Sulfenylation Accompanied by Dealkoxycarbonylation of β-Keto Esters, Geminal Diesters, and α-Cyano Ester in Hexamethylphosphoric Triamide (HMPA)

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In the presence of sodium iodide, diphenyl disulfide reacted with geminal diesters, β-keto esters, and α-cyano esters in hexamethylphosphoric triamide (HMPA) at 150—160 °C to give alkyl phenyl sulfides and α-phenylthio esters, ketones, and nitriles, respectively, along with evolution of carbon dioxide.

It is well-known that geminal diesters, β-keto esters, and α-cyano esters undergo dealkoxycarbonylation when heated with salt, such as sodium chloride or sodium cyanide, in a wet polar aprotic solvent.[1,2] The dealkoxycarbonylation was thought to involve carbanion as an intermediate. Our investigation was undertaken in order to utilize such carbanion for synthetic purposes. We previously reported the intermolecular and intramolecular alkylation of such carbanion.[3] In the present paper, we wish to report sulfenylation of the carbanion, since the sulfenylated compounds are known to be useful intermediates for a variety of organic compounds.[4]

Results and Discussion

When a solution of diethyl malonate, diphenyl disulfide, and sodium iodide in HMPA was heated to 150—160 °C for 1 h, the evolution of carbon dioxide was observed and the disappearance of diethyl malonate was recognized by TLC. From the reaction mixture, ethyl phenyl sulfide and ethyl (phenylthio)acetate were isolated in 40 and 46% yields, respectively, and unreacted diphenyl disulfide was recovered. At the same time, the formation of ethyl acetate was also confirmed. In this reaction, 1.1 equivalents of sodium iodide (which can be regarded as a catalyst) was used, but when 0.2 equivalent of sodium iodide was used, the reaction was found to proceed very slowly.

In order to find the most suitable reaction conditions

$$\underset{\mathbf{1}}{CH_2(COOEt)_2} + \underset{\mathbf{2}}{(PhS)_2} \xrightarrow[HMPA]{NaI} \underset{\mathbf{3}}{PhSCH_2COOEt} + \underset{\mathbf{4}}{PhSEt} + CO_2$$

and to elucidate the reaction mechanism, several experiments were carried out, using a variety of catalysts and solvents or changing the ratio of the reactants. These results are summarized in Table 1.

In view of these results the most effective catalyst is sodium iodide and the most suitable solvent is HMPA. When DMSO or sulfolane was used instead of HMPA, the dealkoxycarbonylation of diethyl malonate was very slow and considerable amounts of unreacted diethyl malonate and diphenyl disulfide were recovered.

Some of possible reaction sequences are shown in the following equations:

$$\underset{\mathbf{1}}{CH_2(COOEt)_2} + X^- \longrightarrow \underset{\mathbf{5}}{[EtOOCCH_2COO^-]} + EtX \quad (1)$$

$$\mathbf{5} \longrightarrow \underset{\mathbf{6}}{[\bar{C}H_2COOEt]} + CO_2 \quad (2)$$

$$\mathbf{6} + PhSSPh \longrightarrow \underset{\mathbf{7}}{PhSCH_2COOEt} + PhS^- \quad (3)$$

Table 1. Effect of metal halide, solvent, and molar ratio of reactants

Molar ratio $CH_2(COOEt)_2$	$(PhS)_2$	MX	Solvent	Time h	Yield (%)[a] $PhSCH_2COOEt$	Others	
1	1	1.3 (LiCl)	HMPA	1.0	4		
1	1	1.0 (LiI)	HMPA	1.0	25		
1	1	1.2 (NaBr)	HMPA	1.1	21		
1	1	1.2 (KI)	HMPA	1.1	35		
1	1	1.1 (NaI)	HMPA	1.1	46		
1	2	1.2 (NaI)	HMPA	1.3	44[b]		
1	1	5 (NaI)	HMPA	0.8	45		
2	1	1 (NaI)	HMPA	1.0	82	Et(PhS)CHCOOEt	8
2	1	2 (NaI)	HMPA	1.0	84	Et(PhS)CHCOOEt	9
1	1	1 (NaI)	DMSO	1.0	13	$CH_2(COOEt)_2$	63
1	1	1 (NaCl)	DMSO	1.0	5	$CH_2(COOEt)_2$	75
1	1	1 (NaI)	sulfolane	1.0	12	$CH_2(COOEt)_2$	65

a) Yields were calculated based on diphenyl disulfide. b) Yield was calculated based on diethyl malonate.

$$\mathbf{6} + CH_2(COOEt)_2 \longrightarrow CH_3COOEt + \underset{\mathbf{8}}{\bar{C}H(COOEt)_2} \quad (4)$$

$$\mathbf{8} + PhSSPh \longrightarrow \underset{\mathbf{9}}{PhSCH(COOEt)_2} + PhS^- \quad (5)$$

$$PhS^- + EtX \longrightarrow PhSEt + X^- \quad (6)$$

$$\mathbf{9} + X^- \longrightarrow \underset{\mathbf{10}}{PhS\bar{C}HCOOEt} + EtX + CO_2 \quad (7)$$

$$\mathbf{10} + EtX \longrightarrow Et(PhS)CHCOOEt \quad (8)$$

As shown in Table 1, use of 2 equivalents of diethyl malonate caused a great increase of the yield, though addition of excess sodium iodide or diphenyl disulfide scarcely affected the yield. These facts suggest that proton transfer (Eq. 4) and the succeeding sulfenylation (Eq. 5) might be involved in the major pathway for the formation of ethyl (phenylthio)acetate and the direct sulfenylation (Eq. 3) might be less important in this case. The formation of ethyl α-(phenylthio)butyrate in the reaction using 2 equivalents of diethyl malonate also supports the importance of the pathway which involves proton transfer (Eqs. 5, 7, and 8).

When ethyl acetoacetate was used instead of diethyl malonate, (phenylthio)acetone (**11**) (47%) was obtained along with α,α-bis(phenylthio)acetone (**12**) (8%). The formation of α,α-bis(phenylthio)acetone also shows the occurrence of proton transfer.

$$CH_3COCH_2COOEt + (PhS)_2 \xrightarrow[HMPA]{NaI} \underset{\mathbf{11}}{PhSCH_2COCH_3} + \underset{\mathbf{12}}{(PhS)_2CHCOCH_3} + PhSEt + CO_2$$

Table 2. Effect of reaction temperature

Reaction temperature (°C)	Yield (%)	
	11	**12**
140—145	35	4
160	47	8
175	34	7

Table 3. Sulfenylation of geminal diesters, β-keto esters, and ethyl cyanoacetate

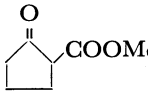
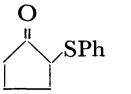
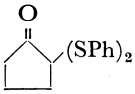
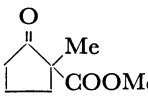
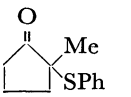
Reactant	Product					
$PhCOCH_2COOEt$	$PhSCH_2COPh$	**13**	36%	$PhCOCH_3$		30%
$NCCH_2COOEt$	$PhSCH_2CN$	**14**	23%	$Et(PhS)CHCN$	**15**	15%
				$(PhS)_2CHCN$	**16**	3%
n-$BuCH(COOEt)_2$	*n*-$Bu(PhS)CHCOOEt$	**17**	40%			
$PhCH_2CH(COOEt)_2$	$PhCH_2(PhS)CHCOOEt$	**18**	46%			
		**19**	47%		**20**	5%
		**21**	49%			
$Me(n\text{-}Pr)C(COOEt)_2$	$Me(n\text{-}Pr)C(PhS)COOEt$	**22**	60%			
$Me_2C(COOMe)_2$	$Me_2(PhS)CCOOMe$	**23**	71%			
$(PhCH)_2C(COOEt)_2$	$(PhCH_2)_2(PhS)CCOOEt$	**24**	66%			

Table 4. Physical properties and analytical data of the products

Product	IR, cm^{-1}	NMR, δ	Mp, (°C)	Ref.
3	1735 (C=O)	1.15 (3H, t), 3.48 (2H, s), 4.07 (2H, q), 7.00—7.52 (5H, m)	oil	5f
11	1710 (C=O)	2.18 (3H, s), 3.50 (2H, s), 7.20 (5H, s)	36—37	5c
12	1710 (C=O)	2.25 (3H, s), 3.75 (1H, s), 7.10—7.53 (10H, m)	42—43	5c
13	1670 (C=O)	4.10 (2H, s), 7.05—7.55 (8H, m), 7.68—8.15 (2H, m)	53—54	5d
14	2230 (C≡N)	3.45 (2H, s), 7.17—7.70 (5H, m)	oil	5e
15	2230 (C≡N)	1.15 (3H, t), 1.80 (2H, dq), 3.55 (1H, t), 7.20—7.81 (5H, m)	oil	
16	2220 (C≡N)	4.75 (1H, s), 7.17—7.85 (10H, m)	oil	
17	1735 (C=O)	1.12 (3H, t), 0.68—2.30 (9H, m), 3.85 (1H, t), 4.05 (2H, q), 7.05—7.55 (5H, m)	oil	5f
18	1730 (C=O)	1.02 (3H, t), 3.06 (2H, dd), 3.68—4.10 (1H, m) 3.94 (3H, q), 7.13—7.50 (5H, m), 7.18 (5H, s)	oil	5f
19	1740 (C=O)	1.60—2.50 (6H, m), 3.45 (1H, t), 7.05—7.65 (5H, m)	oil	5b
20	1740 (C=O)	1.60—2.50 (6H, m), 7.05—7.65 (10H, m)	oil	5b
21	1730 (C=O)	1.25 (3H, s), 1.57—2.73 (6H, m), 7.05—7.45 (5H, m)	oil	5a
22	1730 (C=O)	1.35 (3H, s), 1.17 (3H, t), 0.70—2.15 (7H, m), 4.07 (2H, q), 7.10—7.62 (5H, m)	oil	
23	1730 (C=O)	1.42 (6H, s), 3.56 (3H, s), 7.13—7.50 (5H, m)	41—43	
24	1730 (C=O)	1.08 (3H, t), 3.13 (4H, s), 3.98 (2H, q), 7.08 (10H, s), 7.00—7.52 (5H, m)	oil	

In order to increase the yield of **11** and the ratio of **11** to **12**, the influence of reaction temperature was examined, using HMPA and NaI as solvent and catalyst. Though the ratio scarcely changed, the highest yield of **11** was obtained at 160 °C (Table 2).

Then the reactions of various geminal diesters, β-keto esters, and ethyl cyanoacetate were carried out in HMPA in the presence of sodium iodide at 155—160 °C. α,α-Disubstituted malonic esters and β-keto esters gave the desired sulfenylated products in better yields than geminal diesters, β-keto esters, and α-cyano ester all of which possess active hydrogen. These results are summarized in Table 3. The NMR and IR spectral data of the sulfenylated compounds are also listed in Table 4.

In conclusion, the sulfenylation accompanied by dealkoxycarbonylation was proved to be a useful method for the synthesis of sulfenylated compounds, especially in the case of α,α-disubstituted malonic esters and β-keto esters.

Experimental

Materials. Alkali halides were used after drying at 110—120 °C for several hours in vacuo. HMPA was distilled over sodium hydride under reduced pressure.

Typical Example of the Sulfenylation. A mixture of dimethyl α,α-dimethylmalonate (320 mg, 2 mmol), diphenyl disulfide (436 mg, 2 mmol), sodium iodide (360 mg, 2 mmol), and HMPA (2 ml) was heated at 165—170 °C for 1 h. The mixture was then cooled to room temperature, poured into water (50 ml), and extracted with two portions of ether (50 ml). The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was separated by silica gel TLC (hexane–ether 6: 1), to give methyl α-(phenylthio)-isobutylate (**23**) (298 mg, 71%); mp 41—43 °C, IR(KBr) 1730 cm^{-1} NMR (CCl_4) $\delta=1.4$ (6H, s), 3.55 (3H, s), and 7.1—7.5 (5H, m). Found: C, 62.78; H, 6.63; S, 15.47%. Calcd for $C_{11}H_{14}O_2S$: C, 62.84; H, 6.71; S, 15.22%.

Ethyl α-benzyl-α-(phenylthio)hydrocinnamate (**24**) and ethyl α-methyl-α-(phenylthio)pentanoate (**22**) were obtained from the corresponding disubstituted malonates in a similar manner. Ethyl α-benzyl-α-(phenylthio)hydrocinnamate (**24**). Found: C, 76.37; H, 6.47; S, 8.26%. Calcd for $C_{23}H_{24}O_2S$; C, 76.57; H, 6.43; S. 8.50%. Ethyl α-methyl-α-(phenylthio)pentanoate (**22**). Found: C, 67.07; H, 7.89; S, 12.34%. Calcd for $C_{14}H_{20}O_2S$: C, 66.64; H, 7.99; S, 12.68%.

Other sulfenylated compounds were also obtained by practically the same method as described above. Their structures were confirmed by comparison of their spectral and elemental analyses with those of the authentic samples prepared according to the reported procedures.[5)]

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