Partial Reduction of Dithioacetals with Phosphorus Reagents

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Synopsis. Acyclic dithioacetals **1** derived from di- and monoaryl ketones were monodesulfurized with diphosphorus tetraiodide or dimethyl phosphonate. A side product **5** from the reaction of 9,9-bis(ethylthio)-9*H*-fluorene with phosphorus triiodide suggested the intermediacy of an anionic species.

There have been many studies on the reduction[1] and deprotection[2] of dithioacetals because of their synthetic utility. Previously, we reported that the reaction of dithiolanes with diphosphorus tetraiodide (P_2I_4) selectively gave the corresponding deprotected or reduced products.[3] Here we wish to report that acyclic dithioacetals **1** derived from di- and monoaryl ketones can be monodesulfurized[4] by treatment with P_2I_4[5,6] under mild conditions. In addition, further studies have been carried out using monophosphorus reagents, because the reaction mode of the diphosphorus reagent would be more complex than those of monophosphorus reagents.

Results and Discussion

Reaction of Dithioacetals with Diphosphorus Tetraiodide or Phosphorus Triiodide. As shown in Table 1, the reaction of diaryl ketone dithioacetals of diaryl ketones (**1a**, **1b**, **1c**, **1f**, and **1g**) mainly led to partially reduced products **2**. In the cases of **1d** and **1e**, selectivity and yields of **2d** and **2e** were much improved by the addition of water (Runs 10 and 12). This finding suggested that we use phosphonic acid having both a hydrogen atom and a hydroxyl group instead of P_2I_4, but the yield of **2b** was very low (Run 6). Although dithioacetal **1g** having an alkyl moiety could also be partially reduced, dialkyl ketone dithioacetals were not reduced, but only slowly decomposed.

The second reductive cleavage of the carbon–sulfur bond to yield the corresponding methylene compounds **3** was very slow (Run 2). In the cases of **1c** and **1f**, addition of water accelerated the reduction reaction to give 4-chlorodiphenylmethane (**3c**)[7] and 4-methoxydiphenylmethane (**3f**)[8] (Runs 8 and 15).

When bis(phenylthio) derivative **7** was used instead of **1a**, a monodesulfurized product was not obtained, but diphenylmethane was directly formed from **7** (Run 17).

In Runs 8 and 12, **3c** containing 75% deuterium at the methylene position and **2e** containing 41% deuterium at the methine position were obtained, respectively. In contrast, treatment of **1b** with P_2I_4 in CD_2Cl_2 followed by a workup with D_2O gave **2b** (71% yield) without deuteration. These results suggest that the hydrogen atoms used for the reduction are derived from a trace

Table 1. Reaction of Dithioacetals with P_2I_4 and PI_3[a]

4 **1** **2** **3**

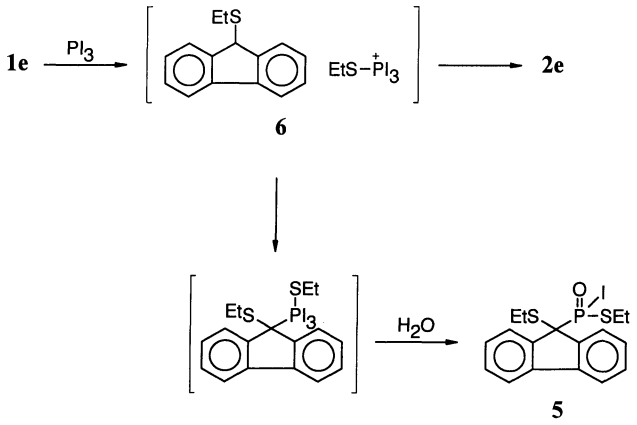
Run	Dithioacetal			Reagent	H_2O	Time	2, 4, and 3	
	R^1	R^2			equiv	h	Yield/%	**2**: **4**: **3**
1	Ph	Ph	**1a**	P_2I_4	0	2.0	85	85:15 —
2				P_2I_4	0	24	51	8:25:67
3	4-O_2N-C_6H_4	Ph	**1b**	P_2I_4	0	1.8	86	94: 6 —
4				P_2I_4[b]	0	1.0	94	49:51 —
5				PI_3	0	1.0	74	49:51 —
6				H_2PHO_3	0	24	14	36:64 —
7	4-Cl-C_6H_4	Ph	**1c**	P_2I_4	0	2.0	94	86:14 —
8				P_2I_4	D_2O, 2	20	80	— 6:94
9	4-Br-C_6H_4	Ph	**1d**	P_2I_4	0	2.0	71	51:49 —
10				P_2I_4	1	0.8	85	89:11 —
11	9,9-Bis(ethylthio)-9*H*-fluorene		**1e**	P_2I_4	0	1.0	93	65:35 —
12				P_2I_4	D_2O, 1	1.5	87	90:10 —
13				PI_3	0	1.0	53[c]	68:32 —
14	4-MeO-C_6H_4	Ph	**1f**	P_2I_4	0	48	49	84:16 —
15				P_2I_4	2	7	72	— 6:94
16	4-O_2N-C_6H_4	Me	**1g**	P_2I_4	0	2.0	88	78:22 —
17	$Ph_2C(SPh)_2$		**7**	P_2I_4	0	24	55[d]	— 22:78

a) Molar ratio, dithioacetal: reagent=1 : 1; CH_2Cl_2; ca. 25 °C. b) Solvent, benzene. c) Phosphonate derivative **5** was isolated in a 26% yield. d) Recovery of **7**, 11%.

Table 2. Reaction of Dithioacetals with Dimethyl Phosphonate[a)]

Dithioacetal		1	Base	Temp	Time	Yield of 2
R^1	R^2			°C	h	%
Ph	Ph	**1a**	DBU	80	18	75
			NaOMe	65	15	0
4-Cl-C_6H_4	Ph	**1c**	DBU	25	66	84
9,9-Bis(ethylthio)-9*H*-fluorene		**1e**	—	25	24	0
			DBU	25	0.5	84
			NaOMe	60	1.0	93
4-O_2N-C_6H_4	Me	**1g**	DBU	120	92	38

a) Molar ratio, **1** : $HP(O)(OMe)_2$: DBU (or 2 mol dm^{-3} NaOMe in MeOH)=1 : 4 : 4.



Scheme 1.

amount of water present in the reaction system, so it is not neccessary for the reaction atmosphere to be completely dry for the reduction of **1**.

Because the diphosphorus reagent was transformed into a complex mixture, dithioacetals **1** were allowed to react with several monophosphorus reagents. However, the selectivity of **2** against deprotected products **4** was not high. The reaction of **1** with phosphorus tribromide, triethyl phosphite, or dimethyl phosphonate in CH_2Cl_2 failed to give **2**. On the other hand, we succeeded in obtaining 9-fluorenylphosphonate derivative **5** in the reaction of **1e** and phosphorus triiodide (Run 13). The analogous phosphonate derivative could not be obtained from **1b** (Run 5). These results suggest that nucleophilic attack by the trivalent phosphorus reagent upon the sulfur atom in **1e** gives a relatively stable cyclopentadienyl anion or ion-paired intermediate **6**, which would in part combine through the carbon–phosphorus bond to form **5** after an aqueous workup (Scheme 1). On the other hand, **1b** would be transformed into a relatively unstable intermediate and would be protonated to give **2b**.

Selective Partial Reduction of Dithioacetals with Dimethyl Phosphonate. As shown in Table 2, dithioacetals **1a**, **1c**, and **1e** were converted into monodesulfurized products in good yields by treatment with dimethyl phosphonate and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU). By analogy with the above-mentioned results, nucleophilic attack by the phosphorus reagent upon the sulfur atom of **1** resulted in formation of the sulfides **2**. In the case of **1e**, partial reduction was almost complete by using sodium methoxide in methanol instead of DBU.

The monodesulfurization method based on dimethyl phosphonate could not be applied to the partial reduction of dithioacetals derived from dialkyl ketones, but dithioacetal **1g** having an alkyl moiety was transformed into **2g** in a low yield.

Experimental

IR spectra of neat liquid film samples were recorded on a Shimadzu FTIR-4200 infrared spectrometer, and ^1H NMR spectra in $CDCl_3$ on a JEOL JNM-GX270 spectrometer. Spectral data of **1a**,[9)] **1e**,[10)] **1g**,[11)] **2a**,[12)] **2e**,[13)] and **7**[9)] were identical to the reported data.

Preparation of Dithioacetals 1 and 7. Dithioacetals were prepared from the corresponding ketones,[14)] and the yields (%) were much improved by the addition of molecular sieves 3A; **1b** (93), **1c** (74), **1d** (80), **1f** (74).

1-[α,α-Bis(ethylthio)benzyl]-4-nitrobenzene (1b). IR 1580, 1510, 1350, 1100, and 840 cm^{-1}; ^1H NMR δ=1.06 (6H, t, *J*=7.4 Hz), 2.35 (4H, q, *J*=7.4 Hz), and 7.2—8.1 (9H, m). Anal. ($C_{17}H_{19}NO_2S_2$) C, H, N, S.

1-[α,α-Bis(ethylthio)benzyl]-4-chlorobenzene (1c). IR 1480, 1440, 1090, and 1015 cm^{-1}; ^1H NMR δ=1.06 (6H, t, *J*=7.7 Hz), 2.33 (4H, q, *J*=7.7 Hz), and 7.2—7.5 (9H, m). Anal. ($C_{17}H_{19}ClS_2$) C, H, Cl, S.

1-[α,α-Bis(ethylthio)benzyl]-4-bromobenzene (1d). IR 1480, 1440, 1390, and 1000 cm^{-1}; ^1H NMR δ=1.07 (6H, t, *J*=7.6 Hz), 2.33 (4H, q, *J*=7.6 Hz), and 7.2—7.5 (9H, m). Anal. ($C_{17}H_{19}BrS_2$) C, H, Br, S.

1-[α,α-Bis(ethylthio)benzyl]-4-methoxybenzene (1f). Bp 148—150 °C (bath temp/0.6 mmHg, 1 mmHg=133.322 Pa); IR 1600, 1510, 1500, and 1250 cm^{-1}; ^1H NMR δ=1.07 (6H, t, *J*=7.4 Hz), 2.35 (4H, q, *J*=7.4 Hz), 3.80 (3H, s), and 7.2—7.6 (9H, m). Anal. ($C_{18}H_{22}OS_2$) C, H, S.

Reaction of Dithioacetals with P_2I_4, PI_3, or H_2PHO_3. Synthesis of 1-[α-(Ethylthio)benzyl]-4-chlorobenzene (2c): (A Typical Procedure). A mixture of 1-[α,α-bis(ethylthio)-benzyl]-4-chlorobenzene (**1c**) (105 mg, 0.33 mmol), P_2I_4 (186 mg, 0.33 mmol), and CH_2Cl_2 (4.7 ml) was stirred at room temperature under a nitrogen atmosphere. After 2 h, CH_2Cl_2 (10 ml) and 10% aqueous $NaHSO_3$ (5 ml) were added. The organic layer was washed with brine and concentrated. Purification by preparative TLC (hexane–ethyl acetate 7 : 1) gave 1-[α-(ethylthio)benzyl]-4-chlorobenzene (**2c**) (69 mg, 81% yield) along with 4-chlorobenzophenone (**4c**) (9 mg, 13% yield). Sulfide **2c** showed IR 1490, 1450, 1120, and 1090 cm^{-1}; ^1H NMR δ=1.21 (3H, t, *J*=7.4 Hz), 2.39 (2H, q, *J*=7.4 Hz), 5.14 (1H, s), and 7.2—7.4 (9H, m). Anal. ($C_{15}H_{15}ClS_2$) C, H, Cl, S.

1-[α-(Ethylthio)benzyl]-4-nitrobenzene (2b): IR 1600, 1510, 1340, and 1270 cm^{-1}; ^1H NMR δ=1.23 (3H, t, *J*=7.4 Hz), 2.43

(2H, q, J=7.4 Hz), 5.24 (1H, s), and 7.3—8.2 (9H, m). Anal. ($C_{15}H_{15}NO_2S$) C, H, N, S.

1-[α-(Ethylthio)benzyl]-4-bromobenzene (2d): IR 1480, 1440, 1070, and 1000 cm^{-1}; ^1H NMR δ=1.20 (3H, t, J=7.4 Hz), 2.39 (2H, q, J=7.4 Hz), 5.12 (1H, s), and 7.2—7.4 (9H, m). Anal. ($C_{15}H_{15}BrS$) C, H, Br, S.

1-[α-(Ethylthio)benzyl]-4-methoxybenzene (2f):[15] IR 1610, 1500, 1420, and 1220 cm^{-1}; ^1H NMR δ=1.24 (3H, t, J=7.4 Hz), 2.42 (2H, q, J=7.4 Hz), 3.78 (3H, s), 3.91 (1H, s), and 6.8—7.4 (9H, m).

1-[1-(Ethylthio)ethyl]-4-nitrobenzene (2g): ^1H NMR δ=1.17 (3H, t, J=7.3 Hz), 1.59 (2H, d, J=7.3 Hz), 2.33 (2H, q, J=7.3 Hz), 4.05 (1H, q, J=7.0 Hz), 7.51 (2H, d, J=8.8 Hz), and 8.18 (2H, d, J=8.8 Hz). Anal. ($C_{10}H_{13}NO_2S$) C, H, N, S.

9-(Ethylthio)-9-[(ethylthio)iodophosphinyl]fluorene (5): IR 1450, 1260, 1208, 745, and 538 cm^{-1}; ^1H NMR δ=0.94 (3H, t, J=7.2 Hz), 1.35 (3H, t, J=7.2 Hz), 2.37 (1H, dq, J=11.7 and 7.2 Hz), 2.44 (1H, dq, J=11.7 and 7.2 Hz), 2.99 (1H, tq, J=12.6 and 7.7 Hz), 3.05 (1H, tq, J=12.6 and 7.7 Hz), 7.36—7.55 (4H, m), 7.77 (2H, dd, J=7.4 and 4.1 Hz), 7.99 (1H, dd, J=7.9 and 2.8 Hz), 8.07 (1H, dd, J=7.5 and 2.6 Hz); MS m/z (%) 461 (M^+, 20), 226 (M^+−P(O)ISEt, 100); 165 (M^+−P(O)ISEt−SEt, 50). Anal. ($C_{17}H_{18}IOPS_2$) C, H, I, P.

Reaction of Dithioacetal with Dimethyl Phosphonate: (General Procedure). Dithioacetal **1** and dimethyl phosphonate (4 equiv) were stirred with DBU (4 equiv) or with NaOMe in methanol (2 mol dm^{-3}, 4 equiv). An extractive workup followed by purification by preparative TLC gave **2**.

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