Reactions of Cyclic Peroxides with Aldehydes and Ketones catalysed by Trimethylsilyl Trifluoromethanesulphonate. An Efficient Synthesis of 1,2,4-Trioxanes

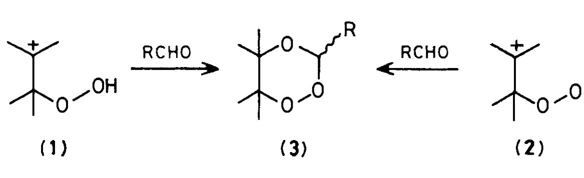
Charles W. Jefford,* John Boukouvalas, and Shigeo Kohmoto

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

Trimethylsilyl trifluoromethanesulphonate is found to be an efficient catalyst for the reaction of 1,4-endoperoxides and 1,2-dioxetanes with aldehydes and ketones to give 1,2,4-trioxanes in high yields.

We have recently shown that β-hydroperoxy cations (**1**) or zwitterionic peroxides (**2**) can be intercepted by aldehydes to give 1,2,4-trioxanes (**3**) (Scheme 1). These fleeting ionic species were produced by the acid-catalysed opening of 1,4-endoperoxides[1] and 1,2-dioxetanes[2] and by the photo-oxygenation of enol ethers[3] and indoles[4], respectively. Although evidence for their existence was unambiguously established by their capture with carbonyl compounds, yields of the resulting trioxanes varied with the experimental conditions and were generally poor for ketones.

Apart from these mechanistic findings, considerable importance attaches to the 1,2,4-trioxane ring itself, since it is the active part of Qinghaosu, a potent antimalarial remedy.[5] As methods for preparing this little-known class of heterocycles are limited,[6] we now describe how the aforementioned cyclization reaction is greatly improved by catalysis with trimethylsilyl trifluoromethanesulphonate (TMSOTf).[7]



Scheme 1

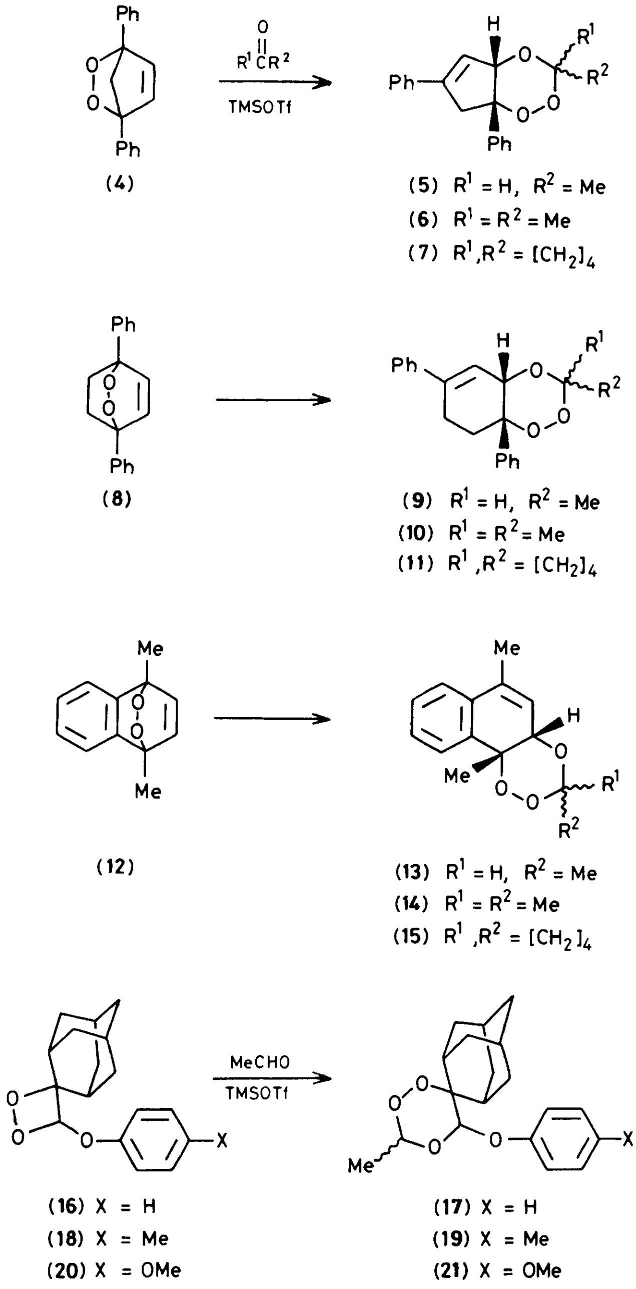
The procedure is simple. The peroxide (0.2 mmol) is mixed with an excess of carbonyl compound (200 μl for acetaldehyde and acetone and 60 μl for cyclopentanone) in dry dichloromethane (2 ml). To this solution at −78 °C TMSOTf (0.3—8.4 equiv.) is added with stirring under nitrogen. Once the reaction is complete (*ca.* 1.5 h), a portion of triethylamine (half the volume of TMSOTf used) is added and the resulting mixture is diluted with dichloromethane (20 ml). The organic layer is washed with water (3 times) and dried ($MgSO_4$). After evaporation of solvent, the 1,2,4-trioxane is preparatively isolated by layer chromatography over silica gel (thickness 2 mm).

Under these conditions, the 1,4-endoperoxides (**4**), (**8**), and (**12**)[8] reacted well with acetaldehyde, acetone, and cyclopentanone to give the corresponding 1,2,4-trioxanes (**5**)—(**7**), (**9**)—(**11**), and (**13**)—(**15**) in consistently high yields. Unaccountably, the 1,2-dioxetanes (**16**), (**18**), and (**20**)[9] failed to react with acetone, but nonetheless gave high yields of trioxanes (**17**), (**19**), and (**21**) with acetaldehyde (Scheme 2 and Table 1).

Table 1. Trimethylsilyl trifluoromethanesulphate catalysed reactions of cyclic peroxides with carbonyl compounds.

Peroxide	Carbonyl compound	TMSOTf (equiv.)	Temp. /°C	Reaction time/h	Trioxane[a]	Yield (%)	Diastereoisomer ratio[b]
(**4**)	MeCH=O	0.3	−78	1.5	(**5**)	74	50:50
		1.1	−78	1.5		88	57:43
		2.8	−78	1.5		82	81:19
		8.4	−78	10 min		85	45:55
		1.1	−30	1.5		75	78:22
		2.8	−30	12		29	100:0
		1.1	20	2 min		62	91:9
	$Me_2C{=}O$	1.1	−78	1.5	(**6**)	81	—
	$[CH_2]_4C{=}O$	1.1	−78	1.5	(**7**)	86	—
(**8**)	MeCH=O	1.1	−78	1	(**9**)	81[c]	64:36
	$Me_2C{=}O$	1.1	−78	1	(**10**)	77[c]	—
	$[CH_2]_4C{=}O$	1.1	−78	1	(**11**)	86[c]	—
(**12**)	MeCH=O	1.1	−78	1	(**13**)	87[d]	76:24
	$Me_2C{=}O$	1.1	−78	1	(**14**)	83[d]	—
	$[CH_2]_4C{=}O$	1.1	−78	1	(**15**)	70[d]	—
(**16**)	MeCH=O	1.1	−78	1	(**17**)	81	67:33
	$Me_2C{=}O$	1.1	−78	1		0[e]	—
(**18**)	MeCH=O	1.1	−78	1	(**19**)	79	64:36
	$Me_2C{=}O$	1.1	−78	1		0[f]	—
(**20**)	MeCH=O	1.1	−78	1	(**21**)	45	68:32
	$Me_2C{=}O$	1.1	−78	1		0[f]	—

[a] All the new compounds, (**7**), (**11**), (**13**), (**14**), and (**15**), gave satisfactory elemental analyses. The others, (**5**), (**6**), (**9**), (**10**), (**17**), (**19**), and (**21**) were identified by comparison with authentic samples (refs. 1,2). [b] In general, the major diastereoisomer has the C(3) substituent on the trioxane part *cis* to the ring junction (except the fourth entry). [c] *Ca.* 10% of 1,4-diphenylcyclohexa-1,3-diene was formed. [d] *Ca.* 5% of 1,4-dimethylnaphthalene was formed. [e] 58% of (16) was recovered. [f] Recovery of the 1,2-dioxetane [(**18**) or (**20**)] was essentially complete.



(4)

(5) $R^1 = H$, $R^2 = Me$
(6) $R^1 = R^2 = Me$
(7) $R^1, R^2 = [CH_2]_4$

(8)

(9) $R^1 = H$, $R^2 = Me$
(10) $R^1 = R^2 = Me$
(11) $R^1, R^2 = [CH_2]_4$

(12)

(13) $R^1 = H$, $R^2 = Me$
(14) $R^1 = R^2 = Me$
(15) $R^1, R^2 = [CH_2]_4$

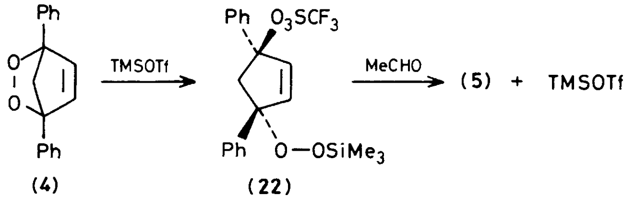
(16) X = H
(18) X = Me
(20) X = OMe

(17) X = H
(19) X = Me
(21) X = OMe

Scheme 2

For reasons of geometry control, all the trioxanes are *cis*-fused to the parent ring,[10] but are formed as diastereoisomers when there are two different substitutents at the C(3) position. Cyclization proceeded in high yields with concentrations of TMSOTf substantially less or more than 1 equivalent. However, longer reaction times as well as higher temperatures markedly altered the ratio of diastereoisomers [cf. (**4**) → (**5**), Table 1).

The first step in the reaction is probably the cleavage of the carbon–oxygen bond of the peroxide by TMSOTf to give the *trans*-3-trimethylsilylperoxy trifluoromethanesulphonate, *e.g.*, (**4**) affords (**22**), which is the masked equivalent of (**1**) and (**2**). Cyclic incorporation of the carbonyl compound gives the trioxane (**5**), thereby shedding TMSOTf and making it available for further reaction (Scheme 3).



(4)

(22)

Scheme 3

Attempts to detect intermediates such as (**22**) by ^{1}H n.m.r. spectroscopy at low temperature and studies on the stereoselectivity of this new reaction of TMSOTf are under way. Structural details of these and other trioxanes will be published elsewhere.

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

Received, 3rd January 1984; Com. 009

References

1 C. W. Jefford, D. Jaggi, J. Boukouvalas, and S. Kohmoto, *J. Am. Chem. Soc.*, 1983, **105**, 6497.
2 C. W. Jefford, J. Boukouvalas, and S. Kohmoto, *Helv. Chim. Acta*, 1983, **66**, 2615.
3 C. W. Jefford, S. Kohmoto, J. Boukouvalas, and U. Burger, *J. Am. Chem. Soc.*, 1983, **105**, 6498; C. W. Jefford, J. Boukouvalas, and S. Kohmoto, *Chimia*, 1983, **37**, 429.
4 C. W. Jefford, D. Jaggi, G. Bernardinelli, J. Boukouvalas, and S. Kohmoto, *Helv. Chim. Acta*, submitted for publication.
5 Liu Jingming, Ni Muyun, Fan Jufen, Tu Youyou, Tu Zhaohua, Wu Yulin, and Zhou Weishan, *Acta Chim. Sin.*, 1979, **37**, 129; G. Schmid and W. Hofheinz, *J. Am. Chem. Soc.*, 1983, **105**, 624; Xu Xing-xiang, Zhu Jie, Huang Dazhong, and Zhou Weishan, *Acta Chim. Sin.*, 1983, **41**, 574.
6 V. Subramanyam, C. L. Brizuela, and A. H. Soloway, *J. Chem. Soc., Chem Commun.*, 1976, 508; M. Schulz and K. Kirschke in 'Organic Peroxides,' vol. 3, ed. D. Swern, R. E. Krieger, Florida, original, 1972, reprint, 1981, pp. 109—110; W. Adam and A. Rios, *Chem. Commun.*, 1971, 822; G. B. Payne and C. W. Smith, *J. Org. Chem.*, 1957, **22**, 1682; M. Miura, M. Nojima, and S. Kusabayashi, *J. Chem. Soc., Chem. Commun.*, 1981, 581; H. Yamamoto, M. Akutagawa, H. Aoyama, and Y. Omote, *J. Chem. Soc., Perkin Trans.* 1, 1980, 2300.
7 R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, 1981, **37**, 3899.
8 G. O. Schenck, W. Müller, and H. Pfennig, *Naturwissenschaften*, 1954, **41**, 374; D. J. Coughlin, R. S. Brown, and R. G. Salomon, *J. Am. Chem. Soc.*, 1977, **99**, 655; H. J. Kuhn, Diplomarbeit, Universität Göttingen (1959) cited in '1,4-Cycloaddition Reactions,' ed. J. Hamer, Academic Press, New York, 1967, ch. 10, p. 271; H. H. Wasserman and D. L. Larsen, *J. Chem. Soc., Chem. Commun.*, 1972, 253.
9 W. Adam and L. A. Arias Encarnación, *Chem. Ber.*, 1982, **115**, 2592.
10 W. S. Johnson, *Acct. Chem. Res.*, 1968, **1**, 1; H. O. House, 'Modern Synthetic Reactions,' 2nd edn., W. A. Benjamin, Menlo Park, California, 1972, pp. 593, 609.