On the Acylation of 1,3-Benzoxathiole Systems

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The acylation on 1,3-benzoxathiole systems, as well as the effect of the stoichiometry of the catalyst on the yields of ketones and of breaking products of the O-C-S bonds is here described.

It has previously been shown [1] that the electrophilic substitution reactions on 1,3-benzoxathiole derivatives, except for nitration reactions, take place in position 5, i.e., para to the oxygen atom. Although acylation reactions have already been widely studied for many years, and several catalysts and reaction conditions [2], as well as many acylating agents have been examined, nevertheless, only a few studies focused their attention on the effects of an excess of catalysts in acylation reactions, whereas the influence of the stoichiometry of the catalyst, particularly in the acylation of aryl ethers, has been highly neglected. The effects exerted by the quantity of catalyst on the acylation of aryl ethers [3] and thioanisole [4] have been studied in literature only in recent times.

In this work, the acylation reactions on 1,3-benzoxathiole systems are studied, as well as the effect of the stoichiometry of the catalyst on the yields of ketones and cleavage products of the O-C-S bonds. First the acylation reactions on benzoxathiole systems with acetic anhydride and catalysts such a zinc chloride, titanium tetrachloride, perchloric acid and aluminium trichloride, were examined. It was noted that, although benzoxathiole substrates are activated systems, acylation takes place with satisfactory yields

only in the presence of strong Lewis acids. With zinc chloride, acylation takes place with very low yields (10-20%). More satisfactory results are obtained with titanium tetrachloride in carbon tetrachloride and with perchloric acid. The best yields (50-70%) are obtained with aluminium chloride in nitrobenzene. The optimum ratio between substrate and catalyst is 1:1.5. In all reactions about 10-15% of unreacted, unaltered product is found, and only one acylation product II (Table 1, 2) is isolated.
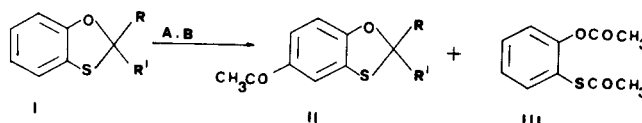
The position of the acetyl group was determined by cleaving the benzoxathiole bridge of the compounds II with Ni-Raney and by subsequent comparison of the obtained products with authentic samples. In all cases, it was observed that acylation always takes place in the para-position to the oxygen atom of the benzoxathiole ring. The effect of the quantity of catalyst on the acylation reaction of 1,3-benzoxathiole systems with acetyl chloride was also

Table 1

5-Acetyl-2,2-disubstituted-1,3-benzoxathioles IIa-g

Product	R	R₁	% Yield by method A	% Yield by method B	Molecular Formula	Analyses Calcd./Found C	H	S
IIa	H	H	75	79	$C_9H_8O_2S$	59.97	4.47	17.79
						60.04	4.45	17.75
IIb	CH_3	C_2H_5	55	70	$C_{12}H_{14}O_2S$	64.83	6.35	14.42
						64.80	6.33	14.40
IIc	C_2H_5	C_2H_5	60	70	$C_{13}H_{16}O_2S$	66.07	6.83	13.57
						66.02	6.83	13.50
IId	CH_3	$n\text{-}C_3H_7$	55	75	$C_{13}H_{16}O_2S$	66.07	6.83	13.57
						66.10	6.80	13.58
IIe	CH_3	$iso\text{-}C_4H_9$	60	80	$C_{14}H_{18}O_2S$	67.16	7.25	12.81
						67.10	7.22	12.89
IIf	R....R₁ =	$(CH_2)_4$	65	83	$C_{13}H_{14}O_2S$	66.64	6.02	13.68
						66.60	6.03	13.70
IIg	R....R₁ =	$(CH_2)_5$	68	84	$C_{14}H_{16}O_2S$	67.71	6.50	12.91
						67.68	6.54	12.87

A = acetic anhydride and Lewis acid (1:1.5) in nitrobenzene. B = acetyl chloride and Lewis acid (1:1) in dichloromethane.

Table 2

Physical Data of IIa-g

Product	bp (°C mm Hg) or mp (°C)	n_D^{18}	IR cm⁻¹ C=O	¹H-NMR ppm (deuteriochloroform)
IIa	127	—	1660	7.80-6.78 (m, 3H aromatic) 5.76 (s, 2H, CH_2), 2.52 (s, 3H, CH_3)
IIb	175/30	1.576	1670	7.78-6.78 (m, 3H aromatic), 2.49 (s, 3H, $COCH_3$), 2.02 (q, 2H, CH_2-CH_3 J = 7.3 Hz), 1.80 (s, 3H, CH_3), 1.06 (t, 3H, CH_2CH_3)
IIc	180/20	1.575	1680	7.80-6.70 (m, 3H, aromatic), 2.51 (s, 3H, $COCH_3$), 2.00 (m, 4H, $2CH_2CH_3$), 1.17 (t, 6H, $2CH_2CH_3$, J = 7.2 Hz)
IId	175/15	1.564	1680	7.76-6.82 (m, 3H aromatic), 2.50 (s, 3H, $COCH_3$), 2.30-1.15 (m, 4H, CH_2CH_2-CH_3, J = 7.9 Hz), 1.83 (s, 3H, CH_3), 0.97 (t, 3H, -CH_2CH_3)
IIe	148/20	1.545	1680	7.78-6.73 (m, 3H aromatic), 2.51 (s, 3H, $COCH_3$), 1.98 (m, 3H, CH-CH_2), 1.80 (s, 3H, CH_3), 0.97 (d, 6H, $CH(CH_3)_2$, J = 8 Hz)
IIf	59	—	1680	7.76-6.73 (m, 3H aromatic), 2.51 (s, 3H, $COCH_3$), 2.46-1.58 (m, 8H, $(CH_2)_4$)
IIg	200/15	1.635	1680	7.80-6.70 (m, 3H aromatic), 2.50 (s, 3H, $COCH_3$), 2.4-0.7 (m, 10H, $(CH_2)_5$)

examined, the reactions have carried out at $-10°$ and dichloromethane was used as solvent and aluminium chloride as catalyst. The reaction was checked by taking small portions of the reaction mixture, which were washed in dilute hydrochloric acid, dried on sodium sulphate and examined by hplc with a column in normal phase. Besides the acetylation product II, the *o*-hydroxybenzenethiol diacetate III [5] was obtained in varying quantities from the cleavage of the oxathiole ring.

Table 3

Acylation of 1,3-Benzoxathiole With Acetyl Chloride

Reaction	Mole ratio Ia:Aluminum Chloride	% Yield IIa	% Yield III
1	1:1	79	10
2	1:1.5	40	20
3	1:2	33	30

The reaction takes place with the initial formation of the acylium ion [6] which may attack both the benzene ring, giving the acylation product II, and the ether and thioether bonds of the heterocyclic ring, giving the diesther III.

The 1,3-benzoxathiole system proved to be extremely sensitive to the stoichiometry of the catalyst, as can be seen from the data reported in Table 3.

The variation of the catalyst concentration allowed a direct relation with the products. Using stoichiometric quantities of catalyst and substrate, the yield of the product II is about 80% (the reaction is complete in an hour), whereas the yield of the breaking product is 10-15%. If the catalyst quantity is increased, acylation is strongly inhibited, whereas an increase of the cleavage product takes place.

Using the same reaction conditions, the amount of III is determined by the bulk of the substituents in position 2, reaching a maximum when R = R_1 = CH_3 and decreasing as the steric demand of the substituents increases.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus (capillary method) and are uncorrected. All boiling points were uncorrected and obtained from distillation or with a boiling point apparatus. Infrared spectra were determined on a Perkin Elmer model 157G spectrophotometer using either potassium bromide mulls or neat liquids between sodium chloride plates. The nmr spectra were determined on a Varian FT 80A spectrometer using tetramethylsilane as internal reference. The glc analyses were performed on a Carlo Erba GV instrument equipped with SE-30 column (2 m × 0.5 cm, 10% on carbowax 20M). The hplc was performed using a Carlo Erba Model 8700-11 liquid chromatograph. A uv-visible Varichron detector, a CDS 111 L data system and a Varian 9176 recorder were employed. Samples were separated on column Lichrosorb S_{10} 100; the eluent was petroleum-ether-diethyl ether (80:20) at 2.0 ml/minute. Microanalyses for CHNS were carried out on a Carlo Erba Model 1106 Elemental Analyser.

Starting Materials.

1,3-Benzoxathiole (Ia) and 2,2-dialkyl-1,3-benzoxathioles I(b-g) were prepared by a reported method [7].

General Method for the Preparation of Derivatives IIa-g.

Method A.

To a mixture of Ia-g (0.05 mole) and anhydrous aluminum chloride (0.075 mole) in nitrobenzene (50 ml), acetic anhydride (0.05 mole) was added dropwise maintaining the temperature at $-10°$. After stirring for an additonal 1.5 hours at 0°, the mixture was poured onto 100 g of ice and extracted with chloroform. The extract was washed (in turn) in 10% sodium carbonate and in water, and dried over anhydrous sodium sulphate. After solvent evaporation *in vacuo*, the crude products IIa-g were purified by distillation *in vacuo* or recrystallization from ethanol.

Method B.

To a well stirred mixture of Ia-g (0.05 mole); methylene chloride (50 ml) and aluminum chloride (0.05 mole), acetyl chloride (0.05 mole) was added maintaining the temperature at $-10°$. After stirring for an additional hour at $-10°$, the mixture was poured onto 100 g of ice and extracted with chloroform. The organic layer was washed successively in cold 10% sodium hydroxide and in water. It was then dried and evaporated to afford the crude products IIa-g, which were chromatographed on a

silica gel column, using petroleum ether-diethyl ether (5:1). Initial elution gave a starting material (5-15%). Subsequent elution afforded pure IIa-g, yield 70-85%. The third elution afforded an o-hydroxybenzenethiol diacetate, identified by analytical and spectroscopic data and by comparison with authentic samples [5].

Action of Raney Nickel Catalyst on IIa-g.

A solution of IIa-g (0.0025 mole) in 95% ethanol (2.5 ml) was refluxed for 2 hours with Raney Nickel (0.5 g). The resulting mixture was filtered, evaporated *in vacuo* and the residue diluted with diethyl ether. The glc analysis showed a peak with the same retention time as *p*-hydroxyacetophenone.

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