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A CONVENIENT SYNTHESIS OF SULFENYLATED ACTIVE METHYLENE COMPOUNDS USING DIARYL DISULFIDES

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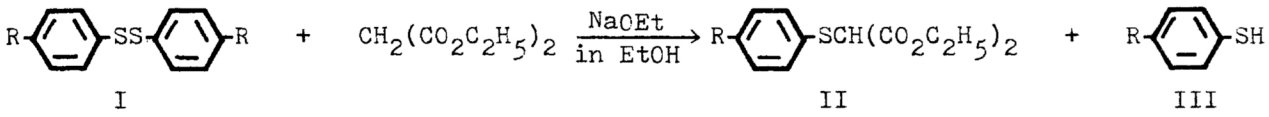
A novel preparation of sulfenylated active methylene compounds has been investigated by the reaction of diaryl disulfides with active methylene compounds in a basic media. Malonates, acetoacetate, acetylacetone, and malononitrile gave selectively the corresponding monosulfenylated compounds at room temperature. At elevated temperatures, only malononitrile afforded a disulfenylated compound, while reactions with other active methylene compounds resulted in decomposition of the monosulfenylated products.

Diethyl malonate or ethyl acetoacetate has been generally used as a carbanion source to give valuable synthetic intermediates, while disulfides have never been used as the substrate. Recently, two methods for the sulfenylation of active methylene compounds using thiolsulfonates[1] and sulfenamides[2] have been reported.

Previous work in our laboratory has demonstrated that a hindered phenol, such as 2,6-di-t-butylphenol, reacts with diaryl disulfides in the presence of a base to give a hindered phenol sulfenylated at the para-position in good yield.[3] The reaction involves a nucleophilic attack of a carbanion of the hindered phenol, which is one of the mesomeric forms of a phenolate anion, on the sulfur atom of the disulfides. This shows that the mesomeric carbanion has a highly thiophilic character. The observation prompted us to investigate a new route to the synthesis of sulfenylated active methylene compounds using diaryl disulfides, since anions of active methylene compounds are stabilized by resonance structures similar to the case of the hindered phenol.

When a mixture of di-p-tolyl disulfide (Ia), diethyl malonate, and sodium in abs. ethanol was stirred at room temperature for 1 hr followed by the neutralization with 3N hydrochloric acid, diethyl p-tolylthiomalonate (IIa)[4] was obtained, which

was isolated by a preparative column chromatography on silica gel using hexane and benzene as eluents, along with p-thiocresol (IIIa). Even when the reaction time



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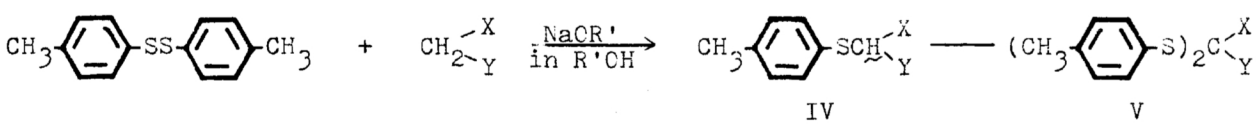
was extended in the use of equimolar amounts of the reactants, a fair amount of the malonate was always recovered. This suggests an occurrence of a reverse reaction, which was confirmed by a control experiment of the reaction of IIa with IIIa under the basic conditions.[5] The use of 3 equivalents of diethyl malonate and sodium gave the thiomalonate IIa in an isolated yield of 76%, which means a conversion yield of 96% based on the consumed disulfide. The similar reactions using various diaryl disulfides were examined and the corresponding arylthiomalonates were obtained as listed in Table I.

Table I. Sulfenylation of Diethyl Malonate using Diaryl Disulfides I

	R	Isolated Yield, % II*	III	Bp of II °C (mmHg)	Anal for II** C, %	H, %	S, %
a	CH_3	76 (96)	75	138-140 (0.5)	59.57 (59.55	6.29 6.43	11.59 11.36)
b	H	77 (95)	80	135 (0.5)#			
c	Cl	77(100)	75	130-133 (0.2)	51.58 (51.58	5.09 4.99	10.59 10.59)
d	Br	41 (90)	55	144-145 (0.5)	44.84 (44.97	4.39 4.35	9.36 9.23)

* Conversion yield based on the consumed disulfide is given in parentheses.
** Calculated values are given in parentheses. # Lit bp, 203-205°C/23mmHg (Ref. 6).

In a similar way, reaction of di-p-tolyl disulfide with the other active methylene compounds gave good results (Table II). The reaction with malononitrile gave p-tolylthiomalononitrile at room temperature, while it gave bis(p-tolylthio)-malononitrile under refluxing in ethanol. On the other hand, the reaction with



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malonates, acetylacetone, or ethyl acetoacetate could not give the corresponding disulfenylated compounds even under refluxing in ethanol, resulting in decomposition

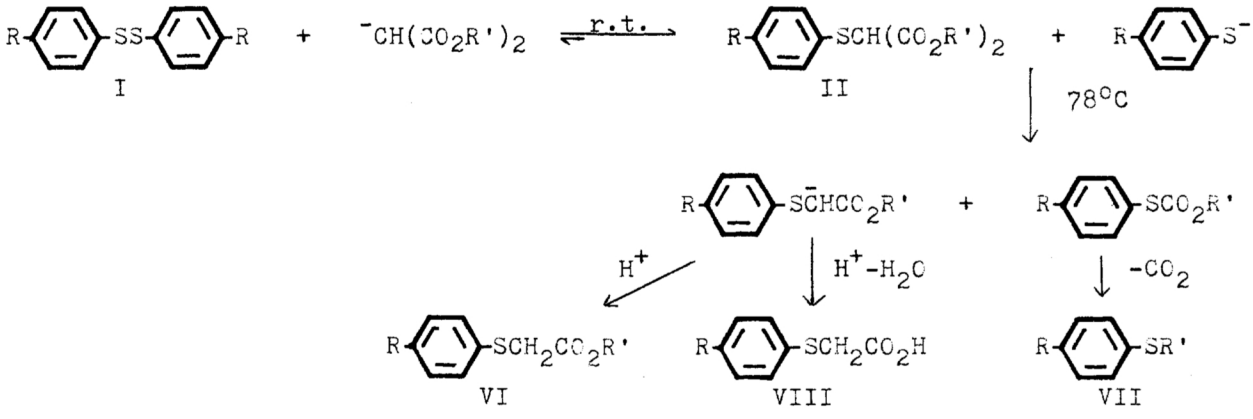
Table II. Sulfenylated Active Methylene Compounds

$CH_2^{X}_{Y}$	Solvent	Reaction Temp.	Product*	Yield, %	Mp, °C or (Bp, °C/mmHg)	Chemical Shift of H, δ
$CH_2(CO_2CH_3)_2$	MeOH	room	IV	51	35	4.3
$CH_2(CO_2t\text{-}Bu)_2$	t-BuOH	room	IV	78	oil**	4.2
$CH_2(COCH_3)_2$	EtOH	room	IV#	65	50-52	17.2
$CH_3COCH_2CO_2Et$	EtOH	room	IV	64	(105-110/0.2)	13.7
$CH_2(CN)_2$	EtOH	room	IV	98	98	4.5
$CH_2(CN)_2$	EtOH	reflux	V	38	96	-

* Satisfactory elemental analyses were obtained for all new compounds. ** This compound decomposes at 160°C on distillation. # Lit mp, 53°C (Ref. 7).

of the monosulfenylated products. For example, when the reaction of Ia with diethyl malonate was carried out under refluxing in ethanol, IIa was obtained in only 31% yield, and ethyl p-tolylthioacetate (VIa, 28% yield), ethyl p-tolyl sulfide (VIIa, 34% yield) and p-tolylthioacetic acid (VIIIa, 6% yield) were simultaneously formed as by-products. The decomposition product VIa was also obtained in a yield of 33%, when a solution of IIa and sodium ethoxide in ethanol was refluxed. Concerning the thermal decomposition, dimethyl phenylthiomalonate has already been reported to pyrolyze on heating at temperature around 160°C to give methyl phenylthioacetate.[8)]

Thus, the reaction may be explained by the following scheme. As the main reaction, a carbanion of malonate attacks on a sulfur atom of disulfide to form the dialkyl arylthiomalonate and thiolate anion. Side reactions are caused by an additional attack of the thiolate anion on two points of the thiomalonate. An attack on the sulfur atom leads to the reverse reaction to give the starting substances, i. e. the disulfide and the malonate. At elevated temperatures, an attack on the carbonyl carbon occurs to give arylthioacetate and arylthioformate. A similar type



of decarbethoxylation by an attack of ethoxide anion has often been observed during the alkylation of malonates or β-keto esters.[9] The thioformate is unstable in the basic conditions to decompose to alkyl aryl sulfide, which was confirmed by a control experiment using an authentic sample of ethyl p-tolylthioformate prepared from sodium p-tolylthiolate and ethyl chloroformate. p-Tolylthioacetic acid is probably formed by hydrolysis during the neutralization.

The nmr spectra of these sulfenylated compounds in carbon tetrachloride are very informative about their structures. The methine protons of the thiomalonates and thiomalononitrile have their resonance at the region of δ 4.2 ~ 4.5, which shows the keto form structure. However, the sulfenylated acetylacetone and acetoacetate exsist as the enol form, for their enolic protons come at the very low field values of δ 17.2 and 13.7, respectively.

Since the disulfides are easily available and the thiophenols formed simultaneously can be easily converted to the starting diaryl disulfides by oxidation, the sulfenylation using diaryl disulfides would afford a convenient method for the preparation of sulfenylated active methylene compounds.

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