A New Ready, High-Yielding, General Procedure for Acetalization of Carbonyl Compounds[1]

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Carbonyl compounds are smoothly and rapidly acetalized by treatment with alcohols, in anhydrous acetonitrile, in the presence of polystyryl diphenyl phosphine – iodine complex as catalyst. Open and cyclic acetals, including 1,3-dioxolanes, 1,3-oxathiolanes, and 1,3-dithiolanes, of miscellaneous aldehydes and ketones have been successfully prepared in this way. The isolation of the product is very easily performed, by simple filtration of the polymer-linked phosphine oxide which is formed in the reaction.

Acyclic and cyclic acetals, as well as dithioacetals and oxathioacetals (1,3-oxathiolanes), are commonly encountered in synthetic organic chemistry, as they are conveniently used for protection of the carbonyl group of aldehydes or ketones.

The acetalization reaction is mostly carried out in alcoholic media, using Brønsted acid catalysts. Under the equilibrating conditions, water is formed which must be removed from the reaction mixture by either physical or chemical methods.[2]

As a part of a current study on synthetic application of triarylphosphinehalogen complexes,[3,4] we have now devised a quite new procedure to prepare acetals, directly from carbonyl compounds and alcohols or diols (dithiols and hydroxythiols as well), in anhydrous medium, avoiding water formation. In fact, under our conditions, the carbonyl compound is treated in anhydrous acetonitrile with polystyryl diphenyl phosphine-iodine complex (polystyryl diphenyl iodophosphonium iodide) and, after some minutes, with the desired "-ol" reagent. An

Table. Direct Acetalization Reactions Catalyzed by Polystyryl Diphenyl Phosphine-Iodine Complex

Carbonyl Compound	Reagent	Ratio[a]	Time (min)	Product	Yield[b] (%)	m.p. (°C) or b.p. (°C)/mbar	Molecular Formula[c] or Lit. Data	^{1}H-NMR ($CDCl_3$) δ (ppm)
1a	**2c**	1:4:1.2	60	**3ac**	80	108/16	102–103/12[12]	2.0 (s, 3H, CH_3); 3.9 (s, 4H, $-OCH_2CH_2O-$)
	2c[d]	1:4:1.2	60	**3ac**	87			
	2d	1:4:1.2	60	**3ad**	98	141/15	131/4[13]	2.1 (s, 3H, CH_3); 3.3 (s, 4H, $-SCH_2CH_2S-$)
	2e[d]	1:4:1.2	60	**3ae**	92	114/15	106/3[14]	1.8 (s, 3H, CH_3); 3.3 (m, 2H, $-SCH_2-$); 4.2 (m, 2H, $-CH_2O-$)
1b	**2d**	1:4:1.2	60	**3bd**	86	108–109	106[15]	3.4 (s, 4H, $-SCH_2CH_2S-$)
	2e	1:4:1.2	90	**3be**	88	45–46	42–43[14]	3.2 (t, 2H, J = 6.0 Hz, $-SCH_2-$); 4.2 (t, 2H, J = 6.0 Hz, $-CH_2O-$)
1c	**2d**	1:4:1.2	60	**3cd**	98	137/4	109/0.9[16]	3.5 (s, 4H, $-SCH_2CH_2S-$); 5.7 (s, 1H, $-CH=$)
	2e	1:4:1.2	60	**3ce**	85	62–63	60–63[17]	3.4 (t, 2H, J = 6.0 Hz, $-SCH_2-$); 3.9 (t, 2H, J = 6.0 Hz, $-CH_2O-$); 5.9 (s, 1H, $-CH=$)
1d	**2c**[d]	1:3:1.2	45	**3dc**	90	oil	$C_9H_{16}O_2$ (156.2)	0.8 (d, 3H, J = 5.0 Hz, CH_3); 3.9 (s, 4H, $-OCH_2CH_2O-$)
	2d	1:1:1.2	20	**3dd**	95	oil	$C_9H_{16}S_2$ (188.4)	0.8 (d, 3H, J = 5.0 Hz, CH_3); 3.2 (s, 4H, $-SCH_2CH_2S-$)
1e	**2a**[d]	1:2:1.2	60	**3ea**	80	115/15	106/13[18]	0.9 (s, 9H, t-C_4H_9); 3.3 (s, 6H, $-OCH_3$)
	2c	1:3:1.2	15	**3ec**	90	27–30	$C_{12}H_{22}O_2$ (198.3)	0.9 (s, 9H, t-C_4H_9); 3.9 (s, 4H, $-OCH_2CH_2O-$)
	2c[d]	1:3:1.2	15	**3ec**	98			
	2b	1:2:1.2	60	**3eb**	92	oil	$C_{18}H_{36}S_2$ (316.6)	0.9 (s, 9H, t-C_4H_9); 2.7 (m, 4H, $-CH_2S-$)
	2d	1:1:1.2	10	**3ed**	98	63–65	$C_{12}H_{22}S_2$ (230.4)	0.9 (s, 9H, t-C_4H_9); 3.3 (s, 4H, $-SCH_2CH_2S-$)
1f	**2c**[d]	1:1:1.2	30	**3fc**	94	107–110	113[6]	3.8 (s, 4H, $-OCH_2CH_2O-$)
	2d	1:1:1.2	15	**3fd**	97	145–146	142–144[19]	3.3 (s, 4H, $-SCH_2CH_2S-$)
	2e	1:1:1.2	15	**3fe**	95	134–136	133–134[19]	2.9 (m, 2H, $-SCH_2-$); 4.0 (m, 2H, $-CH_2O-$)
1g	**2c**[d]	1:6:2.0	60	**3gc**	83	166–167	161–165[19]	3.8 (s, 4H, $-OCH_2CH_2O-$); 5.3 (m, 1H, $-CH=$)
	2d	1:6:2.0	30	**3gd**	94	190–192	191–192[19]	3.1 (s, 4H, $-SCH_2CH_2S-$); 5.3 (m, 1H, $-CH=$)
	2e	1:6:2.0	45	**3ge**	90	181–183	183–184[19]	3.2 (t, 2H, J = 6.0 Hz, $-SCH_2-$); 4.3 (t, 2H, J = 6.0 Hz, $-CH_2O-$); 5.3 (m, 1H, $-CH=$)
1h	**2c**[d]	1:1:1.2	30	**3hc** (only at C-3)	92	157–158	155–156[20]	3.9 (s, 4H, C-3, $-OCH_2CH_2O-$)
	2c	1:6:2.0	90	**3hc**	90	153–155	157–160[20]	3.8 (s, 8H, C-3 and C-17, $-O(CH_2)_2O-$)
	2d	1:1:1.2	10	**3hd** (only at C-3)	98	198–200	$C_{21}H_{32}OS_2$ (364.6)	3.3 (s, 4H, C-3, $-SCH_2CH_2S-$)
	2d	1:6:2.0	60	**3hd**	96	174–175	$C_{23}H_{36}S_4$ (440.8)	3.2 (s, 8H, C-3 and C-17, $-S(CH_2)_2S-$)
1i	**2c**[d]	1:1:1.2	30	**3ic**	84	97/40	115/60[21]	3.9 (s, 4H, $-OCH_2CH_2O-$); 5.3 (t, 1H, J = 6.5 Hz, $-CH=$)
	2d	1:1:1.2	10	**3id**	98	oil	$C_{10}H_{20}S_2$ (204.4)	3.4 (s, 4H, $-SCH_2CH_2S-$); 4.5 (t, 1H, J = 7.0 Hz, $-CH=$)
	2e	1:1:1.2	15	**3ie**	85	oil	$C_{10}H_{20}OS$ (188.3)	3.1 (m, 2H, $-SCH_2-$); 3.8 (m, 2H, $-CH_2O-$); 5.1 (t, 1H, J = 6.0 Hz, $-CH=$)
1j	**2f**	1.1:1:1.2	30	**3jf**	98	118–120	117–118[22]	1.3, 1.5 (2s, 6H, $2CH_3$); 4.0, 4.2 (2m, 2H, H-2, H-3)

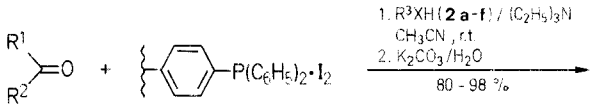
[a] Substrate: reagent: catalyst molar ratio.

[b] Yield of isolated product. Purity >94%.

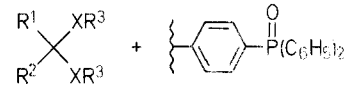
[c] Satisfactory microanalysis obtained: C ±0.47, H ±0.32. Exceptions **3dc**, C +0.92; **3dd**, C −0.58; **3ec**, C −0.78; **3hd**, C +0.55; **2hd**, C −0.62; **2ie**, C −0.73.

[d] Reaction carried out in the presence of triethylamine.

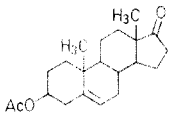
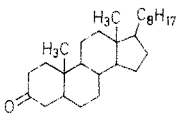
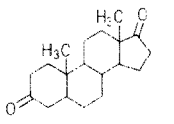
adduct is first formed, due to the occurrence of the positively charged phosphorus atom in the complex and the electron-rich carbonyl oxygen, thus enabling the carbonyl carbon atom to undergo nucleophilic attack by a molecule of the "-ol" reagent. The subsequent non-equilibrium step of the reaction is loss of polymer-linked phosphine oxide and thereby formation of an oxygen-stabilized carbocation, known to be intermediate in acetalization reactions,[5] that can be attacked by a second reagent molecule to afford the final product.

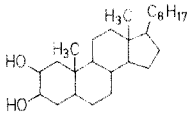


1a-j



3ac-jf (X = O, S)

1	R^1	R^2	1	R^1	R^2
a	C_6H_5	CH_3			
b	C_6H_5	C_6H_5			
c	C_6H_5	H	g		
d	$-(CH_2)_4CH(CH_3)-$				
e	$-(CH_2)_2CH(t\text{-}C_4H_9)(CH_2)_2-$				
f			h		
			i	$n\text{-}C_7H_{15}$	H
			j	CH_3	CH_3

2		2	
a	CH_3OH	e	$HO-(CH_2)_2-SH$
b	$n\text{-}C_4H_9SH$		
c	$HO-(CH_2)_2-OH$	f	
d	$HS-(CH_2)_2-SH$		

This procedure appears to be quite general for aliphatic and aromatic aldehydes and ketones, as shown in the Table. The reaction is carried out under mild conditions, at room temperature, and is generally fast and high-yielding. In order to prevent sometimes undesirable acidity of the medium, anhydrous triethylamine was added portionwise throughout the course of the reaction. An additional very important feature of the procedure is represented by its very simplified work-up that in principle requires only filtration of the suspended polymeric material and evaporation of the filtrate for product isolation. Comparison experiments, performed according to literature procedures,[6-8] led in general to less satisfactory results, in consideration of both reaction time and yield.

Polystyryl diphenyl phosphine-iodine complex is an easy to prepare,[3] handy, semicrystalline solid, reasonably stable at room temperature. When dried and kept properly, it can be stored for weeks at room temperature, under argon (or nitrogen) atmosphere. The somewhat high cost of the starting polystyryl diphenyl phosphine does not actually represent a limitation of this procedure, if one considers that the polymer-linked phosphine oxide formed in the reaction can be readily reduced to the original phosphine form with trichlorosilane.[9]

When comparing with one of the most reliable, reported practical methods to prepare acetals under anhydrous and non-equilibrating conditions, i.e. the trimethylsilyl triflate catalyzed reaction of carbonyl compounds with alkoxytrimethylsilanes,[10] our procedure still represents an effective improvement, in view of the possibility of preparing dithioacetals and oxathioacetals, beside simple acetals. Considering also its ready feasibility and simplified work-up, this procedure should find rather broad application in synthesis. As an example, work on carbohydrates is already in progress in our laboratory.

Unless stated otherwise, all reagents were obtained commercially and used without further purification. Anhydrous acetonitrile (reagent grade, Carlo Erba) was obtained according to the literature.[11] Polystyryl diphenyl phosphine (PDP) was purchased from Fluka AG (Switzerland). Preparation of the iodine complex (PDP-I_2) was already reported elsewhere.[3]

Acetophenone 1,3-Dioxolane (3ac); Typical Procedure:

To a magnetically stirred suspension of polystyryl diphenylphosphine-iodine complex (1.2 mmol – iodine units; prepared *in situ* or stored[3]) in anhydrous acetonitrile (15 ml) in a 50-ml round bottomed flask equipped with a septum, at room temperature and under a dry argon (or nitrogen) atmosphere, a solution of acetophenone (**1a**; 0.12 g; 1.0 mmol) in the same solvent (3 ml) is added *via* syringe in one portion. After 15–20 min a 1 molar solution of ethanediol (**2c**) in anhydrous acetonitrile (4.0 ml) is also added in one portion. [If necessary, (see text): anhydrous triethylamine (2.0 mmol), diluted by the same solvent, is added *via* microsyringe at regular intervals over the reaction time.] TLC monitoring (eluent: hexane/ether, 9:1) show the complete disappearance of the starting ketone within 40 min. Solid potassium carbonate (excess) is then added, and the suspension is stirred for 2 min and finally filtered. The residual solid is washed with ether (3 × 10 ml) and the combined filtrate, after shaking with 5 normal sodium thiosulfate solution (3 × 5 ml) and water (2 × 10 ml) is dried with sodium sulfate and concentrated by rotary evaporation, leaving a residue consisting of the practically pure (TLC, ^{1}H-NMR) acetophenone 1,3-dioxolane (**3ac**); yield: 0.14 g (87%) (Table).

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This work is dedicated to the memory of Prof. G. Laonigro.

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