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# Condensations Effected by the Alkali Amides. VI. Studies in the Acylation of Methyl 2-Thienyl Ketone[1]

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The following equation represents the over-all reaction for the base-induced synthesis of β-diketones. While considerable work[2a,b,c,d,e] has been reported on the use of the Claisen condensation to

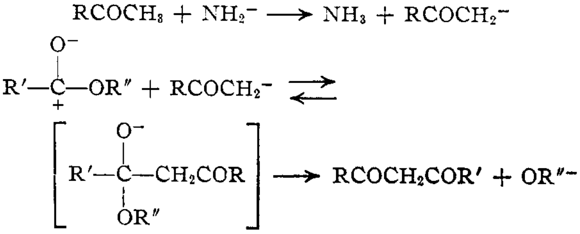
$$RCOCH_3 + R'CO_2R'' \xrightarrow{\text{base}} R''OH + RCOCH_2COR'$$

prepare a large variety of β-keto esters and β-diketones, no detailed study had been made prior to the present work to determine the effect on the reaction by (1) keeping R and R′ constant and varying R″ and (2) keeping R and R″ constant and varying R′.

In the present investigation these effects have been evaluated in a semiquantitative manner. Because of the interest in this Laboratory in the synthesis of heterocyclic β-diketones, we have studied (1) the condensations of methyl 2-thienyl ketone (R is the 2-thienyl group) with a series of acetic acid esters (R′ is $CH_3$ and R″ is $CH_3$, $C_2H_5$, iso-$C_3H_7$, *t*-$C_4H_9$ and $C_6H_5$) and (2) the reactions of this ketone with a number of other aliphatic and aromatic esters (R″ is $C_2H_5$ and R′ is $C_2H_5$, iso-$C_3H_7$, *t*-$C_4H_9$, $C_6H_5$, *p*-$ClC_6H_4$ and *p*-$CH_3OC_6H_4$).

There is a striking resemblance between the mechanisms which have been proposed for the ammonolysis of esters,[3] the alkaline hydrolysis of esters[4] and the Claisen acylation of ketones.[5] These reactions are all similar in that each involves the initial attack of a Lewis base on the carbonyl carbon atom of the ester. The hydrolysis and ammonolysis reactions differ from the Claisen condensation in that in the first two reactions, the attacking reagent, *i.e.*, the ammonia molecule or the hydroxide ion, is already available in the medium but in β-diketone formation, the ketone anion must first be formed before reaction can occur. However, using the triphenylmethane indicator method,[6] it has been shown that methyl 2-thienyl ketone is rapidly and apparently completely converted to its anion by sodium amide.

The following equations illustrate the mechanism of the Claisen acylation of ketones and may readily be compared with the ammonolysis[3] and hydrolysis[4] of esters. The β-diketone formed is then converted to its anion by the extra equivalent of ketone anion which is present.



$$RCOCH_3 + NH_2^- \longrightarrow NH_3 + RCOCH_2^-$$

$$R'-\overset{O^-}{\underset{+}{C}}-OR'' + RCOCH_2^- \rightleftharpoons$$

$$\left[ R'-\overset{O^-}{\underset{OR''}{C}}-CH_2COR \right] \longrightarrow RCOCH_2COR' + OR''^-$$

The relative order of reactivity of the esters has been determined by the interaction of the esters with the anion of methyl 2-thienyl ketone under carefully controlled conditions and then isolating the β-diketones produced. In all cases great care was taken to get a high material balance on the reactants. In order to minimize side-reactions,[7] the condensations were carried out by the interaction of two equivalents of sodium amide, two equivalents of the ketone and one equivalent of the acylating ester.

It may be seen (Table I) that the order of reactivity of the esters of acetic acid in the Claisen condensation is as follows: phenyl > methyl > ethyl > isopropyl > *t*-butyl. These results agree with the currently accepted concept of the electron releasing effects of alkyl and aryl groups. However, it should be pointed out that a steric factor may also be increasingly operative in the order methyl < ethyl < isopropyl < *t*-butyl which would make it more difficult for the ketone anion to attack the carbonyl carbon of the ester in the order given.

When the rate of condensation of several aliphatic ethyl esters (Table II) of the structure $RCO_2C_2H_5$ was studied, the order of reactivity was found to be R = methyl > ethyl > isopropyl > *t*-butyl. These results are analogous to those described above. It will be observed that the interaction of ethyl trimethylacetate with the anion of the ketone gave no β-diketone. This result agrees with the observations of Day and coworkers[4] who noted that methyl trimethylacetate is ammonolyzed at a much slower rate than *t*-butyl acetate when compared with methyl acetate. These workers have explained their results as follows: "The greater retardation effect of the $R_3C$ grouping in methyl trimethylacetate can be attributed to the closer proximity of that group to the carbonyl carbon than in the case of *t*-butyl acetate." A similar explanation is applicable to our results.

Finally three aromatic ethyl esters (Table II) of the structure $R_{Ar}CO_2C_2H_5$ were condensed with methyl 2-thienyl ketone and the relative reac-

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[1] For paper V in this series, see Barkley and Levine, THIS JOURNAL, **72**, 3699 (1950).

[2] (a) Adams and Hauser, *ibid.*, **66**, 1220 (1944); (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945); (c) Harris and Levine, *ibid.*, **70**, 3360 (1948); (d) Harris and Levine, *ibid.*, **71**, 1120 (1949); (e) Hauser and Hudson, "Organic Reactions," Vol. I, Chapter 9.

[3] Gordon, Miller and Day, THIS JOURNAL, **70**, 1946 (1948).

[4] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., pp. 121, 211, 212.

[5] Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944).

[6] Levine and Hauser, *ibid.*, **66**, 1768 (1944).

[7] The most important side reaction is the possible attack of the amide ion at the carbonyl carbon of the ester.

tivity was found to be $R_{Ar}$ = $p$-$ClC_6H_4 > C_6H_5 > p$-$CH_3OC_6H_4$. Apparently the inductive effect of the para chlorine atom in ethyl *p*-chlorobenzoate greatly enhances the positive charge on the polarized form of the carbonyl group, while the methoxyl group in ethyl anisate feeds electrons into the ring with the result the extent of the positive charge on the carbonyl carbon is decreased.

The results obtained in this study parallel closely those obtained by Day and co-workers[3] on the ammonolysis of esters; they agree with the published data on the alkaline hydrolysis of esters;[4] they substantiate the data of Vavon, Barbier and Thiebaut[8] on the rate of reaction between Grignard reagents and esters.

TABLE I

SYNTHESIS OF ACETYL 2-THENOYLMETHANE BY ACETYLATION OF METHYL 2-THIENYL KETONE[a]

| Acetate ester | Ester addn. time in hr. | Reflux time in hr. | Yield, % |
|---|---|---|---|
| Methyl[b] | 0.50 | 5.0 | 61.6 |
| | .333 | 1.0 | 46.4 |
| | .166 | 0.25 | 3.9 |
| Ethyl[b] | .50 | 5.0 | 53.8 |
| Isopropyl | .50 | 5.0 | 7.0 |
| | .50 | 10.0 | 38.4 |
| *t*-Butyl | .50 | 10.0 | 21.6 |
| Phenyl[b] | .50 | 5.0 | 51.8 |
| | .333 | 1.0 | 54.2 |
| | .166 | 0.25 | 50.3 |

[a] B. p. 128–131° at 8 mm., m. p. 35–37° (see ref. 2c). [b] 0.4 mole of sodium amide, 0.4 mole ketone and 0.2 mole of ester used; in all other runs 0.8 mole of sodium amide, 0.8 mole of ketone and 0.4 mole of ester used.

TABLE II

SYNTHESIS OF ACYL 2-THENOYLMETHANES BY ACYLATION OF METHYL 2-THIENYL KETONE

| Ester, ethyl | Ester addn. time in hr. | Reflux time in hr. | 2-Thenoylmethane | B. p., °C. (mm.)[e] | Yield, % |
|---|---|---|---|---|---|
| Acetate[a] | 0.50 | 5.0 | Acetyl | 128–131 (8) | 53.8 |
| Propionate[a] | .50 | 5.0 | Propionyl | 126–129 (5) | 44.5 |
| Isobutyrate | .50 | 5.0 | Isobutyryl | 132–135 (5) | 11.3 |
| Trimethylacetate | .50 | 5.0 | Trimethylacetyl | | 0.0[b] |
| Benzoate[a] | .166 | 5.0 | Benzoyl | 78–78.5 (m. p.) | 48.2 |
| | .166 | 1.0 | | | 5.6 |
| Anisate[a] | .166 | 5.0 | Anisoyl[c] | 124–124.5 (m. p.) | 18.7 |
| *p*-Chlorobenzoate[a] | .166 | 1.0 | *p*-Chlorobenzoyl[d] | 130–131 (m. p.) | 47.5 |

[a] See footnote *b* of Table I. [b] After decomposition (see exptl.), the reaction mixture gave a slight enol test with alcoholic ferric chloride soln., but no $\beta$-diketone could be isolated by distillation or the copper chelate method (see ref. 2b). [c] *Anal.* Calcd. for $C_{14}H_{12}O_3S$: C, 64.59; H, 4.65; Found: C, 64.82; H, 4.78. [d] *Anal.* Calcd. for $C_{13}H_9O_2ClS$: C, 58.98; H, 3.43. Found: C, 58.88; H, 3.57. [e] See ref. 2c.

## Experimental

Since all the runs were carried out in essentially the same way except for the time required for the addition of the acylating esters and the reflux periods (see Tables I and II), only one experiment will be described in detail.

**Synthesis of *p*-Chlorobenzoyl 2-Thenoylmethane.**—Using the method previously described,[2c] 0.4 mole of sodium amide was prepared from 9.2 g. (0.4 mole) of sodium and liquid ammonia in a 1000-ml. three-neck, round-bottom flask equipped with a dibutyl phthalate-sealed stirrer, a reflux condenser and an addition funnel (when 0.8 mole of sodium amide was used, a 2000-ml. flask was employed). The sodium amide was suspended in 250 ml. of anhydrous ether and the mixture refluxed vigorously for one-half hour. Methyl 2-thienyl ketone (50.4 g., 0.4 mole, b. p. 78–78.5° at 5 mm.) diluted to 125 ml. with anhydrous ether was added at such a rate as to keep the ether rapidly refluxing. The mixture was then refluxed and stirred twenty minutes longer to ensure complete conversion of the ketone to its anion. Then, 0.2 mole (36.9 g.) of ethyl *p*-chlorobenzoate, b. p. 95–97° (4 mm.), diluted to 125 ml. with anhydrous ether was added over a ten-minute period and the mixture stirred and refluxed for sixty minutes longer. The contents of the flask was poured onto 1 kg. of ice to which 150 ml. of concentrated hydrochloric acid had been added and the mixture stirred until all the solid present had dissolved. The mixture was extracted with four 100-ml. portions of ether (in the other runs the mixtures were extracted with 100-ml. portions of ether until the extracts no longer gave a positive enol test with alcoholic ferric chloride solution), and the combined ethereal phases dried over Drierite, filtered and the solvent distilled. The residue was fractionated in vacuum to remove 48.8 g. of a mixture of unreacted ester and excess ketone, b. p. 75–110° (5 mm.). The residue, which solidified, was recrystallized twice from 95% ethanol to give 25.2 g. (47.5%) of *p*-chlorobenzoyl 2-thenoylmethane, m. p. 130–131°. *Anal.* Calcd. for $C_{13}H_9O_2ClS$: C, 58.98; H, 3.43. Found: C, 58.88; H, 3.57.

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## Summary

A study has been made of the relative reactivity of a number of esters in the Claisen condensation with methyl 2-thienyl ketone.

For acetate esters the following order of reactivity has been found: $C_6H_5 > CH_3 > C_2H_5 >$ iso-$C_3H_7 > t$-$C_4H_9$. For esters of the type $RCO_2C_2H_5$ the order found is $R = CH_3 > C_2H_5 >$ iso-$C_3H_7 > t$-$C_4H_9$. With aromatic esters of the structure $R_{Ar}CO_2C_2H_5$ the relative reactivity is $p$-$ClC_6H_4 > C_6H_5 > p$-$CH_3OC_6H_4$.

The reactivity of the various esters parallels the results reported in the literature for the ammonolysis and alkaline hydrolysis of esters.

A comparison between the ammonolysis and alkaline hydrolysis of esters with the Claisen acylation of ketones has been made.

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[8] Vavon, Barbier and Thiebaut, *Bull. soc. chim.*, [5] **1**, 806 (1934).