Notes

[Chem. Pharm. Bull. 36(3)1135—1138(1988)]

Reaction of Cyclic Silyl Phosphites with Haloacetones

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(Received July 22, 1987)

The reaction of cyclic silyl phosphites (**2**) with haloacetones (**3**) was investigated. When oxirane compounds were used as scavengers of trimethylsilyl halides, cyclic acetonylphosphonates (**4**) were obtained directly. Treatment of 2-trimethylsilyloxy-1,3,2-dioxaphosphorinane (**2a**) with bromoacetone (**3b**) or iodoacetone (**3c**) in propylene oxide gave **4a** in 24% and 41% yields, respectively. With cyclohexane oxide, the reaction of **2a** with **3c** in MeCN at reflux gave **4a** in 50% yield. Treatment of 5,5-dimethyl-2-trimethylsilyloxy-1,3,2-dioxaphosphorinane (**2b**) with **3c** in the same manner gave **4b** in 43% yield.

Keywords——cyclic silyl phosphite; haloacetone; cyclic acetonylphosphonate; enolphosphate; Arbuzov reaction; Perkow reaction; carbonyl adduct; trimethylsilyl halide scavenger

Phosphonic acids and their esters have become increasingly important compounds in recent years because of their useful biological properties.[1] We are interested in the preparation of cyclic acetonylphosphonates (**4**), which are key intermediates for the synthesis of 1,4-dihydropyridine-5-cyclic phosphonates with calcium antagonistic activity.[2] Compounds **4** are obtained from the reactions of cyclic phosphites with haloacetones,[3] but the reactions produce complex mixtures due to competitive Perkow and Arbuzov reactions and the formation of ring-opened products. In particular, the synthetic method used to obtain 2-acetonyl-2-oxo-1,3,2-dioxaphosphorinane (**4a**) is not suitable for industrial application because of the exothermic neat reaction and low yield.

The synthesis of bis(trimethylsilyl) acetonylphosphonates utilizing diethyl trimethylsilyl phosphite has been described by Hata and co-workers,[4] but the direct preparation of dialkyl acetonylphosphonates has not been reported. We describe here a new method of preparing **4** directly from cyclic silyl phosphites (**2**) and haloacetones (**3**).

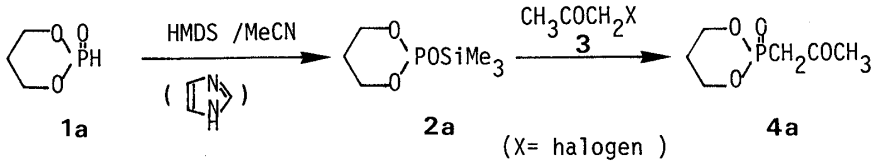
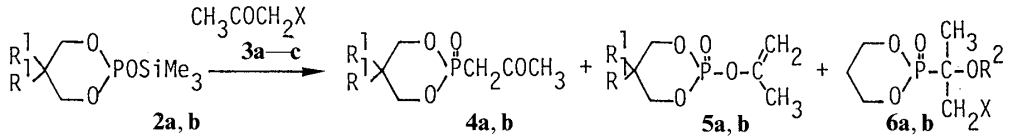


Chart 1

Results and Discussion

The silylation of hydrogen phosphites, in general, has been carried out with trimethylsilyl chloride (TMS-Cl) and triethylamine.[5] In the same manner, the cyclic hydrogen phosphite (**1a**) gave **2a** in 36% yield, but silylation with hexamethyldisilazane (HMDS) in the presence of

TABLE I. Reaction of Silyl Phosphites (**2**) with Haloacetones (**3**)



2a, b **4a, b** **5a, b** **6a, b** (R^2 = H, $SiMe_3$)

a: R^1 = H **3a**: X = Cl
b: R^1 = Me **3b**: X = Br
3c: X = I

Run	2 R^1	3 X	Scavenger[a]	Solvent	Temperature (°C)	Product (yield, %) 4	5	6
1	H	Cl	—	—	r.t.	—	14	70[b]
2	H	Br	PO	—	−10→r.t.	24	44	Trace
3	H	I	PO	—	−10→r.t.	41	6	—
4	H	I	PO	MeCN	50	46	9	—
5	H	I	CHO	—	r.t.	25	12	—
6	H	I	CHO	MeCN	Reflux	50	Trace	—
7	Me	I	PO	—	−10→r.t.	27	4	—
8	Me	I	CHO	MeCN	Reflux	43	Trace	—

a) PO = propylene oxide, CHO = cyclohexene oxide. *b*) Yield of **6** is indicated as the total yield of **6** (R^2 = H) and **6′** (R^2 = $SiMe_3$). r.t. = room temperature.

imidazole as a catalyst[6] in MeCN gave **2a** in 84% yield.

In the reaction of **2** with **3b** and **3c**, TMS-halides (TMS-X: X = Br and I) are simultaneously generated, and cause cleavage of the ester bond.[7] Therefore, the use of a scavenger of TMS-X in the reaction in desirable in order to obtain **4**. An oxirane compound, such as propylene oxide (PO), epichlorohydrin, methyl glycidol, or cyclohexene oxide, which is highly reactive with TMS-X, was employed as the scavenger of TMS-X. Among them, PO and cyclohexene oxide are especially suitable.

First, the reaction of **2** with **3** was carried out in an excess of PO at −10 °C to room temperature, except for chloroacetone (**3a**). The reaction mixture was separated by chromatography on silica gel, and the non-separated fraction was analyzed by nuclear magnetic resonance (NMR) spectroscopy. The results are summarized in Table I. The reaction of **2a** with **3a** without a solvent at room temperature gave mainly the 1 : 1 carbonyl adduct (**6a**, 70%) with the enolphosphate (Perkow product, **5a**, 14%) as a minor product. The yield of **6a** is the total yield of both silylated (**6a′**) and non-silylated (**6a**) forms. When bromoacetone (**3b**) was employed in this reaction, the acetonylphosphonate (Arbuzov product, **4a**) was obtained in 24% yield, in addition to **5a** and **6b**. The use of iodoacetone (**3c**), substituted with a stronger leaving group, gave mainly **4a** (41%), with **5a** (6%) as a minor product. These results show that the reaction mode is changed by the halogen atom of **3** as follows: **3a**, adduct≫Perkow; **3b**, adduct≪Perkow>Arbuzov; **3c**, Perkow≪Arbuzov. These reaction modes lead to somewhat different results from the reaction of acyclic silyl phosphite with **3a** (adduct) and **3b** (Perkow > Arbuzov).[4]

In respect to the effect of temperature on the reaction of phosphites with **3**, it has been that the Arbuzov product increases at high temperatures.[8] When the reaction of **2a** with **3c** was carried out in the presence of PO in MeCN at 50 °C, the yield of **4a** was slightly increased (46% yield as a colored oil). Using 5 eq of cyclohexene oxide as a scavenger at room temperature, the yield of **4a** was 25%. However, when the reaction was carried out in MeCN at reflux, compound **4a** was obtained in 50% yield as a colorless oil. Thus, the use of cyclohexene oxide at high temperatures in MeCN afforded a better result.

Similarly, the reaction of 5,5-dimethyl-2-trimethylsilyloxy-1,3,2-dioxaphosphorinane (**2b**) with **3c** gave **4b** in 27% yield when PO was used at −10 °C and in 43% yield when cyclohexene oxide was used in MeCN at reflux.

Experimental

All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a Shimadzu IR-435 spectrometer. NMR spectra were taken on a Varian YX-200 spectrometer. Chemical shifts are given in δ (ppm) with tetramethylsilane as the internal standard. Flash chromatography was performed on silica gel (Merck, Kiesel gel 60H).

2-Oxo-1,3,2-dioxaphosphorinane (1a) and 5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinane (1b)——The title compounds were prepared from dimethyl phosphite with 1,3-glycols as described by Oswald.[9]

Silylation of 1——2-Trimethylsilyloxy-1,3,2-dioxaphosphorinane (**2a**): HMDS (32.2 g, 0.2 mol) was added to a stirred solution of **1a** (24.4 g, 0.2 mol) in the presence of imidazole (0.27 g, 4 mmol) in MeCN (30 ml) at 40 °C. After the addition, the reaction mixture was refluxed for 4 h and concentrated *in vacuo*. The residue was distilled *in vacuo* to give **2a** (32.7 g, 84%) as a colorless oil, bp 63—65 °C (6 mmHg). NMR ($CDCl_3$) δ: 0.28 (9H, s), 1.25—1.80 (1H, m), 1.95—2.90 (1H, m), 3.30—4.0 (2H, m), 4.17—4.73 (2H, m).

5,5-Dimethyl-2-trimethylsilyloxy-1,3,2-dioxaphosphorinane (2b): **2b** was prepared in 85% yield in the same manner as described for **2a**, bp 82—83 °C (15 mmHg). NMR ($CDCl_3$) δ: 0.25 (9H, m), 0.72 (3H, s), 1.23 (3H, s), 3.19 (2H, t, J=10 Hz), 4.10 (2H, dd, J=10 Hz).

Reaction of 2a with Chloroacetone (3a)——A mixture of **2a** (1.94 g, 0.01 mol) and **3a** (0.92 g, 0.01 mol) was stirred for 16 h at room temperature. The reaction mixture was subjected to flash chromatography on silica gel with AcOEt–hexane to afford, in order of elution, an oily mixture (0.772 g) of the silylated carbonyl adduct (**6a′**, 18%) and **5a** (14%), which was not separated by distillation, and the carbonyl adduct (**6a**, 1.12 g, 52%).

2-(2-Chloro-1-hydroxy-1-methylethyl)-2-oxo-1,3,2-dioxaphosphorinane (**6a**): mp 117—118 °C (from AcOEt). *Anal.* Calcd for $C_6H_{12}ClO_4P$: C, 33.58; H, 5.64. Found: C, 33.45; H, 5.74. MS m/z (%): M^+ −, 122 (100). IR (KBr): 3230, 1250, 1050 cm^{-1}. NMR ($CDCl_3$) δ: 1.78 (3H, d, J=15 Hz, CH_3), 1.86—2.08 (1H, m, >CH), 2.17—2.42 (1H, m, >CH), 3.45 (1H, d, J=18 Hz, OH), 3.83, 3.99 (each of 1H, dd, J=6, 12 Hz, CH_2Cl), 4.38—4.59, 4.63—4.83 (each of 2H, m, 2×$POCH_2$).

Reaction of 2a with Bromoacetone (3b)——Bromoacetone (**3b**, 1.37 g 0.01 mol) was added to a stirred solution of **2a** (1.94 g, 0.01 mol) in PO (8.7 g, 0.15 mol) at −10 °C over a period of 15 min. After the addition, the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was subjected to flash chromatography on silica gel to afford, in order of elution, the enolphosphate **5a** (0.791 g, 44%) containing a trace amount of the silylated carbonyl adduct (**6b′**), an oily mixture (18 mg) of the carbonyl adduct (**6b**) and **1a** (ratio not obtained by NMR), and the acetonylphosphonate (**4a**, 0.433 g, 24%) as an oil.

Reaction of 2a with Iodoacetone (3c)——Iodoacetone (**3c**, 1.84 g, 0.01 mol) was added to a stirred solution of **2a** (1.94 g, 0.01 mol) in PO (8.7 g, 0.15 mol) at −10 °C over a period of 15 min. After the addition, the reaction mixture was warmed to room temperature and stirred for 16 h, then chromatographed on silica gel to afford, in order of elution, **5a** (0.106 g, 6%) as an oil and **4a** (0.73 g, 41%). **4a**[2a] and **5a**[3] were identified by NMR and IR comparisons with authentic samples.

When the above reaction was carried out in MeCN (10 ml) at 50 °C, **4a** was obtained in 46% yield as a colored oil. When the above reaction was carried out with cyclohexene oxide (5 eq) as a scavenger, **4a** was obtained in 25% yield at room temperature, in 42% yield at reflux, and in 50% yield as a colorless oil in MeCN at reflux.

Reaction of 2b with 3c——Iodoacetone (**3c**, 1.84 g, 0.01 mol) was added to a stirred solution of **2b** (2.22 g, 0.01 mol) in PO (8.7 g, 0.15 mol) at −10 °C. The reaction mixture was treated as in the case of **2a** to yield the acetonylphosphonate (**4b**, 0.553 g, 27%) as crystals; mp 89—92 °C, and the enolphosphate (**5b**, 80 mg, 4%) as crystals; mp 69—70 °C. **4b**[2a] and **5b**[3] were identified by NMR and IR comparisons with authentic samples. When the above reaction was carried out with cyclohexene oxide (5 eq) in MeCN, **4b** was obtained in 43% yield.

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