New Decarboxylation, De-ethoxycarbonylation and Desulfonylation, followed by Sulfenylation of some Half-Esters of Malonic Acids and α-Sulfonylmalonic Esters

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The sulfenylation of some half-esters of malonic acids and some α-sulfonylmalonic esters with several sulfenylating reagents was investigated. Evidence was provided that in the case of the half-esters, in which NaH–dimethyl sulfoxide was employed, the formation of α,α-disulfenylated carboxylic esters may occur by two different reaction sequences, initiated either by dianion formation or decarboxylation. It is shown that, in the case of the α-sulfonylmalonic esters, in which diazabicyclooctane in refluxing toluene was employed, two competitive reactions may take place: de-ethoxycarbonylation or desulfonylation, both followed by sulfenylation.

The sulfenylations of sulfones have been the object of our earlier investigations.[1,2] However, recently, we became interested in such sulfenylations which could occur by reaction of the sulfenylating reagents with carbanions generated by decarboxylation of carboxylic acids containing an electron-withdrawing group in the α position. This type of sulfenylation is of advantage over those others which occur through carbanions generated by attack of base on a C–H bond, as it should offer more regioselectivity and, in some cases, stereoselectivity.[3] In search of such reactions we have undertaken some investigations of sulfenylation of α-sulfonyl carboxylic acids.[4]

In this paper we report the results of the sulfenylation of some half-esters of malonic acids, which was extended to α-sulfonylmalonic esters.

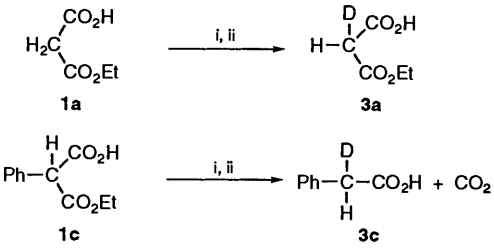
Results and Discussion

Some half-esters of malonic acids, compounds **1a–c**, were submitted to reaction with 2 mol equiv. of NaH in dimethyl sulfoxide (DMSO), followed by addition of 2 mol equiv. of a sulfenylating reagent, such as dimethyl disulfide, *S*-methyl methanethiosulfonate or *N*-methylthiophthalimide (Phthal-SMe), at room temperature. It may be seen (Table 1) that the sulfenylation accompanied by decarboxylation takes place with formation of the corresponding α,α-disulfenylated carboxylic esters **2a–c**. It is noteworthy that the dimethyl-substituted derivative **1d** did not undergo sulfenylation under the same conditions.

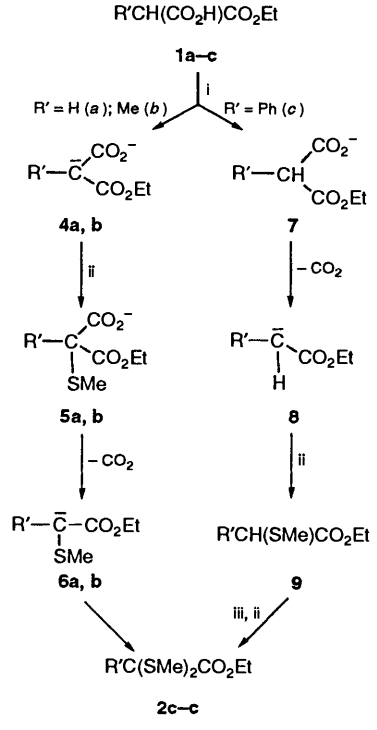
Insight into these reactions was obtained following the evolution of carbon dioxide through the course of reaction, by collection as barium carbonate, as well as by deuteriation experiments. It was observed that while in the case of substrates **1a**, **b** the decarboxylation starts only after the addition of a sulfenylating reagent, in that of compound **1c**, containing a phenyl group, the decarboxylation takes place as soon as NaH is added and, therefore, in the non-sulfenylated carboxylate. This difference was confirmed when deuterium oxide was added to the malonic half-esters in the presence of NaH, in DMSO; in the case of compound **1a** the α-deuteriomalonic half-ester **3a**, and in that of compound **1c** the α-deuterio(phenyl)acetic acid **3c**, were obtained (Scheme 1).

It seems reasonable that the hydrolysis of the ester in the case of substrate **1c** should occur during the D_2O work-up and may be favoured by the inductive effect of the phenyl group.

It may be suggested that substrates **1a**, **b** react with 2 mol equiv. of NaH to give dianions **4a**, **b** which undergo sulfenylation to yield carboxylates **5a**, **b**. The latter are easily decarboxylated to generate carbonanions **6a**, **b**, responsible for the second sulfenylation (Scheme 2).



Scheme 1 *Reagents and conditions:* i, NaH, (2 mol equiv.), DMSO, room temp.; ii, D_2O



Scheme 2 *Reagents:* i, NaH (excess), DMSO; ii, sulfenylation reagent; iii, NaH

The decarboxylative sulfenylation of the methylthio-substituted half-esters is a new reaction. It was reported[5] that the reaction of the carboxylic acids with lithium diisopropylamide–tetrahydrofuran (LDA–THF) and dimethyl disulfide leads to the α-methylthio-substituted carboxylic acids, which do not

Table 1 Reaction of malonic acid half-esters with some sulfenylating reagents in the presence of NaH (2 mol equiv.) in DMSO at room temperature

Malonic acids half-esters **1** $R(R')C(CO_2H)CO_2Et$	Sulfenylating reagents[a]	Sulfenylation products **2** $R'C(SMe)_2CO_2Et$ (Yield %)
a; R = R′ = H	MeSSMe	**2a** 58
	$MeSO_2SMe$	64
	Phthal-SMe	64
b; R = H; R′ = Me	$MeSO_2SMe$	**2b** 55
c; R = H; R′ = Ph	$MeSO_2SMe$	**2c** 59
	Phthal-SMe	66
d; R = R′ = Me	$MeSO_2SMe$	
	Phthal-SMe	

[a] 2 Mol equiv.

undergo decarboxylation. The difference between our reactions with NaH–DMSO and those with LDA–THF is probably due not only to the presence of the sulfonyl group but also to the greater reactivity of the salt-like sodium carboxylate over the covalent lithium carboxylate.

Quite a different mechanism may be suggested for the sulfenylative decarboxylation of the phenylmalonate **1c**. The formation of a dianion is, most probably, inhibited by an accelerated decarboxylation of the carboxylate **7** due to stabilization of the resulting carbanion **8** by the phenyl group. Therefore the first sulfenylation would occur through the carbanion generated from decarboxylation. However, the second sulfenylation would be a common one resulting from the reaction between the α-carbanion of the (methylthio)acetate **9** and the sulfenylating reagent (Scheme 2).

These results show that the formation of dianions may compete with sulfenylation through carbanions, generated by decarboxylation. We presumed that this drawback could be avoided if the carbanions could be generated by de-ethoxycarbonylation of esters.

It has been reported[6] that geminal esters undergo *O*-alkyl cleavage, followed by decarboxylation, when treated with 1,4-diazabicyclo[2.2.2]octane (DABCO) in refluxing xylene. When the α-sulfonyl(methyl)malonic ester **10a** was submitted to reaction with DABCO, in refluxing toluene, followed by addition of *S*-methyl methanethiosulfonate at room temperature, a de-ethoxycarbonylative sulfenylation took place to give the corresponding methylthio-substituted sulfonyl ester **11a**, in ~68% yield (Scheme 3). However, a surprising result was obtained when the α-sulfonyl(phenyl)malonic ester **10b** was submitted to the reaction with the same reagents, in refluxing benzene. Instead of the expected methylthio sulfonyl ester **11b**, the methylthio-substituted malonic ester **12b** was obtained in 84% yield (Scheme 3). This result indicates that, instead of de-ethoxycarbonylative sulfenylation, desulfonylative sulfenylation had occurred. Evidence for the desulfonylation with formation of the corresponding carbanion, which undergoes sulfenylation, in this latter case, was obtained when the reaction was performed in the absence of a sulfenylating reagent, when, after addition of water, the α-phenylmalonate **13b** was isolated (Scheme 3).

Partial desulfonylation was also observed when α-sulfonyl(benzyl)malonate **10c** was treated with DABCO, in refluxing benzene. After addition of water the α-benzylmalonate **13c** was obtained in admixture with α-sulfonyl(phenyl)propionate **14c** (Scheme 3).

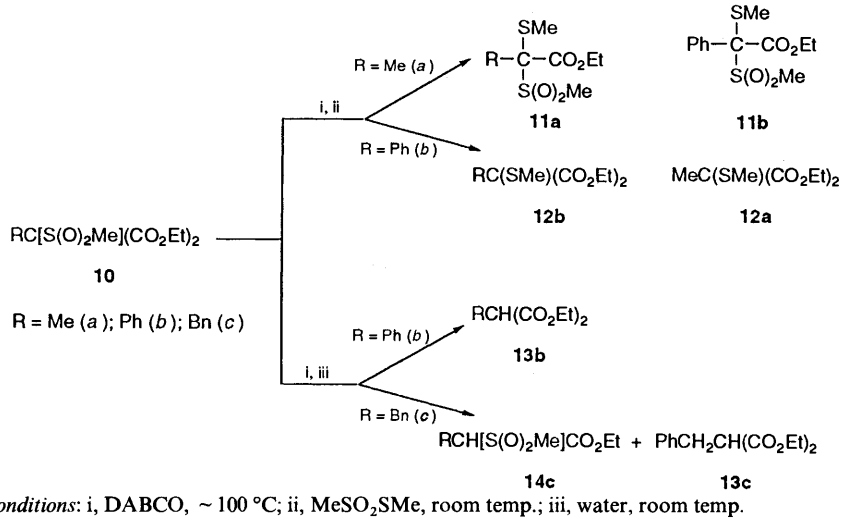
It seems reasonable to suggest that there is a gradual change from de-ethoxycarbonylation to desulfonylation on going from methyl to benzyl to phenyl groups in the α-position. This is an indication that the site of nucleophilic attack of the nitrogen nucleophile depends on the steric accessibility of the electrophilic centre. In the case of desulfonylation it is difficult to predict whether the centre of attack is the carbon atom or the sulfur atom of the SO_2Me group.[7]

It may be emphasized that the sulfenylation of the half-esters of malonic acids, leading to α,α-bis(methylthio)-substituted carboxylic esters, is also of synthetic interest, as the latter compounds are precursors of α-keto esters.[8,9]

Experimental

General.—Microanalyses were performed on a Perkin-Elmer 240B elemental analyser. M.p.s are uncorrected and were determined on a Kofler hot-stage apparatus. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer with $SiMe_4$ as internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer. Chemical shifts are expressed in ppm relative to $SiMe_4$ as internal standard, and *J* values are in Hz. IR spectra were obtained with a Perkin-Elmer FT 238A instrument. Mass spectra were measured at 70 eV with a Finnigan ITD-800 or an INCOS-50 instrument. Gravity chromatography was performed on Merck Kieselgel 60 (70–230 mesh). GLC analyses were performed on a Hewlett-Packard 5890A gas chromatograph equipped with a flame ionization detector, a Hewlett-Packard 3392A integrator, and an HP-1 (10 m × 0.53 mm × 2.65 μm film thickness) capillary column.

Materials.—Malonic acid half-esters **1a–d** were prepared according to literature procedures.[10–13] Diethyl α-methyl-



Scheme 3 *Reagents and conditions*: i, DABCO, ~ 100 °C; ii, $MeSO_2SMe$, room temp.; iii, water, room temp.

thio(alkyl)malonates **12**, as precursors for sulfones **10a–c**, were prepared by direct sulfenylation of the corresponding alkylmalonates, using NaH–DMSO and *S*-methyl methanethiosulfonate, and were identified by comparison with literature physical and spectroscopic data.[14,15]

Preparation of Diethyl Methyl(methylsulfonyl)malonate **10a**. *Typical Procedure.*—A mixture of diethyl methyl(methylthio)malonate **12a** (4.7 g, 21 mmol) and 50% H_2O_2 (3.6 cm^3, 53 mmol) in glacial acetic acid (45 cm^3) was heated at reflux for 90 min. After removal of solvent under reduced pressure, CH_2Cl_2 (30 cm^3) was added to the residue. The organic extract was washed successively with aq. (5% v/v) $NaHCO_3$ and then with water (2 × 10 cm^3), dried over $MgSO_4$, and concentrated to give compound **10a** (4.5 g, 85%) as an oil that required no further purification (Found: C, 42.6; H, 6.5. $C_9H_{16}O_6S$ requires C, 42.9; H, 6.4%); ν_{max}(neat)/cm^{-1} 1741 (CO); δ_H($CDCl_3$) 1.35 (6 H, t, *J* 7, *Me*CH_2O), 1.90 (3 H, s, MeC), 3.30 (3 H, s, $MeSO_2$) and 4.33 (4 H, q, *J* 7, CH_2O); δ_C($CDCl_3$) 164.49, 75.52, 62.86, 39.56, 14.10 and 13.36.

Sulfones **10b** and **10c** were prepared similarly.

Diethyl methylsulfonyl(phenyl)malonate **10b**. Sulfonyl ester **10b** was obtained in 73% yield as crystals, m.p. 87–88 °C (from hexane–chloroform) (Found: C, 53.4; H, 5.7. $C_{14}H_{18}O_6S$ requires C, 53.5; H, 5.8%); ν_{max}(KBr)/cm^{-1} 1741 (CO); δ_H($CDCl_3$) 1.39 (6 H, t, *J* 7, *Me*CH_2O), 3.12 (3 H, s, $MeSO_2$), 4.33 (4 H, q, *J* 7, CH_2O) and 7.40–7.70 (5 H, m, Ph); δ_C($CDCl_3$) 164.05, 129.87, 129.78, 128.71, 128.46, 84.95, 63.41, 40.63 and 13.75.

Diethyl benzyl(methylsulfonyl)malonate **10c**. Sulfonyl ester **10c** was obtained in 72% yield as pale yellow crystals, m.p. 55–57 °C (from hexane–chloroform) (Found: C, 55.0; H, 6.1. $C_{15}H_{20}O_6S$ requires C, 54.9; H, 6.1%); ν_{max}(KBr)/cm^{-1} 1727 (CO); δ_H($CDCl_3$) 1.16 (6 H, t, *J* 7, *Me*CH_2O), 3.19 (3 H, s, $MeSO_2$), 3.74 (2 H, s, C*H*$_2$Ph), 4.23 (4 H, m, *J* 7, CH_2O) and 7.23–7.38 (5 H, m, Ph); δ_C($CDCl_3$) 164.02, 133.64, 130.63, 127.94, 127.33, 81.00, 62.78, 40.27, 33.49 and 13.36.

Decarboxylative Sulfenylation of Malonic Half-esters **1a–d**. *Typical Procedure.*—To NaH (50% in mineral oil; 0.16 g) previously washed with dry hexane (2 × 5 cm^3) under nitrogen, at room temp., was added a solution of malonic half-ester **1a** (0.20 g, 1.5 mmol) in dry DMSO (5 cm^3). After the mixture had been stirred for 30 min at room temp., *S*-methyl methanethiosulfonate (0.38 g, 3.0 mmol) was added dropwise *via* syringe, and the mixture was stirred at room temp. for 4 h before being poured into saturated aq. NH_4Cl (10 cm^3), washed with water (3 × 10 cm^3), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–acetone (9:1 v/v) to give a pale yellow oil (0.15 g, 64%) (99.7% pure by GLC), identified as acetate **2a** by comparison of its physical and spectroscopic properties with those of an authentic sample, prepared according to literature procedure;[16] ν_{max}(neat)/cm^{-1} 1734 (CO); δ_H($CDCl_3$) 1.32 (3 H, t, *J* 7, *Me*CH_2O), 2.35 (6 H, s, MeS), 4.16 (2 H, q, *J* 7, CH_2O) and 4.29 [1 H, s, $(MeS)_2CHCO_2Et$].

The above procedure, using 1 mol equiv. of substrate and 2 mol equiv. of *N*-(methylthio)phthalimide or dimethyl disulfide, afforded compound **2a** in 64 and 58% respectively.

Ethyl α,α-bis(methylthio)propionate **2b**. The procedure described for acetate **2a** was followed using compound **1b** (1.2 g, 8.2 mmol), NaH (50% in mineral oil; 0.8 g) and *S*-methyl methanethiosulfonate (2.1 g, 16.4 mmol). After stirring of the mixture for 10 h at room temp., and work-up as described for acetate **2a**, compound **2b** was obtained as a pale yellow oil (0.88 g, 55%) and required no further purification (Found: C, 42.9; H, 7.0. $C_7H_{14}O_2S_2$ requires C, 43.3; H, 7.3%); ν_{max}(neat)/cm^{-1} 1726 (CO); δ_H($CDCl_3$) 1.31 (3 H, t, *J* 7, *Me*CH_2O), 1.66 (3 H, s, MeC), 2.18 (6 H, s, MeS) and 4.18 (2 H, q, *J* 7, CH_2O); *m/z* 194 (M^+, 21%), 147 (57), 121 (67), 101 (43), 73 (85), 91 (8) and 59 (100).

Ethyl α,α-bis(methylthio)phenylacetate **2c**. The procedure described for the synthesis of acetate **2a** was followed, using compound **1c** (0.42 g, 2.0 mmol), NaH (50% in mineral oil; 0.2 g) and *S*-methyl methanethiosulfonate (0.50 g, 4.0 mmol). After stirring of the mixture for 2 h at room temp., and work-up as described for acetate **2a**, the oily residue was purified by column chromatography on silica gel with hexane–ethyl acetate (9:1 v/v) as eluent, to give a yellow oil (0.30 g, 59%), identified as ethyl α,α-bis(methylthio)phenylacetate **2c** by comparison of its spectroscopic properties with those of an authentic sample prepared according to literature procedure;[17] ν_{max}(neat)/cm^{-1} 1724 (CO); δ_H($CDCl_3$) 1.21 (3 H, t, *J* 7, *Me*CH_2O), 1.96 (6 H, s, MeS), 4.21 (2 H, q, *J* 7, CH_2O) and 7.20–7.60 (5 H, m, Ph).

When *N*-(methylthio)phthalimide was employed as sulfenylating reagent the disulfenylated ester **2c** was obtained in 66% yield.

Deuteriation Experiments. Typical Procedure.—To NaH (50% in mineral oil; 0.12 g), previously washed with dry hexane (2 × 3 cm^3), under nitrogen was added a solution of malonic half-ester **1a** (0.15 g, 1.1 mmol) in DMSO (2 cm^3) dropwise *via* syringe. The mixture was stirred at room temp. for 2 h and D_2O (2 cm^3) was then addded. After being stirred for 1 h, and the addition of dil. hydrochloric acid, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 cm^3). The extract was washed with water (3 × 20 cm^3), dried over $MgSO_4$, and concentrated to yield a liquid (0.10 g, 68%), characterized as α-deuteriomalonic half-ester **3a**; δ_H($CDCl_3$) 1.28 (3 H, t, *J* 7, *Me*CH_2O), 3.46 (1 H, s, *H*CCO_2Et), 4.23 (2 H, q, *J* 7, CH_2O) and 10.8 (1 H, s, CO_2H); *m/z* 133 (M^+, 54%), 116 (100), 89 (36) and 61 (27).

Similar reaction of compound **1c** gave α-deuterio(phenyl)-acetic acid **3c** as the sole product, ν_{max}(neat)/cm^{-1} 3064 and 3032 (OH) and 1703 (CO); δ_H($CDCl_3$) 3.47 (1 H, s, *H*CCOH), 7.10 (5 H, s, Ph) and 11.80 (1 H, s, CO_2H); *m/z* 137 (M^+, 25%), 92 (100), 77 (3) and 65 (19).

Reaction of Compound **10a** *with DABCO and* S-*Methyl Methanethiosulfonate.*—A stirred solution of sulfonyl ester **10a** (3.40 g, 13.5 mmol) and DABCO (7.60, 67.8 mmol) in dry toluene (20 cm^3) was refluxed for 8 h. The reaction mixture was cooled to room temp. and methyl methanethiosulfonate (1.80 g, 14.3 mmol) was added. The mixture was stirred for 6 h at room temp. and then was kept overnight in a freezer. After filtration to remove the suspended solid, the solution was concentrated under reduced pressure. The residue was subjected to silica gel chromatography with hexane–ethyl acetate (7:3 v/v) as eluent, to give compound **11a** (2.08 g, 68%) as a liquid (Found: C, 37.2; H, 6.2. $C_7H_{14}O_4S_2$ requires C, 37.2; H, 6.2%); ν_{max}(neat)/cm^{-1} 1738 (CO); δ_H($CDCl_3$) 1.39 (3 H, t, *J* 7, *Me*CH_2O), 1.92 (3 H, s, MeC), 2.38 (3 H, s, MeS), 3.33 (3 H, s, $MeSO_2$) and 4.37 (2 H, q, *J* 7, CH_2O); δ_C($CDCl_3$) 165.93, 72.64, 62.91, 36.81, 15.27, 13.51 and 12.95.

Reaction of Compound **10b** *with DABCO and* S-*Methyl Methanethiosulfonate.*—The procedure described for the same reaction using compound **10a** was applied to the treatment of sulfonyl ester **10b** (0.50 g, 1.6 mmol) with DABCO (0.90 g, 8.0 mmol) in benzene. After addition of *S*-methyl methanethiosulfonate (0.20 g, 1.6 mmol) and work-up as previously described, the crude product was subjected to silica gel chromatography, with benzene–ethyl acetate (9:1 v/v) as eluent, to give a liquid (0.38 g, 84%), characterized as diethyl methylthio(phenyl)malonate **12b**, by comparison of its spectroscopic properties with those of an authentic sample.[15]

Reaction of Compound **10b** *with DABCO in the Absence of* S-*Methyl Methanethiosulfonate.*—Treatment of compound **10b** (0.5 g, 1.6 mmol) with DABCO (0.90 g, 8.0 mmol) in toluene (3 cm^3), followed by addition of water and work-up as described for compound **10a**, afforded diethyl phenylmalonate **13b** (0.3 g, 79%).

Reaction of Compound **10c** *with DABCO in the Absence of* S-*Methyl Methanethiosulfonate.*—Treatment of compound **10c** (0.10 g, 0.30 mmol) with DABCO (0.18 g, 1.6 mmol) in benzene (3 cm^3), followed by addition of water and work-up as previously described, afforded a mixture of two products. The crude mixture was analysed by GLC (**14c**, 48%; **13c**, 52%) and the products were identified by comparison with GLC retention times of authentic samples. Diethyl benzylmalonate **13c** was commercially available. Compound **14c** was prepared as follows.

Ethyl α-(methylsulfonyl)-β-phenylpropionate **14c**. Dry benzene (10 cm^3) was added to benzyltrimethylammonium hydroxide (0.15 g, 0.36 mmol) (40% w/w in methanol) and the resulting solution was concentrated (avoiding complete dryness). After addition of a solution of sulfonyl ester **10c** (0.10 g, 0.30 mmol) in dry DMSO (1 cm^3), the mixture was stirred at room temp. for 30 min, poured into water (2 cm^3), and extracted with dichloromethane (2 × 3 cm^3). The extract was washed with water (3 × 4 cm^3), dried over $MgSO_4$, and concentrated to yield compound **14c** as an oil (0.06 g, 77%) that required no further purification (Found: C, 56.3; H, 6.2. $C_{12}H_{16}O_4S$ requires C, 56.2; H, 6.3); $\delta_H(CDCl_3)$ 1.16 (3 H, t, *J* 7, $MeCH_2O$), 2.86 (2 H, d, CH_2Ph), 3.12 (3 H, s, $MeSO_2$), 3.64 (1 H, t, $HCCO_2Et$), 4.15 (2 H, q, *J* 7, CH_2O) and 7.50–7.00 (5 H, m, Ph).

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