3,3,9,9-Tetramethyl-1,5,7,11-tetraoxaspiro[5.5]undecane as a reagent for protection of carbonyl compounds

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3,3,9,9-Tetramethyl-1,5,7,11-tetraoxaspiro[5.5]undecane is introduced as a new, stable and chemoselective reagent for the protection of aldehydes and ketones under mild reaction condition in high yield.

Keywords: aldehyde, ketone, protection, spiroorthocarbonate, transacetalisation

The protection of carbonyl groups as acetals or ketals and their subsequent regenerations is an important strategy in a multi-stage organic synthesis.[1] Numerous attempts to improve the efficiency of this process have been investigated and a number of strategies, such as the use of protic acids, Lewis acids, solid acids and ionic liquids as the catalyst, with 1,2-diols, 1,3-diols, 1,2-dithiols, 1,3-dithiols and orthoesters as the protecting reagents,[2] have been reported. Considering the importance of this transformation, the search for a new catalyst and especially a new reagent is still needed. Although some of these methods are carried out under mild reaction conditions and have been widely used in organic synthesis, others suffer from drawbacks such as relatively harsh reaction conditions and long reaction times. The search for an alternative method that can overcome these drawbacks is desirable. Most attempts have been focused on finding new catalysts, rather than new protecting agents.[3-6] In this paper, we wish to introduce 3,3,9,9-tetramethyl-1,5,7,11-tetraoxaspiro[5.5]undecane **(2)** as a promising, efficient and stable reagent for the protection of carbonyl compounds. There is only one report in the literature[7] concerning the use of 1,4,6,9-tetraoxaspiro[4.4]nonane in acetalisation of carbonyl compounds. However, because of its instability and the tedious procedure for its preparation, its application has been limited.

The spiroorthocarbonate **(2)** used in this study was easily prepared in one step from the reaction of 2,2-dimethyl-1,3-propandiol with dichlorodiphenoxymethane in the presence of pyridine in dry CH_2Cl_2 in 90% yield.[8] The resulted spiroorthocarbonate **(2)** is stable enough (m.p. = 144–146 °C, lit.[8] = 144–145 °C) to be stored at room temperature for a long time.

Initially, the reaction of benzaldehyde with the reagent **(2)** as a model was studied in different solvent systems. As shown in Table 1, aprotic solvents gave better results than the protic ones.

Various carbonyl compounds have been used as substrates to react with the spiroorthocarbonate **(2)** in the presence of catalytic amount of *p*-toluenesulfonic acid (5 mol%) in CH_2Cl_2 to give the protected compounds **3a–s** (Scheme 1).

The reaction proceeds at room temperature in relatively short time and in high yield (Table 2). Although the reactions were monitored by TLC, visual monitoring was also possible. When *p*-toluenesulfonic acid was added to a mixture of aldehyde or ketone **(1a–s)** and the spiroorthocarbonate **(2)**, the colour of the mixture turns from colourless to slightly brownish liquid, indicating acetal or ketal formation. Further on increasing the reaction time, the reverse reaction did not occur. The results in Table 2 clearly demonstrate the efficiency of this method. Aliphatic aldehydes afforded their related 1,3-dioxane with moderate yields (entries **1l** and **1m**). This method is also useful for protection of cinnamaldehyde (entry **1k**). Ketones can also be converted to the corresponding ketals but the reaction time was longer than aldehydes. This method is also applicable for protecting of relatively unreactive and steric-hindered ketones such as benzophenone and diisopropylketone (entries **1o** and **1p**). These ketones failed to react with most of the previous reported reagents.[9-12]

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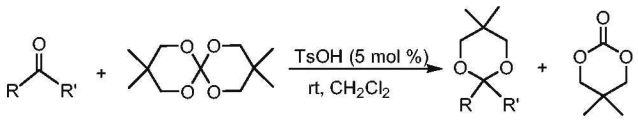
Table 1 The solvent effect on yield and time of the typical protection of benzaldehyde

Entry	Solvent	Time/min	Yield/%
1	CH_2Cl_2	10	95
2	CH_3CN	10	75
3	$CHCl_3$	60	80
4	EtOH	No reaction	–
5	MeOH	No reaction	–
6	DMSO	30	56



1a-s **2** **3a-s** **4**

Scheme 1

Since the reaction of ketone is slower than aldehyde, this method can be used for the protection of an aldehyde in the presence of a ketone. An equimolar concentration of benzaldehyde, acetophenone and spiroorthocarbonate **(2)** yielded only the protected aldehyde.

On the other hand, water is not produced in this method unlike the other reported procedures which use alcohols. Thus, the method can be especially useful for protection water-sensitive aldehydes and ketones. (entry **1s**)

In summary, the advantages of this method of protection of carbonyl compounds are chemoselectivity, mild reaction conditions, stability of the reagent, irreversibility and suitability for water-sensitive aldehydes and ketones and high yields.

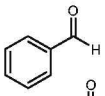
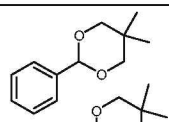
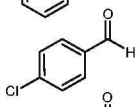
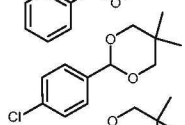
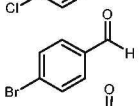
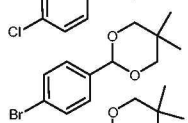
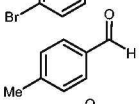
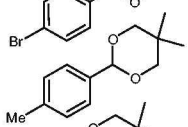
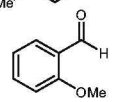
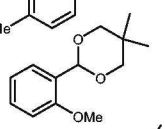
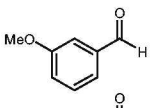
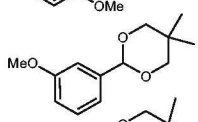
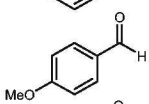
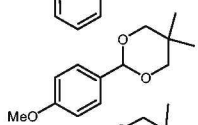
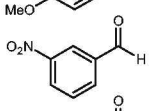
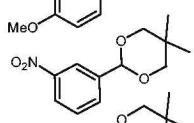
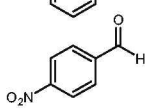
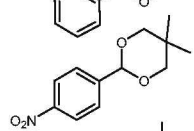
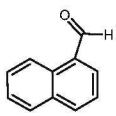
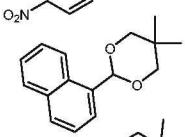
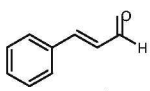
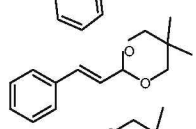
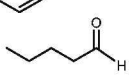
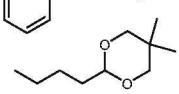
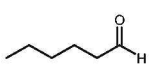
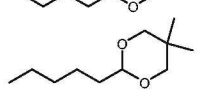
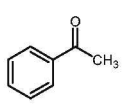
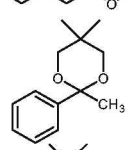
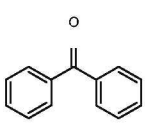
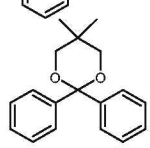
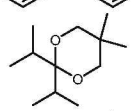
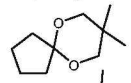
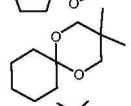
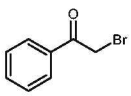
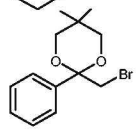
Experimental

The ^1H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. The mass spectra were obtained on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyser.

General procedure for the preparation of spiroorthocarbonate **(2)**: A solution of dichlorodiphenoxymethane (0.01 mol, 2.69 g) in dry CH_2Cl_2 (10 ml) was added dropwise in an ice-bath at 0–5 °C to a solution of neopentyl glycol (0.01 mol, 1.04 g) and pyridine (0.02 mol, 1.58 g) in dry CH_2Cl_2 (20 ml). After the addition was completed, the mixture was stirred for 2 h. Then, the solid was filtered off and the mother-liquor was washed with 5% NaOH solution and water, respectively. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting solid was recrystallised from ethyl acetate. Yield = 90%, m.p. = 144–146 °C, lit.[8] = 144–145 °C.

General procedure for the protection of aldehydes and ketones **(1a–s)**: A solution of anhydrous *p*-toluenesulfonic acid (5 mol%, 8.6 mg) in CH_2Cl_2 (1 ml) was added to a magnetically stirred solution of 3,3,9,9-tetramethyl-1,5,7,11-tetraoxaspiro[5.5]undecane

Table 2 Protection of different aldehydes and ketones by reaction with spiroorthocarbonate (**2**)

Entry	Substrate	Time/min	Product	Yield/%[a]	[Ref.][b]
1a		10		95	[9]
1b		5		96	[9]
1c		5		95	[12]
1d		10		90	[12]
1e		15		84	–
1f		15		79	–
1g		15		83	[9]
1h		5		94	[12]
1i		3		97	[9]
1j		15		71	[12]
1k		10		85	[9]
1l		15		82	[9]
1m		15		85	[9]
1n		30		88	[9]
1o		45		69	–
1p		60		70	–
1q		40		89	[9]
1r		30		91	[9]
1s		45		80	–

[a]Isolated yield. [b]The products are characterised from their spectra and comparison with authentic samples which were prepared according to lit.[12]

(1 mmol, 0.216 g) and aldehyde or ketone (1 mmol) in CH_2Cl_2 (2 ml). The solution was stirred and the progress of the reaction was monitored by TLC using petroleum ether: ethylacetate (8:2) as eluent. After the reaction was complete, the solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether: ethylacetate (8:1). The first separated fraction was the protected aldehyde or ketone while the second separated fraction was the cyclic carbonate **(4)**. The spectral data of the purified acetals or ketals were in accordance with those of the authentic samples which were prepared according to literature[12]. The authentic cyclic carbonate **(4)** was prepared from the reaction of 2,2-dimethyl-1,3-propandiol with diethyl carbonate according to literature[13] and its spectroscopic data were the same as compound **(4)**.

2-(2-methoxyphenyl)-5,5-dimethyl-1,3-dioxane **(3e)**: ^{1}H NMR ($CDCl_3$, ppm) δ 0.85 (s, 3H, $-CH_3$), 1.32 (s, 3H, $-CH_3$), 3.62 (ABA'B' q, 4H, $-CH_2$), 3.77 (s, 3H, $-OCH_3$), 5.33 (s, 1H, CH), 7.23 (m, 4H, Ar). IR (ν, cm^{-1}) 3007, 2979, 1125. *m/z* 222 (M^+). Anal. Calcd for $C_{13}H_{18}O_3$; C, 70.24; H, 8.16; Found C, 70.18; H, 8.16%.

2-(3-methoxyphenyl)-5,5-dimethyl-1,3-dioxane **(3f)**: ^{1}H NMR ($CDCl_3$, ppm) δ 0.81 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 3.69 (ABA'B' q, 4H, $-CH_2$), 3.82 (s, 3H, $-OCH_3$), 5.37 (s, 1H, CH), 7.31 (m, 4H, Ar). IR (ν, cm^{-1}) 3010, 2993, 1130. *m/z* 222 (M^+). Anal. Calcd for $C_{13}H_{18}O_3$; C, 70.24; H, 8.16; Found C, 70.12; H, 8.01%.

5,5-dimethyl-2,2-diphenyl-1,3-dioxane **(3o)**: ^{1}H NMR ($CDCl_3$, ppm) δ 1.00 (s, 6H, $-CH_3$), 3.61 (s, 4H, $-CH_2$), 7.54 (m, 10H, Ar). IR (ν, cm^{-1}) 3015, 2990, 1155. *m/z* 268 (M^+). Anal. Calcd for $C_{18}H_{20}O_2$; C, 80.56; H, 7.51; Found C, 80.46; H, 7.44%.

2,2-diisopropyl-5,5-dimethyl-1,3-dioxane **(3p)**: ^{1}H NMR ($CDCl_3$, ppm) δ 1.03 (s, 6H, $-CH_3$), 1.16 (d, 12H, $-CH_3$), 2.45 (m, 2H, –CH), 3.88 (s, 4H, $-CH_2$). IR (ν, cm^{-1}) 2946, 1115. *m/z* 200 (M^+). Anal. Calcd for $C_{12}H_{24}O_2$; C, 71.95; H, 12.08; Found C, 71.88; H, 11.97%.

2-(bromomethyl)-5,5-dimethyl-2-phenyl-1,3-dioxane **(3s)**: ^{1}H NMR ($CDCl_3$, ppm) δ 0.60 (s, 3H, $-CH_3$), 1.39 (s, 3H, $-CH_3$), 3.34 (s, 2H, $-CH_2Br$), 3.58 (ABA'B' q, 4H, $-CH_2$), 7.43 ppm (m, 5H, –Ar). IR (ν, cm^{-1}) 3010, 2975, 1175, 920. *m/z* 284 (M^+), 286 (M + 2). Anal. Calcd for $C_{13}H_{17}BrO_2$; C 54.75; H 6.01; Found C, 54.66; H, 5.92%.

5,5-dimethyl-1,3-dioxane-2-one **(4)**: (Yield = 65–93%, m.p. = 104–106 °C, *lit.*[13] 107–109 °C), ^{1}H NMR ($CDCl_3$, ppm) δ 1.05 (s, 6H, $-CH_3$), 4.26 (s, 4H, $-CH_2$). IR (ν, cm^{-1}) 2980, 1712, 1110. *m/z* 130 (M^+). Anal. Calcd for $C_6H_{10}O_3$; C 55.37; H 7.74; Found C, 55.17; H, 7.58%.

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References

1 T.W. Greene and P.G.M. Wuts, *Protective groups in organic synthesis*, 3rd edn, John Wiley & Sons, New York, 1991.
2 G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi and P. Righi, *Chem. Rev.*, 2004, **104**, 199.
3 C. Singh and H. Malik, *Org. Lett.*, 2005, **7**, 5673.
4 M. Barbasiewicz and M. Makosza, *Org. Lett.*, 2006, **8**, 3745.
5 M. Matoba, T. Kajimoto, K. Nishide and M. Node, *Chem. Pharm. Bull.*, 2006, **54**, 141.
6 P. Wang, H. Hu and Y. Wang, *Org. Lett.*, 2007, **9**, 1533.
7 D.H.R. Barton, C.C. Dawes and P.D. Magnus, *J. Chem. Soc., Chem. Commun.*, 1975, 432.
8 P. Mues and H.J. Buysch, *Synthesis*, 1990, 249.
9 B. Wang, Y. Gu, G. Song, T. Yang, L. Yang and J. Suo, *J. Mol. Cat. A: Chem.*, 2005, **233**, 121.
10 B.K. Banik, M. Chapa, J. Marquez and M. Cardona, *Tetrahedron Lett.*, 2005, **46**, 2341.
11 H. Adibi and H. Jafari, *J. Fluorine Chem.*, 2007, **128**, 679.
12 H. Eshghi, M. Rahimizadeh and S. Saberi, *Catal. Commun.*, 2008, **9**, 2460.
13 G. Schneider, M. Halmos, P. Meszaros and O. Kovacs, *Monatsh. Chem.*, 1963, **94**, 426.