DEACYLATION OF AROMATIC KETONES

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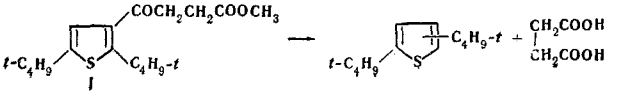
The methyl esters of β-(2,5-di-tert-butyl-3-thenoyl)propionic and γ-(2,5-di-tert-butyl-3-thenoyl)butyric acids are deacylated by prolonged refluxing with a mixture of hydrochloric and formic acids to form di-tert-butylthiophene and aliphatic dicarboxylic acids (succinic and glutaric acids, respectively). The same process also occurs on heating 2,5-di-tert-butyl-3-acetylthiophene under the same conditions. Practically no deacylation occurs on refluxing these thiophene derivatives with hydrochloric acid alone or with a mixture of hydrochloric acid and acetic acid. Attempts to deacylate methyl β-(2,5-diethyl-3-thenoyl)propionate were unsuccessful. Assumptions regarding the peculiarities of deacylation in the 2,5-dialkyl-3-acylthiophene series associated with the geometry of the thiophene ring are expressed.

The acylation of aromatic compounds, like nitration, is usually described as an irreversible process. However, in at least some cases it can be considered to be reversible, as, for example, when the acylation is accomplished by means of polyphosphoric acid [1], which may be the reason for deacylation of the ketone when the temperature is raised. The first observations regarding this reaction were made in 1885 [2] and, despite the number of studies that followed this report, the limits of its applicability and the problem of the deacylation mechanism remain insufficiently clear. Relatively recently a review [3] appeared in which, in addition to new data, a mechanism was presented which, in our opinion, reflects only one side of the problem and does not consider the specifics of the attacking agent and other factors whereas, as will be seen below, they can play an essential role in the process. The point of view that disruption of coplanarity promotes deacylation should, however, be considered to be quite well founded. The experimental basis for this conclusion is the fact that the capacity for deacylation is inherent only in those ketones which have alkyl substituents in at least one ortho position with respect to the acyl group; moreover, the reaction proceeds more readily, the bulkier the substituent.

We encountered this reaction during an attempt to saponify methyl β-(2,5-di-tert-butyl-3-thenoyl)-propionate (I) by refluxing it with a mixture of hydrochloric and formic acids, i.e., under the conditions often used for the hydrolysis of esters. We were unable to obtain the expected β-(2,5-di-tert-butyl-3-thenoyl)propionic acid (II) via this path but isolated di-tert-butylthiophene and succinic acid.



Chromatographic analysis indicated that the di-tert-butylthiophene obtained is a mixture of the 2,5- and 2,4-isomers.*

As was made clear in our subsequent experiments, several other compounds – methyl γ-(2,5-di-tert-butyl-3-thenoyl)butyrate (III) and 2,5-di-tert-butyl-3-acetylthiophene (IV) – have a similar ability to deacylate.

* It is well known that 2,5-di-tert-butylthiophene is readily isomerized to 2,4-di-tert-butylthiophene by the action of acidic reagents, particularly aluminum chloride [4].

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In addition, we made the observation (which seems important to us) that, under the indicated conditions, methyl β-(2,5-diethyl-3-thenoyl)propionate (V) undergoes virtually no deacylation and is only saponified to the corresponding acid (VI). If one considers the above-examined role of an ortho substituent, it becomes clear that the conditions for the deviation from coplanarity are still absent when there is an ethyl group in the 2-position of the thiophene ring, and they develop only on introduction of the sterically larger tert-butyl group into this position. It can be assumed that this is associated with the numerical values of the formal valence angles for the α- and β-positions of the thiophene ring (HC(2)C(3) 128°41' and HC(3)C(2) 123°17', respectively [5]) which exceed the value (120 deg) for the benzene ring. This is satisfactorily apparent with Stuart-Briegleb models.

Our second observation, which is, we felt, of interest for a more detailed study and examination of the mechanism, consists of the specific role of formic acid in the deacylation of ketones of the thiophene series. Its presence undoubtedly has a pronounced accelerating effect on the deacylation. The fact that III is deacylated to only a neglible extent on refluxing with hydrochloric acid or a mixture of hydrochloric and acetic acids and gives the corresponding keto acid (VII) is a rather clear illustration of this. We currently do not have data to express well-founded concepts regarding this specific role of formic acid.

EXPERIMENTAL

The di-tert-butylthiophene used in this study was isolated by fractional distillation of the vessel residues from the preparation of tert-butylthiophene by the reaction of thiophene with tert-butyl chloride in carbon disulfide in the presence of stannic chloride [6]. The di-tert-butylthiophene fraction boiling at 218-219 deg, which, according to gas-liquid chromatography,* contains ~ 80% 2,5-di-tert-butylthiophene and ~ 20% of the 2,4-isomer, was subjected to acylation.

Acylation of Di-tert-butylthiophene. A solution of 16 ml of stannic chloride in 20 ml of benzene was added dropwise to a stirred solution of 24.5 g (0.12 mole) of di-tert-butylthiophene and 19.5 g (0.13 mole) of carbomethoxypropionyl chloride in 90 ml of benzene at 2-5 deg. The mass was stirred at room temperature for 1 h and then decomposed with dilute (1:5) hydrochloric acid, which was added gradually to the reaction mixture at 5-10 deg. The organic layer was separated and washed with dilute hydrochloric acid and NaCl and $NaHCO_3$ solutions. The extract was dried with magnesium sulfate and vacuum-distilled to give 30.1 g (78%) of I with bp 160 deg (2 mm) and mp 74-76 deg (from hexane). Found %: C 66.0, 66.0; H 8.3, 8.4; S 10.3, 10.3. $C_{17}H_{26}O_3S$. Calc. %: C 65.8; H 8.4; S 10.3. I contained ~ 5% of methyl β-(3,5-di-tert-butyl-2-thenoyl)propionate (according to gas-liquid chromatography).

Compound III was similarly obtained in 75% yield and had bp 168-170 deg (~2 mm) and mp 53-55 deg (from hexane). Found %: C 67.1, 67.0; H 8.7, 8.7; S 9.9, 10.0. $C_{18}H_{28}O_3S$. Calc. %: C 66.6; H 8.7; S 9.9. Compound III did not contain isomer impurities (according to gas-liquid chromatography).

The same method was used to obtain V in 81% yield with bp 152-154 deg (~ 2 mm). Found %: C 60.7, 60.9; H 6.9, 6.9; S 12.2, 12.3. $C_{13}H_{18}O_3S$. Calc. %: C 61.4; H 7.1; S 12.6.

2,5-Di-tert-butyl-3-acetylthiophene (IV) was synthesized via the method described in [7].

Deacylation of Methyl β-(2,5-Di-tert-butyl-3-thenoyl)propionate (I). A mixture of 17.3 g of keto esters I, 40 ml of dilute (1:1) hydrochloric acid, and 200 ml of 85% formic acid was refluxed for 20 h, ~ 100 ml of the liquid was removed by distillation at normal pressure, 100 ml of water was added to the residue, and ~ 100 ml of liquid was again removed by distillation. The distillate was diluted with water to a volume of 300 ml and extracted with CCl_4. The extract was washed with a salt solution and a salt–sodium carbonate solution and dried with $CaCl_2$. The residue after removal of the solvent was fractionated to give 9.17 g (76%) of di-tert-butylthiophene with bp 217-218 deg and n_D^{20} 1.4923, which contained ~ 70% of 2,5-di-tert-butylthiophene and ~ 30% of the 2,4-isomer (according to NMR). The residue after distillation of a portion of the liquid from the reaction mass at atmospheric pressure was treated with charcoal and evaporated in vacuo to give a residue of 6.82 g (94%) of a solid with mp 182 deg (from water), which did not depress the melting point of succinic acid and had an acid equivalent of 59.5, as compared with 59 calculated for succinic acid.

Replacement of formic acid by acetic acid in this experiment gave 91% of β-(2,5-di-tert-butyl-3-thenoyl)propionic acid (II) with mp 162-164 deg (from toluene–hexane). Found %: C 65.0, 65.0; H 8.4, 8.2;

* All analyses were carried out with a column (2 m by 0.4 cm) with Apiezon (5%) on Chromosorb W at ~ 180 deg.

S 10.7, 10.8. $C_{16}H_{24}O_3S$. Calc. %: C 64.8; H 8.2; S 10.8. Compound II was also isolated in 78% yield by the saponification of I with 10% NaOH.

Deacylation of Methyl γ-(2,5-Di-tert-butyl-3-thenoyl)butyrate (III). A mixture of 12 g of keto ester III, 20 ml of concentrated hydrochloric acid, and 200 ml of 85% formic acid was refluxed for 6 h and then worked up as indicated above to give 5.84 g (80%) of 2,5-di-tert-butylthiophene which contained less than 5% of the 2,4-isomer (according to NMR) and 4.5 g (92%) of glutaric acid with mp 98-99 deg.

Refluxing of keto ester III in a mixture of acetic and hydrochloric acids gave 95% of γ-(2,5-di-tert-butyl-3-thenoyl)butyric acid (VII) with mp 84-85 deg (from hexane). Found %: C 65.4, 65.7; H 8.4, 8.5; S 10.5, 10.3. $C_{17}H_{26}O_3S$. Calc. %: C 65.8; H 8.4; S 10.3.

Deacylation of 2,5-Di-tert-butyl-3-acetylthiophene (IV). A mixture of 14.2 g of 2,5-di-tert-butyl-3-acetylthiophene (IV), 50 ml of dilute (1:1) hydrochloric acid, and 80 ml of 85% formic acid was refluxed for 27 h; 50 ml of water was added; and a portion of the liquid was removed by distillation until evolution of the oil had ceased. The distillate was extracted with ether, and the extract yielded 4.7 g (40%) of di-tert-butylthiophene. Deacylation did not occur on prolonged heating of IV with hydrochloric acid alone.

Refluxing of 13.6 g of methyl β-(2,5-diethyl-3-thenoyl)propionate (V) in a mixture of 20 ml of concentrated hydrochloric acid and 200 ml of 85% formic acid for 10 h gave 11.6 g (90%) of β-(2,5-diethyl-3-thenoyl)propionic acid with mp 79-80 deg [8].

As a consequence of steric hindrance, esters of ω-(2,5-di-tert-butyl-3-thenoyl)alkanoic acids (I and III) and the corresponding keto acids (II and VII) did not form semicarbazones with semicarbazide, but were reduced by hydrazine hydrate under the conditions of the Kishner reaction.

Kishner Reduction of γ-(2,5-Di-tert-butyl-3-thenoyl)butyric Acid (VII). Compound VII (10 g) was treated in accordance with the method in [9] with 9 ml of hydrazine hydrate and 9 g of KOH in 45 ml of diethylene glycol to give 54% of δ-(2,5-di-tert-butyl-3-thienyl)valeric acid with bp 185-189 deg (~ 2 mm) and mp 89-90 deg (from dilute alcohol). Found %: C 68.7, 68.9; H 9.4, 9.5; S 10.8, 10.8. $C_{17}H_{28}O_2S$. Calc. %: C 68.9; H 9.5; S 10.8.

β-(2,5-Di-tert-butyl-3-thenoyl)propionic acid (II) was similarly reduced to give 40% of γ-(2,5-di-tert-butyl-3-thienyl)butyric acid with bp 182-184 deg (4 mm) and mp 111-112 deg (from dilute alcohol). Found %: C 67.9, 68.2; H 9.2, 9.1; S 11.3, 11.3. $C_{16}H_{26}O_2S$. Calc. %: C 68.0; H 9.3; S 11.3.

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