S. Kohmoto, and G. Bernardinelli, *Helv. Chim. Acta*, 1984, **67**, 1104; C. W. Jefford, J. Boukouvalas, and S. Kohmoto, *J. Photochem.*, 1984, **25**, 537; C. W. Jefford, J. Boukouvalas, and S. Kohmoto, *J. Chem. Soc., Chem. Commun.*, 1984, 523; C. W. Jefford, D. Jaggi, S. Kohmoto, J. Boukouvalas, and G. Bernardinelli, *Helv. Chim. Acta*, 1984, **67**, 2254.
- 2 C. W. Jefford, S. Kohmoto, J. C. Rossier, and J. Boukouvalas, *J. Chem. Soc., Chem. Commun.*, 1985, 1783.
- 3 C. W. Jefford, J. C. Rossier, and G. D. Richardson, *J. Chem. Soc., Chem. Commun.*, 1983, 1064.
- 4 E. C. Hermann and J. A. Snyder, U.S. Pat. 3,325,478 (Cl. 260-239.1), June 13, 1967, Appl. November 17, 1964, and August 9, 1966; *Chem. Abstr.*, 1967, **67**, 90798b.
- 5 A. Richard, *Ann. Chim. (Paris)*, 1910, **21**, 360; J. S. Nimitz and H. S. Mosher, *J. Org. Chem.*, 1981, **46**, 211.
- 6 M. Igarashi and H. Midorikawa, *J. Org. Chem.*, 1964, **29**, 2080.
- 7 J. Anatol and A. Medète, *Synthesis*, 1971, 538.
- 8 C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 1.
- 9 Reviews: J. M. Brown, in 'Comprehensive Organic Chemistry,' eds. D. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 2, p. 779; A. J. L. Cooper, J. Z. Ginos, and A. Meister, *Chem. Rev.*, 1983, **83**, 321.
- 10 W. Adam and O. Cueto, *J. Org. Chem.*, 1977, **42**, 38; W. Adam, A. Alzérreca, J.-C. Liu, and F. Yany, *J. Am. Chem. Soc.*, 1977, **99**, 5768.