Eliminative Ring Fission of 1,2,4-Trioxan-5-ones. A New Approach to α-Keto Acids

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6-Mono-R-substituted 1,2,4-trioxan-5-ones readily undergo base-catalysed O–O bond cleavage to furnish α-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 β-hydroperoxy cations or their equivalents.[1] 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.[2] 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 α-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 α-keto acid (**4**).

The reaction is illustrated by some typical 1,2,4-trioxan-5-ones (**3a—j**) which are conveniently prepared from α-hydroperoxy carboxylic acids.[3] The conversion procedure is simple. A solution of the trioxanone (**3**) (1—5 mmol) in 10—50% Et_3N–CH_2Cl_2 (0.5—2 ml) is allowed to stand at room temperature (Table 1). The corresponding α-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_2Cl_2 after treatment with saturated aqueous $NaHCO_3$. Acidification (2 M HCl) of the aqueous phase followed by extraction with CH_2Cl_2 furnishes the α-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_3N 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 α-hydroperoxy acids used for preparing the trioxanones do not themselves produce α-keto acids in the presence of base. Rather, Grob fragmenta-

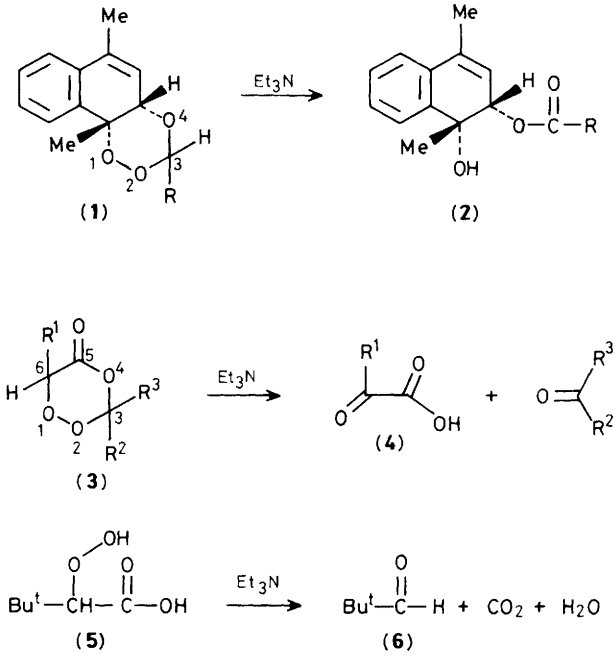

Table 1. Et_3N–catalysed cleavage of some 1,2,4-trioxan-5-ones (**3**) to give α-keto acids (**4**).[a]

Entry	1,2,4-Trioxan-5-one[b]	Reaction time/h	% Yield of (**4**)[c]
1	(**3a**), R^1 = 1-Ad; R^2–R^3 = –$[CH_2]_5$–	24	100[d]
2	(**3b**), R^1 = 1-Ad; R^2 = R^3 = Me	16	82
3	(**3c**), R^1 = Bu^t; R^2–R^3 = –$[CH_2]_5$–	60	79[e]
4	(**3d**), R^1 = Bu^t; R^2–R^3 = 2-Ad	16	73
5	(**3e**), R^1 = R^3 = Bu^t; R^2 = H	16	67
6	(**3f**), R^1 = Bu^t; R^2 = H, R^3 = Me	3	87
7	(**3g**), R^1 = Bu^n; R^2–R^3 = –$[CH_2]_5$–	16	97[f]
8	(**3h**), R^1 = Bu^n; R^2–R^3 = 2-Ad	16	81
9	(**3i**), R^1 = n-Hexyl; R^2–R^3 = –$[CH_2]_5$–	58	95[f,g]
10	(**3j**), R^1 = n-Hexyl; R^3–R^3 = 2-Ad	62	83
11	(**3k**), R^1, C-6-H = –$[CH_2]_5$–; R^2–R^3 = –$[CH_2]_5$–	30 days	0[h]

[a] All reactions were performed at room temperature (20—25 °C). [b] 1-Ad = Admantan-1-yl; 2-Ad = adamantan-2-ylidene. [c] Yields refer to isolated products exhibiting satisfactory spectral properties (^{13}C and ^1H n.m.r.; i.r.). [d] 1-Adamantylglyoxylic acid, colourless crystals, m.p. 89—90 °C (from CH_2Cl_2–hexane, 9:1, at −30 °C, lit.[4] m.p. 102—104 °C; ^{13}C n.m.r. ($CDCl_3$, 50 MHz) δ 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. [e] Ref. 5. [f] Ref. 6. [g] Ref. 7. [h] (**3k**) was totally recovered.

tion[8] 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[9] and has merit in being short and easy to perform, enabling any α-substituted acetic acid to be converted into its α-keto acid *via* its α-hydroperoxy derivative.[10]

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