A Convenient Method for the Preparation of *S*-Esters of Thio Analogs of Malonic Acid

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Synopsis. 2-Carboxyethanethioic *S*-esters ($RSCOCH_2COOH$) and propanebis(thioic) *S,S'*-diesters ($RSCOCH_2COSR$) were easily prepared in high yields by the direct condensation of malonic acid with thiols in the presence of ethyl polyphosphate (PPE).

In the previous paper[1] we reported that various thiocarboxylic *S*-esters were easily prepared by the direct condensation of carboxylic acids with thiols in the presence of ethyl polyphosphate (PPE).[2] The method compares favorably with others reported hitherto, in terms of simplicity, efficiency, generality, and in particular, the applicability to acid and/or base sensitive compounds such as penicillin G.

On the other hand, 2-carboxyethanethioic *S*-esters and propanebis(thioic) *S,S'*-diesters have been noticed as the useful intermediates for organic synthesis. The former esters are closely related to malonyl *S*-CoA and, in fact, undergo decarboxylative *C*-acylation under virtually natural conditions.[3,4] The latter ones are used for the synthesis of ethanol derivatives[5] and heterocycles.[6] We report herein a facile method for the preparation of these compounds from malonic acid and thiols using PPE as the condensation reagent.

When a thiol was treated with large excess of malonic acid[7] in PPE containing chloroform and tetrahydrofuran (THF), the condensation proceeded smoothly at room temperature without decarboxylation, and the corresponding 2-carboxyethanethioic *S*-esters (**1a**—**h**)

$$CH_2(COOH)_2 + RSH \xrightarrow[\text{in } CHCl_3\text{-THF}]{\text{PPE}} RSCOCH_2COOH$$
1a—h

were produced in high yields. The results are summarized in Table 1. Since malonic acid is inexpensive, its use in excess detracts little from the utility of this process.

Next, we tried to prepare propanebis(thioic) *S,S'*-diesters. This was easily achieved by the treatment of malonic acid with two equivalents of thiols in PPE at room temperature. All the cases examined afforded

$$CH_2(COOH)_2 + 2\,RSH \xrightarrow{\text{PPE}} CH_2(COSR)_2$$
2a—g

the expected *S,S'*-diesters (**2a**—**g**) in excellent yields. The results are listed in Table 2. It is noted that sterically crowded *S,S'*-bis(2,4,6-trimethylphenyl) propanebis(thioate) (**2d**) was also prepared in a satisfactory yield.

We believe the present method has the superior attributes of high yields, ease of operation, and attractive economics.[8,9]

Experimental

Spectra. Proton NMR spectra were measured on a JEOL C-60HL spectrometer. The chemical shifts are given in ppm with TMS as an internal standard. Infrared spec-

TABLE 1. 2-CARBOXYETHANETHIOIC *S*-ESTERS ($RSCOCH_2COOH$)

R	Product	Yield %	Mp θ_m/°C	IR $\nu_{C=O}$/cm^{-1}	^{1}H-NMR δ	Found(Calcd)(%) C	H
C_6H_5	**1a**	88	74.0—75.5 (C_6H_6-C_6H_{14}) Lit,[a] 72—73	1690, 1710	3.62(s, 2H), 7.40(br s, 5H) 10.66(br s, 1H)	55.17 (55.09	4.17 4.11)
$C_6H_5CH_2$	**1b**	90	62—63 (C_6H_6-C_6H_{14})	1680, 1730	3.70(s, 2H), 4.26(s, 2H), 7.41(s, 5H), 9.5—9.9(br s, 1H)	57.29 (57.13	4.82 4.79)
o-$CH_3OC_6H_4$	**1c**	65	90—91 (C_6H_6)	1700, 1730	3.78(s, 2H), 3.92(s, 3H), 6.94—7.76 (m, 4H), 11.03(s, 1H)	53.25 (53.09	4.45 4.45)
2,4,6-$(CH_3)_3C_6H_2$	**1d**	88	112.0—113.5 (C_6H_6-C_6H_{14})	1680, 1730	2.33(br s, 9H), 3.66(s, 2H), 6.97(s, 2H), 11.05(s, 1H)	60.50 (60.48	5.93 5.92)
$C_2H_5OOCCH_2$	**1e**	73	Oil	1690(sh), 1730	1.29(t, J=7.5 Hz, 3H), 3.66(s, 2H), 3.72(s, 2H), 4.20(q, J=7.5 Hz, 2H), 11.08(s, 1H)	40.37 (40.77	5.09 4.89)
C_2H_5	**1f**	90	30—31 (C_6H_6-C_6H_{14})	1680, 1720	1.30(t, J=7.5 Hz, 3H), 2.97(q, J=7.5 Hz, 2H), 3.57(s, 2H), 10.86(s, 1H)	40.06 (40.53	5.48 5.44)
n-C_4H_9	**1g**	80	Oil Lit[b], Oil	1685, 1720	0.70—1.90(m, 7H), 2.97(t, J=7.0 Hz, 2H), 3.61(s, 2H), 10.98(s, 1H)	47.45 (47.71	6.99 6.86)
t-C_4H_9	**1h**	78	44—45 (C_6H_{14})	1680, 1720	1.49(s, 9H), 3.48(s, 2H), 10.86 (br s, 1H)	47.81 (47.71	6.80 6.86)

a) Ref. 8b. b) Ref. 4.

Table 2. Propanebis(thioic) *S,S'*-diesters [$CH_2(COSR)_2$]

R	Product	Yield %	Mp θ_m/°C [Bp θ_b/°C (Torr)†]	IR $\nu_{C=O}$/cm^{-1}	^{1}H-NMR δ	Found(Calcd)(%) C	H
C_6H_5	**2a**	94	94—95 (C_6H_6-C_6H_{14}) Lit,[a] 94	1695, 1720	3.93(s, 2H), 7.47(br s, 10H)	62.60 (62.48	4.26 4.19)
$C_6H_5CH_2$	**2b**	98	39—40 (C_6H_6-C_6H_{14})	1670, 1695(sh)	3.63(s, 2H), 4.08(s, 4H), 7.22(br s, 10H)	64.81 (64.53	5.16 5.10)
o-$CH_3OC_6H_4$	**2c**	88	70.0—71.5 (CH_3OH)	1690, 1710(sh)	3.75(s, 6H), 3.84(s, 2H), 6.75—7.65(m, 8H)	58.68 (58.60	4.65 4.63)
2,4,6-$(CH_3)_3C_6H_2$	**2d**	98	77—78 (C_6H_6-C_6H_{14})	1670, 1710	2.33(s, 18H), 3.84(s, 2H), 6.97(s, 4H)	68.01 (67.71	6.54 6.49)
$C_2H_5OOCCH_2$	**2e**	85	Oil	1680, 1705, 1735	1.27(t, J=7.5 Hz, 6H), 3.68(s, 4H) 3.83(s, 2H), 4.15(q, J=7.5 Hz, 4H)	42.77 (42.85	5.19 5.23)
C_2H_5	**2f**	95	[100[b](0.5)] [Lit,[c] 109(2.5)]	1675, 1695(sh)	1.30(t, J=7.5 Hz, 6H), 2.93(q, J= 7.5 Hz, 4H), 3.68(s, 2H)	43.65 (43.72	6.21 6.29)
n-C_4H_9	**2g**	94	[150[b](0.4)]	1670, 1690(sh)	0.73—1.90(m, 14H), 2.91(t, J=7.0 Hz, 4H), 3.67(s, 2H)	53.29 (53.19	8.04 8.12)

a) Ref. 9d. b) Bath temperature. c) Ref. 9c. † 1 Torr≈133.322 Pa.

tra were recorded on a Hitachi 215 spectrophotometer. Products were identified by NMR and IR spectra together with elemental analyses.

Materials. PPE was prepared according to the method described in the Ref. 2. *o*-Methoxybenzenethiol[10] and 2,4,6-trimethylbenzenethiol[11] were synthesized by the methods described in the literatures. Other thiols were purchased from Tokyo Kasei Kogyo, Co., Ltd. and used without further purification.

*General Procedure for the Preparation of 2-Carboxyethanethioic S-Esters (**1a—h**).* A thiol (0.025 mol) was added to a stirred mixture of finely powdered malonic acid (10.4 g, 0.10 mol), PPE (15 g), purified chloroform (60 ml), and THF (10 ml).[12] After stirring for 30 h at room temperature, the reaction mixture was diluted with ether (200 ml) and treated successively with saturated aqueous $NaHCO_3$ solution (150 ml, 100 ml, and 50 ml). The combined aqueous extracts were acidified to pH 1—2 with 10% hydrochloric acid and extracted with chloroform (100 ml×2). The extracts were dried over Na_2SO_4 and concentrated by a rotary evaporator. The residue was purified by filtration through a column packed with silica gel (*ca.* 70 g) with benzene–ethyl acetate (1:1) as the eluent. Crystalline products were further purified by recrystallization.

*General Procedure for the Preparation of Propanebis(thioic) S,S'-Diesters (**2a—g**).* A mixture of malonic acid (10.4 g, 0.10 mol) and a thiol (0.20 mol) was stirred with PPE (30 g) at room temperature for 20 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (600 ml) and the product was extracted into ether (150 ml×2). The combined extracts were washed with aqueous $NaHCO_3$ solution and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through a column packed with silica gel (*ca.* 70 g) with benzene. Evaporation of the solvent *in vacuo* afforded practically pure product, which was further purified by recrystallization or distillation under reduced pressure (Kugelrohr apparatus).

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7) The use of one equivalent of malonic acid to a thiol resulted in lower yield of the 2-carboxyethanethioic *S*-ester. For example, the treatment of malonic acid with one molar equivalent of benzenethiol afforded **1a** and **2a** in 40% and 36% yields, respectively.

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9) For the other methods for the preparation of propanebis(thioic) *S,S'*-diesters, see a) Ref. 5; b) Ref. 6; c) S. Scheithauer and R. Mayer, *Chem. Ber.*, **100**, 1413 (1967); d) E. Ziegler and H. Junck, *Monatsh. Chem.*, **86**, 29 (1955); e) K. Miyaki and S. Yamagishi, *J. Pharm. Soc. Jpn.*, **76**, 1196 (1956).

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12) THF was necessary to achieve high yield.