The Conjugate Addition of Glyoxalate-Derived Anion Equivalents by Phase Transfer Catalysis

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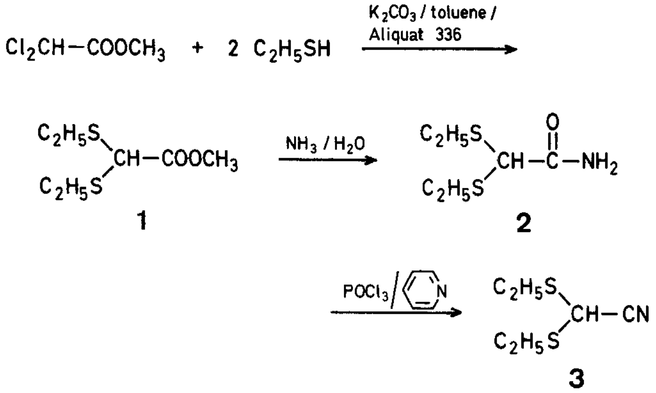
Thioacetals of α-oxoesters are widely utilized as intermediates in organic synthesis, for example, in the preparation of alkaloids[1], metabolite microbials[2,3], and carbohydrates[4,5]. The conjugate addition of carbonyl anion equivalents derived from glyoxylic acid to Michael receptors has been studied[1,6,7] and the influence of the counterion and the solvent on 1,2- or 1,4-addition selectivity evaluated[8]. The practical application of these reactions suffers from certain limitations in scope and they involve generally the use of anhydrous aprotic solvents, inert atmosphere, and alkyllithium derivatives or alkaline metal hydrides.

We now report the successful utilization of highly reactive carbanions derived from methyl bis[ethylthio]acetate (**1**) and bis[ethylthio]acetonitrile (**3**) in Michael additions to α,β-unsaturated compounds (**4–8**) by phase transfer catalysis. To our knowledge, no examples of this reaction are known, and only recently an unsuccessful attempt has been reported[9]. The procedure we describe is a very convenient alternative to preparations of 2,5-dioxoesters and nitriles, and related compounds, because of ready availability of the reagents, the mild reaction conditions, the easy performance and work-up, and the excellent yields of the products.

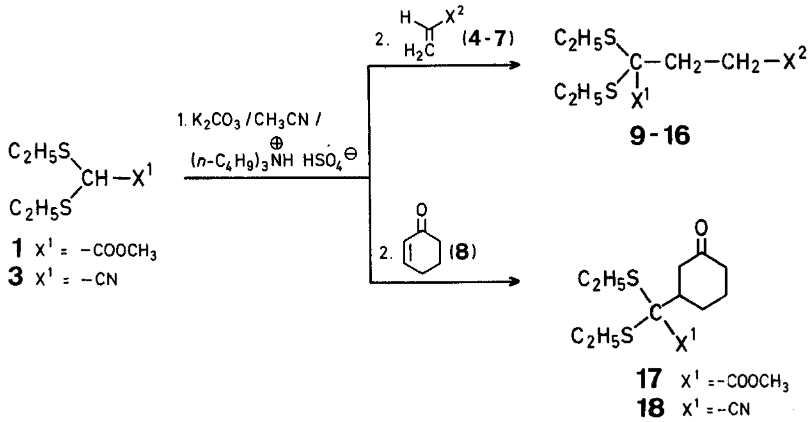


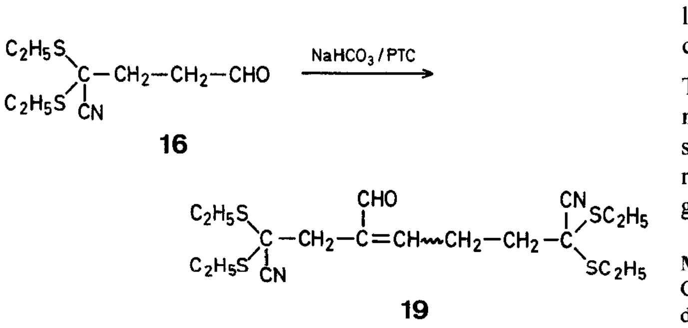
Methyl bis[ethylthio]acetate (**1**), a readily available compound[9,10,11], is first converted to bis[ethylthio]acetamide (**2**) with aqueous ammonia and subsequently transformed to bis[ethylthio]acetonitrile (**3**) with phosphoryl chloride in pyridine[12] in 65% overall yield.

The reactions of **1** or **3** with the Michael acceptors **4–8** in the presence of four equivalents of potassium carbonate and a 5% molar solution of tetrabutylammonium hydrogen sulfate in acetonitrile as solvent with efficient stirring lead to the corresponding 1,4-addition products **9–18** (Table 1). In any case, under these reaction conditions traces of 1,2-adducts were detected.

The nitrile **3** reacts at room temperature with **4, 5, 6,** and **8** to give the corresponding adducts **10, 12, 14,** and **18** in almost quantitative yields (Table 1). The reaction with **8** proceeds slower, probably due to steric factors. The addition of **3** to acrolein (**7**) is performed at 0°C with sodium hydrogen carbonate in order to minimize the undesired polymer formation. However, this attempt affords, in low yield, a mixture of two products, the desired 1,4-addition product **16** and its self aldol-condensation/dehydration product **19**.

The ester **1** is much less reactive than nitrile **3** in the mentioned reaction conditions. Therefore, except in the case of acrolein, reflux in acetonitrile is needed to carry out the additions, because at room temperature only a low conversion (30–60%) is observed even after 12 h. The reaction of **1** with **4**, **5**, and **6** affords the 1,4-adducts **9**, **11**, and **13**, respectively, in excellent yields. The lower yields obtained in the cases of **7** and **8** are due to self-condensation of cyclohexenone and polymerization of acrolein, respectively, under these reaction conditions (Table 1).





The use of **1** and **3** for the introduction of the glyoxylic moiety by phase transfer catalysis in different electrophilic substrates provides further synthetic possibilities. A systematic study on alkylation of compounds **1** and **3** is in progress.

Methyl Bis[ethylthio]acetate (1):

Compound **1** can be prepared according to the literature procedures[10,11]. More conveniently, the procedure reported on a 0.02 mol

Table 1. Michael Additions of **1** and **3** to α,β-Unsaturated Compounds **4-8**

Acceptor	X^2	Donor	Molar ratio[a] acceptor/donor	Reaction conditions time [min]/temp. [°C]	Product No.	X^1	X^2	Yield[b] [%]	b.p./torr[c] [°C]	Molecular formula[d]	
4	—CO—CH$_3$	**1**	1.1/1	90/80°	**9**	—COOCH$_3$	—CO—CH$_3$	89	135°/0.1	$C_{11}H_{20}O_3S_2$	(264.4)
		3	1/1	20/20°	**10**	—CN	—CO—CH$_3$	94	130°/0.1	$C_{10}H_{17}NOS_2$	(231.4)
5	—COOCH$_3$	**1**	1.1/1	90/80°	**11**	—COOCH$_3$	—COOCH$_3$	91	150°/0.1	$C_{11}H_{20}O_4S_2$	(280.4)
		3	1.1/1	72/20°	**12**	—CN	—COOCH$_3$	92	140°/0.1	$C_{10}H_{17}NO_2S_2$	(247.4)
6	—CN	**1**	1.1/1	90/80°	**13**	—COOCH$_3$	—CN	86	140°/0.1	$C_{10}H_{17}NO_2S_2$	(247.4)
		3	1.1/1	15/20°	**14**	—CN	—CN	94	130°/0.1	$C_9H_{14}N_2S_2$	(214.4)
7	—CHO	**1**	5[e]/1	60/20°	**15**	—COOCH$_3$	—CHO	30[f]	140°/0.1	$C_{10}H_{18}O_3S_2$	(250.4)
		3	1.1/1	60[g]/0°	**16**	—CN	—CHO	7[f, h]	135°/0.1	$C_9H_{15}NOS_2$	(217.4)
8	—	**1**	5/1	60/80°	**17**	—COOCH$_3$	—	35[f, i]	195°/0.1	$C_{13}H_{22}O_3S_2$	(290.4)
		3	1.1/1	15/80°	**18**	—CN	—	82	190°/0.1	$C_{12}H_{19}NOS_2$	(257.4)
				60/20°				88			

[a] The reactions were performed on a 3 mmolar scale.

[b] Yields refer to product isolated by Kugelrohr distillation.

[c] Oven temperature during Kugelrohr distillation.

[d] Satisfactory microanalyses obtained: C ±0.30, H ±0.27, N ±0.26, S ±0.36.

[e] In two parts of 2.5 equivalents each, at the beginning and at 30 min.

[f] Isolated by chromatography on silica gel with toluene/ethyl acetate (20:1) as solvent.

[g] With sodium hydrogen carbonate (4 equiv) as base.

[h] The self-condensation product **19** is isolated by chromatography on silica gel with toluene/ethyl acetate (10:1) as solvent in 12% yield.

[i] Based on recovered starting material (30%).

scale in Ref.[9] is followed employing methyl dichloroacetate (71 g, 0.5 mol), ethanethiol (68.2 g, 1.1 mol), anhydrous potassium carbonate (390 g, 2.8 mol), Aliquat 336 (1.22 g, 3 mmol), and toluene (620 ml). To maintain a good yield on our scale, the reaction time is extended from 8 to 18 h. The progress of the reaction is monitored by G.L.C. [10% Carbowax 20 M, 4 mm × 1 m column at 180°C]; yield: 82%; b.p. 127°C/15 torr (Lit.[9], b.p. 120°C/10 torr).

Bis[ethylthio]acetamide (2):

A mixture of **1** (19.4 g, 0.1 mol) and concentrated aqueous ammonia (400 ml) is stirred at room temperature overnight. After cooling (0°C), a first crop of pure amide is obtained by filtration (13.9 g). The filtrate is extracted with dichloromethane (3 × 70 ml). The extracts are dried with magnesium sulfate and the solvent evaporated to give additional product (0.8 g); total yield: 14.7 g (82%). An analytical sample is obtained by recrystallization from ethyl acetate/hexane; m.p. 108-109°C.

$C_6H_{13}NOS_2$	calc.	C 40.19	H 7.31	N 7.81	S 35.76
(179.3)	found	40.02	7.39	7.57	36.10

I.R. (KBr): $\nu = 3390, 3190, 1655\ \text{cm}^{-1}$.

^{1}H-N.M.R. (CDCl$_3$): $\delta = 6.45$ (broad, 2H, N$\underline{H}_2$, exchangeable with D$_2$O); 4.33 (s, 1H, CH); 2.72 (q, $J = 7.5$ Hz, 4H, SC$\underline{H}_2$CH$_3$); 1.26 ppm (t, $J = 7.5$ Hz, 6H, SCH$_2$C$\underline{H}_3$).

Bis[ethylthio]acetonitrile (3):

To an ice-cooled (0°C) solution of bis[ethylthio]acetamide (**2**; 8.95 g, 0.05 mol) in pyridine (90 ml) is added phosphoryl chloride (6.5 ml, 10.89 g, 0.07 mol) dropwise with stirring over 10 min. The mixture is maintained at 5-10°C for 90 min, poured into ice/water (500 ml), then acidified to pH 2-3 with dilute hydrochloric acid, and extracted with ether (4 × 80 ml). The ethereal solution is dried with magnesium sulfate and the solvent removed in vacuo. The crude nitrile **3** is purified by distillation; yield: 6.45 g (80%); b.p. 116°C/11 torr.

$C_6H_{11}NS_2$	calc.	C 44.68	H 6.87	N 8.68	S 39.76
(161.3)	found	44.66	6.97	8.68	40.03

I.R. (film): $\nu = 2228\ \text{cm}^{-1}$.

^{1}H-N.M.R. (CCl$_4$): $\delta = 4.47$ (s, 1H, CH); 2.81 (q, $J = 7$ Hz, 4H, SC$\underline{H}_2$CH$_3$); 1.35 ppm (t, $J = 7$ Hz, 6H, SCH$_2$C$\underline{H}_3$).

Michael Addition of Glyoxylic Derivatives 1 and 3 to α,β-Unsaturated Compounds 4-8; General Procedure:

To a mixture of **1** or **3** (3 mmol) and the corresponding α,β-unsaturated compound **4-8** (3.3 mmol) in acetonitrile (10 ml) are added finely powdered anhydrous potassium carbonate (*1.66 g, 12 mmol*) and tetrabutylammonium hydrogen sulfate (51 mg, 0.15 mmol). The mixture is magnetically stirred during the time and at the temperature indicated (Table 1). Reaction mixtures are checked by T.L.C. on silica gel with toluene/ethyl acetate (20:1) or G.L.C. The inorganic salts are filtered off by suction and washed with acetonitrile (20 ml). The filtrates are evaporated in vacuo to give an oily residue. The pure products **9-18** (Table 1) are obtained by Kugelrohr distillation at reduced pressure unless otherwise stated. The quaternary ammonium salt can be removed from the crude residue before distillation by addition of dichloromethane (50 ml) and washing with water (2 × 5 ml), but it does not improve the method.

Table 2. Spectral Data of Compounds **9-19**

Compound	I.R. (Film)[a] ν [cm^{-1}]	^{1}H-N.M.R. (CCl$_4$/TMS)[b] δ [ppm]
9	1725, 1715 (CO)	1.2 (t, 6H, SCH$_2$C$\underline{H}_3$, $J = 7.5$ Hz); 2.12 (s, 3H, COCH$_3$); 1.9-2.3 (m, 2H, C$\underline{H}_2$CH$_2$CO); 2.3-2.9 (m, 2H, CH$_2$CO); 2.57 (q, 4H, SC$\underline{H}_2$CH$_3$, $J = 7.5$ Hz); 3.73 (s, 3H, COOCH$_3$)
10	2232 (CN), 1720 (CO)	1.35 (t, 6H, SCH$_2$C$\underline{H}_3$, $J = 7$ Hz); 2.17 (s, 3H, COCH$_3$); 2.0-2.4 (m, 2H, C$\underline{H}_2$CH$_2$CO); 2.5-3.1 (m, 2H, CH$_2$CO); 2.85 (q, 4H, SC$\underline{H}_2$CH$_3$, $J = 7$ Hz)
11	1735 (CO)	1.2 (t, 6H, SCH$_2$C$\underline{H}_3$, $J = 7.5$ Hz); 1.9-2.9 (m, 4H, CH$_2$—CH$_2$); 2.58 (q, 4H, SC$\underline{H}_2$CH$_3$, $J = 7.5$ Hz); 3.6, 3.7 (2s, 3H each, COOCH$_3$)
12	2224 (CN), 1742 (CO)	1.32 (t, 6H, SCH$_2$C$\underline{H}_3$, $J = 7$ Hz); 2.1-3.0 (m, 4H, CH$_2$); 2.82 (q, 4H, SC$\underline{H}_2$CH$_3$, $J = 7$ Hz); 3.62 (s, 3H, COOCH$_3$)
13	2245 (CN), 1725 (CO)	1.24 (t, 6H, SCH$_2$C$\underline{H}_3$, $J = 7.5$ Hz); 1.8-2.9 (m, 4H, CH$_2$); 2.62 (q, 4H, SC$\underline{H}_2$CH$_3$, $J = 7.5$ Hz); 3.74 (s, 3H, COOCH$_3$)

Table 2. (Continued)

Compound	I.R. (Film)[a] ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS)[b] δ [ppm]
14	2250, 2226 (CN)	1.33 (t, 6H, $SCH_2C\underline{H}_3$, $J=7$ Hz); 1.9-3.1 (m, 4H, CH_2); 2.83 (q, 4H, $SC\underline{H}_2CH_3$, $J=7$ Hz)
15	1725 (CO)	1.2 (t, 6H, $SCH_2C\underline{H}_3$, $J=7.5$ Hz); 1.9-2.8 (m, 4H, CH_2); 2.58 (q, 4H, $SC\underline{H}_2CH_3$, $J=7.5$ Hz); 3.71 (s, 3H, $COOCH_3$); 9.71 (s, 1H, CHO)
16	2222 (CN), 1721 (CO)	1.34 (t, 6H, $SCH_2C\underline{H}_3$, $J=7$ Hz); 1.9-2.9 (m, 4H, CH_2); 2.84 (q, 4H, $SC\underline{H}_2CH_3$, $J=7$ Hz); 9.83 (s, 1H, CHO)
17	1720 (CO)	1.22 (t, 6H, $SCH_2C\underline{H}_3$, $J=7.5$ Hz); 1.4-3.0 (m, 9H, CH_2, CH); 2.65, 2.68 (2q, 4H, $SC\underline{H}_2CH_3$, $J=7.5$ Hz); 3.74 (s, 3H, $COOCH_3$)
18	2220 (CN), 1712 (CO)	1.33 (t, 6H, $SCH_2C\underline{H}_3$, $J=7$ Hz); 1.4-3.1 (m, 9H, CH_2, CH); 2.85 (q, 4H, $SC\underline{H}_2CH_3$, $J=7$ Hz)
19[c]	2220 (CN), 1690 (CO), 1640 (C=C)	1.35 (t, 12H, $SCH_2C\underline{H}_3$, $J=7$ Hz); 1.9-2.9 (m, 6H, CH_2); 2.87 (q, 8H, $SC\underline{H}_2CH_3$, $J=7$ Hz); 6.65 (t, 1H, $CH_2-C\underline{H}=C$); 9.45 (s, 1H, CHO)

[a] Recorded on a Perkin-Elmer 257 spectrometer.

[b] Recorded on a Varian EM-360 spectrometer (60 MHz).

[c] M.S. (10 eV): m/e (rel. int. %) = M^+ (absent), 355 (3), 293 (13), 256 (100), 231 (6), 194 (32); recorded on a Hitachi-Perkin-Elmer RMU-6MG spectrometer.

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