Efficient Preparation of 1,2,4,5-Tetroxanes from Bis(trimethylsilyl) Peroxide and Carbonyl Compounds

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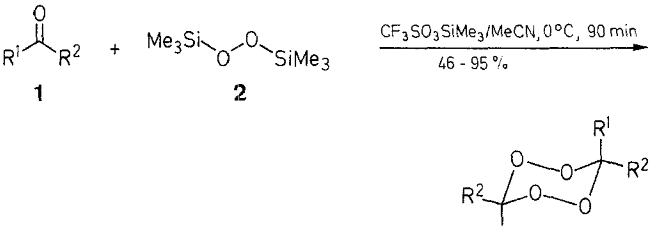
Symmetrically 3,6-disubstituted and 3,3,6,6-tetrasubstituted 1,2,4,5-tetroxanes are prepared in good yields by the condensation of bis(trimethylsilyl) peroxide with aldehydes and ketones in the presence of trimethylsilyl trifluoromethanesulfonate.

In the course of a program aimed at synthesizing cyclic peroxides with potential antimalarial activity,[1] we needed to prepare some 1,2,4,5-tetroxanes for comparison. As a class, they have attracted much attention,[2-6] for example, the dispiro derivatives serve as precursors to macrolactones used in perfumery.[7] Despite numerous reports on the formation of 1,2,4,5-tetroxanes,[2,3,8-12] few are of preparative value. The most efficient method involves the acid-catalyzed condensation of hydrogen peroxide with ketones,[13-14] Unfortunately, its utility is limited by the potential hazard arising from the need to use concentrated solutions of hydrogen peroxide.[15]

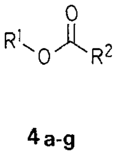
We now describe a convenient synthesis of 1,2,4,5-tetroxanes, which exploits a safer analogue of hydrogen peroxide, namely bis(trimethylsilyl) peroxide (**2**).[16]

The procedure entails the treatment of a carbonyl compound with peroxide **2** in the presence of a Lewis acid. Typically, cyclohexanone (**1a**), **2**, and trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) in acetonitrile at 0°C, furnished the dispiro-substituted tetroxane **3a** in 92% yield after purification (Table). A careful choice of solvent, temperature and catalyst is essential to suppress formation of ε-caprolactone **4a**, which can arise by Baeyer-Villiger oxidation of the ketone[17] or decomposition of **3a**.[18] In fact, the same reagents have been reported to give mainly **4a** under milder conditions.[17]

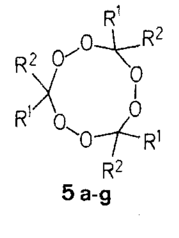


1 **2**

3 a-g



4 a-g



5 a-g

1, 3–5	R^1	R^2
a	$-(CH_2)_5-$	
b	$-CH_2C(CH_3)_2CH_2C(CH_3)_2CH_2-$	
c	$-(CH_2)_2O(CH_2)_2-$	
d	CH_3	CH_3
e	H	C_6H_5
f	H	n-C_5H_{11}
g	H	n-C_9H_{19}

Table. Preparation of Symmetrically 3,6-Di- and 3,3,6,6-Tetrasubstituted 1,2,4,5-Tetroxanes **3** from Aldehydes and Ketones **1** and Bis(trimethylsilyl) Peroxide (**2**)

Tetroxane	Yield[a] (%)	mp (°C)	Molecular Formula[b,c] and/ or Lit. mp (°C)	^{13}C-NMR[d], δ C-3 and C-6
3a	92	128–130	128–130[13]	108.1 (s)[4]
3b	65	183–184	184–186[13]	110.0 (s)
3c	87	157–158	$C_{10}H_{16}O_6$ (232.3)	106.1 (s)
3d	95	130–132	130–132[12]	107.5 (s)
3e	46	200–201	201–202[9]	108.6 (d)
3f	64	54–55	33–34[9] $C_{12}H_{24}O_4$ (232.4)	108.7 (d)
3g	51	66–67	47–50[10] $C_{20}H_{40}O_4$ (344.6)	108.7 (d)

[a] Yield of isolated pure product based on the carbonyl partner.

[b] In all cases, satisfactory microanalyses obtained: C, H ±0.27%.

[c] Mol. wt. determinations: **3c**, 247; **3f**, 221; **3g**, 335.

[d] Recorded at 50 MHz on a Varian XL-200 spectrometer in $CDCl_3$, except for **3e** (CD_2Cl_2).

The present procedure worked equally well with other ketones (**1b–d**) and aldehydes (**1e–g**) enabling the corresponding 1,2,4,5-tetroxanes **3b–g** to be readily prepared in yields of 46–95% (Table). In all instances, traces of by-products such as **4a–g** and trimeric peroxides **5a–g** were easily removed by recrystallization.

The tetroxanes derived from aldehydes were produced in a stereocontrolled manner, since only the *trans*-3,6-disubstituted derivatives **3e–g** were formed. As expected, the *trans* derivatives **3f, g** were characterized by having nearly identical ^{1}H-NMR signals for the methine protons [$\delta = 5.87-5.88$ (t, 1H, $J = 5.2$ Hz) at 360 MHz in $CDCl_3$)]. Moreover, their structures, together with that of **3e**, were further confirmed by correct microanalyses, molecular weights, and concordant ^{13}C-NMR data (Table). It is worth noting that as the previously reported melting points and ^{1}H-NMR data for **3f** and **3g** are significantly different from ours [$\delta = 5.68$ (t, $J = 4.5$ Hz) and $\delta = 6.16$ (t, $J = 4.5$ Hz), respectively[9,10]], the compounds cannot be the same.

This new method is simple to perform and provides a less hazardous preparation of symmetrically di- and tetrasubstituted 1,2,4,5-tetroxanes from readily available starting materials. Moreover, it demonstrates the utility of bis(trimethylsilyl) peroxide (**2**) as a peroxide-transfer agent.[19]

3,3,6,6-Tetramethyl-1,2,4,5-tetroxane (3d); Typical Procedure:

To a cool (0°C) solution of trimethylsilyl triflate (3.40 g, 15 mmol) in dry MeCN (3.5 mL), bis(trimethylsilyl) peroxide[16] (**2**; 2.70 g, 15 mmol) is added by syringe dropwise during 4 min under N_2 with stirring. Then, a solution of acetone (**1d**; 0.58 g, 10 mmol) in dry MeCN (1.5 mL) is introduced dropwise by syringe over 30 min. at 0°C. After stirring for 90 min. at 0°C, the reaction mixture is treated with a 10% aq. solution of $NaHCO_3$ (50 mL) followed by extraction with CH_2Cl_2 (3 × 30 mL). The combined extract is washed with brine (2 × 30 mL), dried (Na_2SO_4) and evaporated to give a colorless solid (0.74 g). Recrystallization from MeOH gives **3d** (0.70 g, 95% yield) as a colorless solid; mp 130–132°C (Lit.[12] mp 130–132°C).

For the preparation of **3g**, a mixture of MeOH and $CHCl_3$ is used for recrystallization. Brine instead of aq. $NaHCO_3$ is used for work-up of **3e–g**.

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