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Facile Synthesis of 2,5-Diacylthiophenes. II. The Reaction of Diketo Sulfides with 1,2-Diketones

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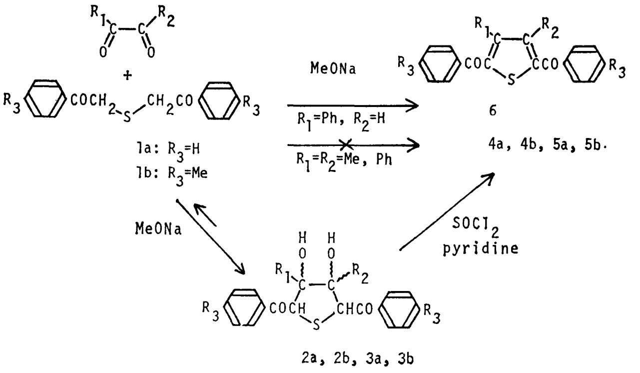
Synopsis. The base-catalyzed reaction of diketo sulfides $(RCOCH_2)_2S$ (R=phenyl, *p*-tolyl) with biacetyl or benzil have provided high yields of 2,5-diacyltetrahydrothiophene-3,4-diol derivatives rather than the expected 2,5-diacylthiophenes. The diols have been transformed cleanly into the corresponding 2,5-diacylthiophenes by treatment with thionyl chloride–pyridine. In contrast, the reaction of the diketo sulfide (R=*p*-tolyl) with phenylglyoxal afforded a 2,5-diacylthiophene directly in good yield.

We have recently demonstrated that the extension of the Hinsberg thiophene synthesis to the diketo sulfides of the type $(RCOCH_2)_2S$, affording 2,5-diacylthiophenes, is very successful when glyoxal is used as the 1,2-dicarbonyl compound and when the reaction is conducted under mild conditions.[1] An obvious extension of the thiophene synthesis is the condensation with 1,2-diketones such as biacetyl and benzil, which have been frequently used in the Hinsberg reaction.[2] When the reaction of α,α'-thiodiacetophenone (**1a**) with biacetyl was conducted under the usual Hinsberg conditions (a rather high concentration of sodium alkoxide), only an intractable tar was obtained. On addition of a dilute methanolic solution of sodium methoxide to a solution of **1a** and biacetyl in methanol at room temperature, a white crystalline precipitate started to separate in a few minutes, in a manner similar to the condensation with glyoxal yielding 2,5-diacylthiophenes. The product isolated at this stage was, however, not the expected thiophene derivative **4a** but an intermediate adduct 2,5-dibenzoyl-3,4-dimethyltetrahydrothiophene-3,4-diol (**2a**). Further addition of the base solution gradually dissolved the precipitate. The resultant dark homogeneous solution gave no crystalline substance. Similar results were obtained for the reactions of **1a** with benzil and **1b** with biacetyl or benzil. On the other hand, the reactions of aliphatic diketo sulfides (R=*t*-butyl, nonyl) gave dark tars with recovery of the starting materials. The yields of the diols **2a**, **2b**, **3a**, and **3b** were very variable, maybe because of the reversibility of the reaction and the complex condensation reactions of the regenerated diketo sulfides. In fact, reproducible high yields could be realized under conditions in which the less soluble diols crystallized out almost completely. The yields and the properties of the diols are summarized in Table 1. The diols thus obtained were pure, judging from their sharp melting points (with decomposition), IR and NMR spectral data, and TLC behavior. Each of them must, therefore,



Scheme 1.

Table 1. The yields and properties of the products

Compound No.	R_1	R_2	R_3	Yield/%	Mp/°C	Molecular Formula	Found(Calcd) (%) C	Found(Calcd) (%) H	IR(KBr) cm^{-1}	NMR($CDCl_3$), δ/ppm R_1, R_2	CHCO	OH
2a	Me	Me	H	91.6	201—202 (dec)	$C_{20}H_{20}O_4S$	67.23 (67.40)	5.66 (5.66)	3500 (ν_{OH}) 1673 (ν_{CO})	1.45	5.21	5.3 (br)
2b	Me	Me	Me	89.7	207.5—208 (dec)	$C_{22}H_{24}O_4S$	68.44 (68.73)	6.25 (6.29)	3450 (ν_{OH}) 1653 (ν_{CO})	1.43	5.20	5.45
3a	Ph	Ph	H	83.8	161.5—162.5 (dec)	$C_{30}H_{24}O_4S$	74.92 (74.98)	5.01 (5.03)	3500 (ν_{OH}) 1665 (ν_{CO})	7.18	6.32	6.00
3b	Ph	Ph	Me	81.1	196—196.5 (dec)	$C_{32}H_{28}O_4S$	75.82 (75.57)	5.53 (5.55)	3390 (ν_{OH}) 1659 (ν_{CO})	7.18	6.31	6.13
4a	Me	Me	H	84.9	101.5—102.5 (lit.[6] 103—104)	$C_{20}H_{16}O_2S$	75.14 (74.97)	5.03 (5.03)	1641 (ν_{CO})	2.37		
4b	Me	Me	Me	95.4	71.5—72.5	$C_{22}H_{20}O_2S$	75.70 (75.83)	5.79 (5.78)	1641 (ν_{CO})	2.37		
5a	Ph	Ph	H	92.6	141—142 (lit.[7] 131.5—132)	$C_{30}H_{20}O_2S$	80.87 (81.06)	4.50 (4.53)	1640 (ν_{CO}) 1625 (ν_{CO})	6.96		
5b	Ph	Ph	Me	88.6	172.5—173	$C_{32}H_{24}O_2S$	81.15 (81.33)	5.04 (5.12)	1654 (ν_{CO})	6.99		
6	Ph	H	Me	67.8	129—130	$C_{26}H_{20}O_2S$	78.64 (78.76)	5.07 (5.08)	1655 (ν_{CO}) 1631 (ν_{CO})	7.22 (Ph) 7.74 (H)		

be one of the seven possible isomers, but the configurations could not be determined on the basis of the available data.[3] The most striking feature of the diols is the sterically hindered nature of the hydroxyl groups, which is evidenced by the unusually slow deuterium exchange of the hydroxyl protons in the diols, especially the bulky phenyl-substituted **3a** and **3b**, and the unexpectedly high Rf values on TLC (silica gel, benzene; 0.29 and 0.71 for **2a** and **3a**, respectively, compared with 0.27 for **1a**).

Although all the attempted dehydrations of the diols under basic (sodium alkoxide/alcohol) or acidic conditions (*p*-toluenesulfonic acid/benzene, phosphorus pentaoxide/benzene, acetic anhydride[3]) gave complex mixtures of products containing the original diketo sulfides and diketones, treatment with thionyl chloride–pyridine at room temperature readily effected the desired conversion to 2,5-diacylthiophenes in high yields, as shown in Table 1. Thus, the condensation of the diketo sulfides with 1,2-diketones was realized in two steps in good overall yields.

The marked difference in reactivity between glyoxal and 1,2-diketones in the reaction with the diketo sulfides led us to investigate the reaction of phenylglyoxal as an intermediate case. The reaction of **1b** with phenylglyoxal under conditions similar to those used for the reaction with 1,2-diketones provided 2,5-di-*p*-toluoyl-3-phenylthiophene (**6**), directly but less efficiently than that with glyoxal.[1]

The resistance of the diols to dehydration, therefore, may be associated with the steric crowding in the diols and the corresponding 2,5-diacylthiophenes. The successful Hinsberg condensation of thiodiacetate esters with 1,2-diketones, in contrast to the present reaction of diketo sulfides, must be ascribed to the neighboring-group assistance by the formation of a δ-lactone intermediate (a Stobbe-type condensation).[4]

Experimental

All the melting points were determined in capillary tubes and are uncorrected. The NMR spectra were recorded on a Hitachi R-20B spectrometer at 60 MHz in deuteriochloroform, with tetramethylsilane as an internal standard. The IR spectra were obtained on a Hitachi 215 spectrophotometer in KBr disks and were calibrated carefully with a polystyrene film.

Reaction of Diketo Sulfides with 1,2-Diketones. The reaction of **1a** with biacetyl yielding **2a** was best carried out as follows. To a stirred solution of **1a** (2.70 g, 10 mmol) and biacetyl (freshly opened, 1.00 g, 11.6 mmol) in 40 ml of methanol was added 0.5 ml of a solution of sodium methoxide (0.5 g of sodium dissolved in 100 ml of methanol) at *ca.* 40 °C. The precipitation of crystals occurred immediately with evolution of heat. After stirring for 1 h, the product was collected by filtration and washed with methanol. To the filtrate, biacetyl (0.5 g) and the base solution (0.5 ml) were added to give, after standing overnight, a small additional amount of the product. The yield of the colorless needles of **2a** amounted to 3.26 g (91.6%); mp 201—202 °C (decomposed with evolution of a gas), recrystallized from chloroform.

Other diols **2b**, **3a**, and **3b** were obtained similarly by the reaction of the diketo sulfides **1a** and **1b** with biacetyl or benzil as shown in Table 1. To be noted is the very slow deuterium exchange of the hydroxyl protons. The hydroxyl and the methine protons appeared close together as singlets in the NMR spectra. In order to make assignments the sample solutions were shaken with a drop of deuterium oxide. The procedure resulted in a slight decrease in the intensities of the hydroxyl peaks of **2a** and **2b** and almost no change in the case of **3a** and **3b**. In order to reduce the intensities of the hydroxyl peaks of **3a** and **3b** appreciably, it was necessary to heat and shake repeatedly.

*Dehydration of the Diols **2a**, **2b**, **3a**, and **3b**.* To a suspension of the diol (4.0 mmol) in 30 ml of chloroform and 4.0 ml of pyridine cooled in an ice bath, was added 4.0 ml of thionyl chloride. The resultant clear yellow solution was stirred at room temperature for 1 h. Then, the solution was poured into ice and water containing hydrochloric acid, and extracted with chloroform. After washing with water, the extracts were dried over magnesium sulfate and filtered through a short column of silica gel. After solvent evaporation, the residue was crystallized from methanol.

*Condensation of **1b** with Phenylglyoxal.* To a stirred, warm solution of **1b** (1.492 g, 5.0 mmol) and phenylglyoxal (freshly prepared,[5] 740 mg, 5.5 mmol) in 10 ml of methanol was added a solution of sodium methoxide (0.5 g of sodium dissolved in 100 ml of methanol, 10 ml) over a 10-min period. Crystals started to separate slowly. After it had been stirred for 30 min, the solution was allowed to stand for 2 d. The product was collected by filtration and washed well with methanol. **6** was obtained as pale yellow granules in 67.8% yield (1.345 g); recrystallized from benzene–methanol; mp 129—130 °C.

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