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NEW PHOSPHONIUM SALTS FOR THE WITTIG SYNTHESIS OF ALDEHYDES FROM KETONES

ACETAL, TRIPHENYL PHOSPHORANE, ENOL ETHER, ACIDIC HYDROLYSIS, NITROXYL

H. SCHLUDE*

Max-Planck-Institut für Biochemie, D-8033 Martinsried, Germany

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Abstract—Two acetals were synthesised with hydroxymethyl triphenylphosphonium chloride as the alcoholic component. Reaction with ketones in the Wittig synthesis yielded enol ethers which were hydrolysed to aldehydes under acid catalysis. Tetrahydropyranyloxy compounds could be hydrolysed under milder conditions whereas, methoxymethyl ethers needed slightly more drastic conditions than the methyl ethers normally used in this synthesis.

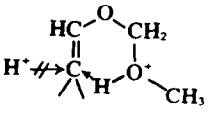
During the synthesis of nitroxyl aldehydes,[1] it was necessary to hydrolyse the methoxy compound **2** (Table 1) to the aldehyde **5** under sufficiently mild conditions to prevent destruction of the reportedly acid-sensitive nitroxyl group[2]. Compound **2** had resulted from a reaction of ketone **1** with the phosphorane from salt **12** (Table 2), commonly used in the Wittig aldehyde synthesis. The attempt was therefore made to obtain the acetal compounds **18** and **19**, not yet known, which might give access to more readily hydrolysable enol ethers.

All the phosphonium salts (**12–16**) previously used for the synthesis of aldehydes have been prepared by reaction of the corresponding chloromethylether with triphenylphosphine.[3-5] Since both the tetrahydropyranyloxy- and the methoxymethyl-derivative of chloromethyl ether had not been reported, another method was tried: synthesis of the acetals **18** and **19** from the easily accessible compound **17**[6,7] by suitable ether formation. In the reaction of **17** with chloromethylmethyl ether, hydrogen chloride was eliminated and the desired salt **18** was formed. On the other hand, the acetal **19** was obtained by addition of **17** to dihydropyran, the acid catalysis arising from the slight decomposition of the starting compound **17** into its components (triphenylphosphine, formaldehyde, and hydrogen chloride) being sufficient.

It was found practicable to synthesise **17** in methylene chloride in homogeneous solution, for reaction in ether[6] rapidly yielded precipitates with inclusion of triphenylphosphine and its hydrochloride. Triphenylphosphine then reacted in the preparation of **18** with the excess chloromethyl ether to give **12**,[4] and **12** and **18** were difficult to separate. The triphenylphosphine hydrochloride also added, without further catalysis, to dihydropyran, forming the tetrahydropyranyl compound **20**, which was useless in the synthesis of aldehydes and equally difficult to separate from **19**.

The ketones **1** and **7** reacted with the phosphonium salts **12**, **18** and **19** under the normal conditions of the Wittig reaction to give the enol ethers **2–4** and **8–10** (yields 80–85%). The amino compounds **8–10** were isolated and treated with hydrolysis mixtures of different acidities. The rate of aldehyde **11** formed was determined by gas chromatography and plotted against acidity (Fig 1).

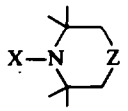
The differences in reactivity of the enol ethers can be explained in this manner. The basicity of an ether oxygen is known to follow the sequence: higher alkyl ether > methyl ether > methoxymethyl ether.[8] This basicity influences the reactivity of the double bond to electrophilic attack;[9] the observed hydrolysis properties of **8–10** fit this sequence. In addition, a neighbouring group effect of the protonated acetal oxygen in the stability of methoxymethyl ethers against hydrolysis can be considered.[10] In



the present case, attack of a proton on the β-carbon of the double bond is made more difficult by the inductive effect of the positive charge. This attack is known to be the primary step of enol ether hydrolysis.[11]

The mildest hydrolysis conditions for the acid-sensitive nitroxyls **2–4** could now be deduced from the diagram (Fig 1). Since the original objective was a direct synthesis of the aldehyde **5** from ketone **1**, purification of the intermediates **3** and **4** was neglected. Despite the mild conditions, however, in all cases simultaneous attack on the radical position took place. In strong acid (curves c and d in Fig 1 for **2** and **3**) complete destruction, in weak acid (curve a for **4**) partial destruction of the radicals was observed,[12] in the course of which hydroxylamines were formed, amongst other products (see below). Since both the unsubstituted nitroxyl **6** and the expected aldehyde **5** proved to be stable under weak acidic conditions (a), the enol ether hydrolysis and the destruction of the nitroxyl

Table 1. Derivatives of 2,2,6,6-tetramethylpiperidine



	X	Z
1	O·	>C=O
2	O·	>C=CHOCH$_3$
3	O·	>C=CHOCH$_2$OCH$_3$
4	O·	>C=CHOTHP[a]
5	O·	>CH—CHO
6	O·	>CH$_2$
7	H	>C=O
8	H	>C=CHOCH$_3$
9	H	>C=CHOCH$_2$OCH$_3$
10	H	>CH=CHOTHP[a]
11	H	>CH—CHO

[a] THP = tetrahydropyranyl-2

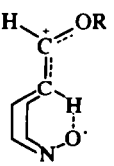
Table 2. Phosphonium salts

$((C_6H_5)_3P^+ - R)Cl^-$

	R
12	CH_3OCH_2-
13	n-$C_4H_9OCH_2$-
14	te-$C_4H_9OCH_2$-
15	$C_6H_5OCH_2$-
16	p-CH_3-$C_6H_4OCH_2$-
17	$HOCH_2$-
18	$CH_3OCH_2OCH_2$-
19	$THPOCH_2$-[a]
20	THP-[a]

[a] THP = tetrahydropyranyl-2

group must be associated, perhaps as shown:



Further studies are required to decide if the proton of the primary step of enol ether hydrolysis does indeed attack the nitroxyl group in a 6-membered ring.

The hydroxylamines from the acidic disproportionation[2] of compounds **2–4** could be reoxidised to nitroxyls by means of Fremy's salt.[1] Yield of aldehyde **5** increased from 10–40% to 30–60% if the radical position was hydrogenated[13] prior to enol ether hydrolysis.

Although the tetrahydropyranyloxy salt **19** thus gave access to enol ethers hydrolysable in acid concentrations two orders of magnitude less than for the methyl ethers normally used, the problem of a direct synthesis of the aldehyde **5** from ketone **1** could not be solved. Nevertheless the Wittig aldehyde synthesis under conditions milder than those presently used might be of general interest.

Spectroscopic data. IR(KI): The C=C bands in the enol ethers **8**, **9**, and **10** were at 1678, 1680, and 1668 cm^{-1}.

^{1}H—NMR ($CDCl_3$): The phosphonium salts **12**, **17**, **18**, **19**, and **20** show signals from all H atoms except the hydroxyl H in **17**. CH_2Cl_2, sometimes included stoichiometrically in the crystals, would interfere in the Wittig reaction by carbenoid mechanisms[14] and could be detected at 5·30(s) ppm if present. The protons at the C atom adjacent to phosphorus were at 5·96 (d, 2H), 5·43 (s, 2H), 5·95 (d, 2H), 5·53 (q, 1H) + 6·21 (q, 1H), and 6·68 (m, 1H) ppm in **12**, **17**, **18**, **19** and **20**. The P–H coupling constants were 4·0, 4·7, and 3·8 + 4·4 cs in **12**, **18** and **19**. The geminal H–H coupling constant was 14 cs in **19**. Impurities of **12** in **18** were determined by the CH_3O-signals: 3·72 ppm in **12**, 3·20 ppm in **18**. HCl-containing **17**, insoluble in $CDCl_3$, was soluble without decomposition in $SOCl_2$. The olefinic protons in **8**, **9** and **10**, were at 5·90, 6·09 and 6·18 ppm. Mass spectra: **8**, **9** and **10** show the *m/e* signals for M^+ and M^+–R (*m/e* − 168).

EXPERIMENTAL

All m.ps are uncorrected. Microanalyses were done by Alfred Bernhardt, Elbach, Germany.

Triphenyl-((methoxy)-methoxymethyl)-phosphonium chloride **18**. HCl was passed into a soln of triphenylphosphine (26·2 g, 100 mmol) in CH_2Cl_2 (100 ml) at 20° with cooling until suspended paraformaldehyde (6 g, 200 mmol) had dissolved and soln was saturated. After refluxing for 4 hr, the solvent was evaporated *in vacuo* at 30°, chloromethylmethyl ether (100 ml, 1·3 mol) was added to the oil and the soln refluxed for 22 hr. Excess reagent was removed *in vacuo* at 30°, the oil dissolved in CH_2Cl_2 (100 ml) and the soln cooled to 0°. 5 N NaOMe in MeOH (about 40 ml required) was added with efficient cooling (to keep temp at 0°) until bromothymol blue indicated alkaline conditions. The solvents were evaporated *in vacuo* at 30°, the residue treated with CH_2Cl_2 (100 ml) on filtration and the combined filtrates evaporated *in vacuo* at 30°. EtOAc (100 ml) was added, before the onset of triphenylphosphine crystallisation, and the emulsion formed was stirred for 30 min until crystallisation of **18** was complete. The crystals were washed with EtOAc (100 ml), then with hexane (50 ml) and dried at 25°/0·001 mm; yield: 16 g (42%) of colourless salt. Recrystallisation was carried out at room temp from CH_2Cl_2/ether (no inclusion of CH_2Cl_2 in the crystals), m.p. 177° dec. (Found: C, 67·63; H, 5·98; Cl, 9·65; P, 8·47; Calc. for $C_{21}H_{22}ClO_2P$ (372·9): C, 67·65; H, 5·95; Cl, 9·51; P, 8·31%).

Triphenyl - ((tetrahydropyranyloxy - 2)methyl) - phosphonium chloride **19**. HCl was passed into a soln of triphenylphosphine (262 g, 1·0 mol) in CH_2Cl_2 (250 ml) at 20°, with cooling, until 37 g (1·0 mol) were absorbed. This soln was added at 20° to a suspension of paraformaldehyde (42 g, 1·4 mol) in CH_2Cl_2 (700 ml) and stirred overnight, the temp kept at 25° by a water-bath. Ether (1L) was added with stirring to the clear filtrate, the ppt formed

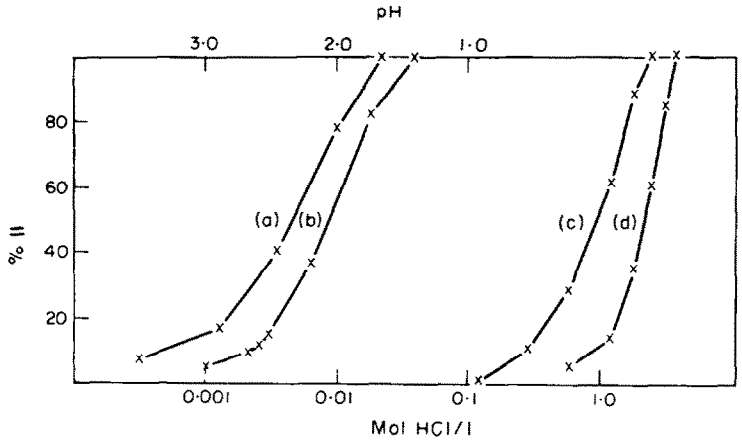


Fig 1. Yield of aldehyde **11** by hydrolysis of enol ethers **8**, **9**, and **10**

a. enol ether **10**, 17 hr, 4°, H_3PO_4
b. enol ether **10**, 17 hr, 4°, HCl
c. enol ether **8**, 16 hr, 4°, HCl
d. enol ether **9**, 19 hr, 4°, HCl

was washed with ether (150 ml), hexane (150 ml) and dried at 11 mm to yield 270 g (82%) of a colourless salt **17**, m.p. 195° dec (Lit 80%,[6] 192–4° dec,[6] 194–8° dec[7]). **17** (165 g, 0·5 mol) was dissolved in CH_2Cl_2 (1L), redistilled dihydropyran (155 ml, 1·7 mol) was added at −10° and the soln kept for 4 days at 0°. 5N NaOMe in MeOH (about 30 ml required) was added until the soln was alkaline (bromothymol blue). The suspension was stirred for 1 hr at room temp with $MgSO_4$ (20 g), filtered, the insoluble part extracted with CH_2Cl_2 and discarded, and the solvents evaporated *in vacuo* at 30°. The oily residue was dissolved in CH_2Cl_2 (200 ml), ether (400 ml) and seed crystals were added. More ether (600 ml) was added while stirring overnight. The ppt was washed with a mixture of CH_2Cl_2 (10 ml) and ether (100 ml), with ether (100 ml), and finally with hexane (100 ml), and dried at 25°/0·001 mm. Yield: 120 g (58% calc. on **17**, 47% calc. on triphenylphosphine) colourless finely powdered **19** of analytical purity, m.p. 125° dec. (Found; C, 69·66; H, 6·29; Cl, 8·64; P, 7·59; Calc. for $C_{24}H_{26}ClO_2P$ (412·9): C, 69·81; H, 6·35; Cl, 8·59; P, 7·50%). Recrystallisation of impure **19** at room temp by addition of ether to acetonitrile solns; CH_2Cl_2 instead of acetonitrile in this procedure yielded crystalline **19**, containing about 1 CH_2Cl_2/mol.

Triphenyl-(tetrahydropyranyl-2)-phosphonium chloride **20**. HCl (10 g, 0·27 mol) was passed into a soln of triphenylphosphine (80 g, 0·3 mol) in a mixture of CH_2Cl_2 (100 ml) and ether (30 ml), with cooling, at 5°. Freshly distilled dihydropyran (40 ml, 0·44 mol) was added and the soln kept 17 hr at 4°. 4N NaOMe in MeOH (about 8 ml required) was added until the soln was alkaline, the suspension was filtered and ether (250 ml) was added to the filtrate. The upper layer was discarded, the residue being dissolved in CH_2Cl_2 (100 ml); ether (250 ml) was then added while stirring overnight at 4°. The ppt was washed with a mixture of CH_2Cl_2 (10 ml) and ether (50 ml), then with ether (100 ml) and dried at 25°/0·001 mm, yield: 91 g (79% calc. on triphenylphosphine) of colourless powder. Recrystallisation at room temp from acetonitrile/ether as for **19**. M.p. 131° dec. (Found: C, 72·29; H, 6·21; Cl, 9·23; P, 8·15; Calc. for $C_{23}H_{24}ClOP$ (382·8): C, 72·15; H, 6·32; Cl, 9·26; P, 8·09%).

Enol ethers of 4-hydroxymethylene-2,2,6,6-tetramethylpiperidine. To 1·2 molar phenyllithium in ether (100 ml, 120 mmol) THF (150 ml) was added with stirring at 0° under N_2. Phosphonium salt (40 g **12**,[4] or 43 g **18**, or 48 g **19**, 115 mmol each) was then added. After 30 min, a soln of ketone **7**[15] (9·3 g, 60 mmol) in THF (20 ml) was added over 5 min at 0°. The mixture was stirred for 2–3 days at room temp, washed twice with 1N NaOH (100 ml portions), and the amines extracted with 8% HOAc aq (100 ml) and then with 1M phosphate buffer pH 5·5 (100 ml). The combined amine extracts were washed with EtOAc (50 ml), made alkaline to pH 12 with 10 M NaOH aq (20 ml), and then extracted 5 times with EtOAc (50 ml portions). The combined organic phases were cleared with carboraffin, dried with Na_2CO_3, filtered, the solvent removed *in vacuo*, and the residues distilled over a spinning band column.

Compound **8**, yield: 9·7 g (84%) colourless oil, b.p. 47°/1·0 mm, $n_D^{20} = 1{\cdot}4734$ (Found: C, 71·91; H, 11·43; N, 7·70; Calc. for $C_{11}H_{21}NO$ (183·3): C, 72·08; H, 11·55; N, 7·64%).

Compound **9**, yield: 10·8 g (85%) colourless oil, b.p. 53°/0·3 mm, $n_D^{20} = 1{\cdot}4717$ (Found: C, 67·45; H, 10·76; N, 6·60; Calc. for $C_{12}H_{23}NO_2$ (213·3): C, 67·56; H, 10·87; N, 6·57%).

Compound **10**, yield: 12·4 g (81%) colourless oil, b.p. 67°/0·0002 mm, $n_D^{20} = 1{\cdot}4888$ (Found: C, 71·27; H, 10·59; N, 5·63; Calc. for $C_{15}H_{27}NO_2$ (253·4): C, 71·10; H, 10·74; N, 5·53%). Storage at −40° yielded crystals, m.p. 24–5°.

Hydrolysis of amino enol ethers **8**, **9**, **10**. Fig 1, experiments c,d: To HCl aq (10 ml, molarities determined by titration in each case) was added **8** or **9** (10 μl each) at 0° and the solns kept overnight in the refrigerator at 4°. Fig 1, experiments a,b: To 1M KH_2PO_4 aq (10 ml), containing **10** (10 μl) was added at 0° conc H_3PO_4 (a) or conc HCl (b) to the desired pH value and the solns kept overnight in the refrigerator.

Gas chromatography was performed in all experiments (a–d), after addition of 10N NaOH to pH 12, extraction of the hydrolysis mixtures with EtOAc (10 ml in 3 portions), and drying with $MgSO_4$. This extraction procedure decreased the aldehyde concentrations in standard mixtures remarkably little and only for low aldehyde contents (within less than 5% error). Gas chromatography conditions were: 0·5 μl of the EtOAc extracts injected into a column of 3% SE 30 on chromosorb WAWDMCS at 118°, helium flow rate 40 ml/min. The method was standardised with a series of mixtures of enol ethers and **11** with a reproducibility of less than 5% error.

To determine the yields of aldehyde **11** which can be isolated, **8**,

9, and 10 (3 mmol each) were hydrolysed in 2·3N, 3·4N, and 0·04N (pH 1·4) HCl (50 ml portions). Excess 10N NaOH was added after 16–19 hr 4° and the solns extracted 3 times with EtOAc (50 ml portions). The combined EtOAc solns were dried with $MgSO_4$, the solvent evaporated *in vacuo*, the residues sublimed at 10 mm from a 55° bath, yielding 79, 71, and 69% yields of crystalline **11**, identical with an authentical sample[1] by mixed m.p. and IR spectrum.

Preparation of crude enol ethers **3** and **4**. To 1·2 molar phenyllithium in ether (100 ml, 120 mmol) THF (150 ml) was added with stirring at 0° under N_2, and then phosphonium salt (41·0 g **18** or 45·5 g **19**, 110 mmol each) was added. After 30 min, a soln of ketone **1**[16] (18·7 g, 110 mmol) in THF (30 ml) was added at 0°. The mixture was stirred for 2–3 days at room temp, then extracted twice with water (100 ml portions), the solvents being evaporated *in vacuo* at 30°. The oily residue was shaken with hexane (200 ml) until crystalline, brownish triphenylphosphine oxide (about 26 g) was formed. The crystals were extracted with hexane (100 ml) and discarded, and the combined hexane solns evaporated *in vacuo*, yielding crude **3** and **4** (20 g and 27 g) as red oils.

Determination of the stabilities of nitroxyl radicals.[12] Nitroxyl **6**,[17] aldehyde **5**,[1] and enol ethers **2**,[1] **3** and **4** were dissolved in THF to about 0·001 molar solns. Aliquots (100 μl) were injected into 2·3N HCl, 3·4N HCl, and pH 1·5 phosphate buffer (3 vol 1M H_3PO_4 + 1 vol 1M KH_2PO_4) (25 ml portions) and kept at 4° for 16–19 hr. Radical concentrations were measured at room temp and compared with solns of untreated aliquot parts (100 μl) in water (25 ml). The reproducibility of measured radical concentrations was within ±10%. In 2.3N and 3.4N HCl, all radical concentrations decreased to less than 1%. In pH 1·5 buffer, radical concentrations **6**, **5**, **2**, and **4** decreased to 90, 87, 89, and 21%.

Direct hydrolysis of nitroxyl enol ethers **2**, **3**, *and* **4**. Enol ethers **2**,[1] **3**, and **4** (1 mmol) were stirred with 2·3N HCl, 3·4N HCl, and phosphate buffer pH 1·5 (30 ml portions) for 16–19 hr at 4°. 10N KOH and KH_2PO_4 aq were added to pH 8, then Fremy's salt was added until the solns remained violet.[1] The impure aldehyde **5** was extracted with EtOAc and did not crystallise on evaporation of the solvent. Weighed amounts of nitroxyl **6**[17] were added to the solns as internal standard and gas chromatography was done under the conditions described at "hydrolysis of amino enol ethers", the method this time being standardised with a scale of mixtures of **5** and **6**. Yields of **5** from **2**, **3**, and **4** thus determined were 45, 10, and 40%.

Hydrolysis of nitroxyl enol ethers **2**, **3**, *and* **4** *via hydroxylamines.* Enol ethers **2**, **3**, and **4** (5 mmol each) were hydrogenated in MeOH (50 ml) over PtO_2,[13] the solvent removed *in vacuo* and the hydroxylamines hydrolysed, reoxidised and determined as described in "direct hydrolysis of nitroxyl enol ethers". Yields of aldehyde **5** determined by gas chromatography were 71, 65, and 50%. Yields of crystalline **5** after sublimation at 50°/0·001 mm were 64, 55, and 32%, identical with an authentical sample[1] (in mixed m.p. and IR spectrum).

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