The Reaction of Trimethylsilyl α-Trimethylsilylperoxy Esters with Ketones and Aldehydes. A Simple, Efficient Synthesis of 1,2,4-Trioxan-5-ones

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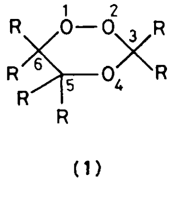
The title compounds readily react in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulphonate to give the corresponding 3,6-substituted 1,2,4-trioxan-5-ones in good yields.

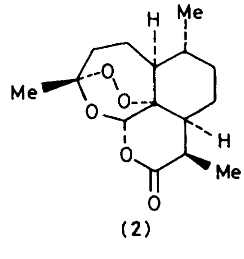
The 1,2,4-trioxane ring system (**1**) has assumed new importance since it constitutes the crucial structural element of the sesquiterpene arteannuin[1] or Qinghaosu (**2**) which is remarkable for its potent anti-malarial activity.[2] Methods for synthesizing 1,2,4-trioxanes are available,[3] but are limited in number and scope,[4] while the related 1,2,4-trioxan-5-ones are relatively unknown as chemical entities.[5] We now report our preliminary results on a short, efficient synthetic route to this new class of oxygen heterocycles.

The procedure essentially consists of allowing trimethylsilyl α-trimethylsilylperoxy esters,[6] exemplified by the t-butyl derivative (**3**; $R^1 = Bu^t$), to react with ketones such as cyclohexanone (**4**; R^2–R^3 = –[CH$_2$]$_5$–), at low temperatures (−78 to −20 °C) in the presence of trimethylsilyl trifluoromethanesulphonate (**5**) as catalyst.[7] The corresponding 3,6-substituted trioxanones (**6**) are formed cleanly and in good yield. The presumed side product, hexamethyldisiloxane (**7**), was not isolated.

In a typical experiment, cyclohexanone (**4**; R^2–R^3 = –[CH$_2$]$_5$–) (5 mmol) was added to a mixture of (**3**; $R^1 = Bu^t$) (5 mmol) and trimethylsilyl trifluoromethanesulphonate (**5**) (22 mg) in dry dichloromethane (1.5 ml) as solvent under an argon atmosphere at −78 °C. The mixture was stirred and allowed to warm to −20 °C over 4 h. Dry pyridine (0.1 ml) was added and the resulting mixture was poured into a satur-



(1)



(2)

Table 1. Yields of 1,2,4-trioxan-2-ones (**6**)[a] from α-trimethylsilylperoxy esters (**3**).

(**3**)	(**4**)	Yield of compound (**6**) (%)
$R^1 = Bu^t$	R^2–R^3 = –$[CH_2]_5$–	90
,,	R^2 = H, R^3 = Ph	25[b]
,,	$R^2 = R^3$ = Me	45
,,	R^2 = H, R^3 = Me	57[b]
,,	Adamantanone	81
R^1 = adamantyl	R^2–R^3 = –$[CH_2]_5$–	91
,,	R^2 = H, R^3 = Ph	45[b]
,,	$R^2 = R^3$ = Me	76
,,	R^2 = H, R^3 = Me	56[b]
,,	Adamantanone	81

[a] All compounds are new and gave acceptable elemental analyses.
[b] Stereochemistry not assigned.

ated aqueous sodium hydrogen carbonate solution at 0 °C and extracted with ether (3 × 10 ml). After removal of solvent, the crude product was purified by column chromatography over silica gel using diethyl ether as eluant. 3-t-Butyl-1,2,5-trioxaspiro[5.5]undecan-4-one, (**6**; $R^1 = Bu^t$, R^2–R^3 = –$[CH_2]_5$–) was obtained in 90% yield; satisfactory elemental analyses were obtained, ^{1}H n.m.r. spectrum ($SiMe_4$, $CDCl_3$): δ 1.10 (s, 9H), 1.00—2.10 (m, 10H), 4.35 (s, 1H).

The condensation procedure also worked efficiently with aldehydes and other ketones as well as with other silylperoxy esters (Table 1). However, the use of trimethylsilyl trifluoromethanesulphonate as catalyst proved indispensable. No reaction occurred without it nor when tetra-n-butylammonium fluoride was used instead. The essential step, the elimination of hexamethyldisiloxane from (**3**) consists in the formal creation of a β-peroxy cation, which we have shown elsewhere reacts efficiently with the carbonyl function to yield 1,2,4-trioxanes.[8]

In view of the ready availability of α-hydroperoxy carboxylic acids,[9] the above described procedure can be considered to be the first general approach to 1,2,4-trioxan-5-ones.

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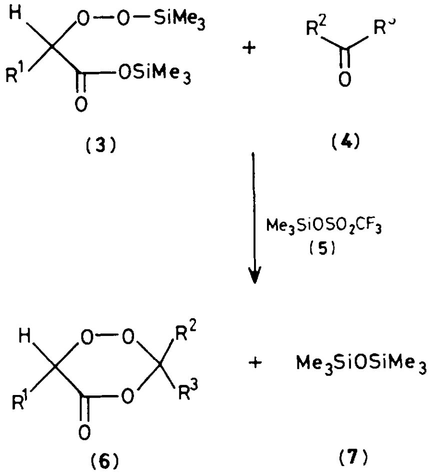

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