

THE SODIUM-PROMOTED CLAISEN ESTER CONDENSATIONS OF ETHYL PERFLUOROALKANECARBOXYLATES

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Abstract—Sodium has been used to promote the Claisen ester condensation of ethyl trifluoroacetate and ethyl acetate to give ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate and then 1,1,1-trifluoroacetone by acidic hydrolysis. Sodium has also been used in the preparation of the α -methyl-, α -ethyl, and α -ethoxy- $\gamma\gamma\gamma$ -trifluoroacetoacetate esters and of the 4,4,5,5,6,6,6-heptafluorobutyrylacetate ester from which the corresponding ketones have been prepared by hydrolysis. Some comments are made on the mechanism of Claisen condensations involving perfluoroesters and of the role of sodium in promoting them.

THERE are two main methods for the preparation of alkyl perfluoroalkyl ketones, typified by 1,1,1-trifluoroacetone: one involves the reaction of a methyl Grignard reagent with trifluoroacetic acid¹ or one of its derivatives;² and the other^{3,4} the acidic hydrolysis of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate, itself prepared⁴⁻⁷ by the Claisen condensation of ethyl acetate with ethyl trifluoroacetate. The latter method is preferred as the first is not readily applicable when large quantities (> 20 g) of 1,1,1-trifluoroacetone are required. The reagent most frequently used for promoting this type of Claisen condensation is sodium ethoxide;^{4,5,7} sodium hydride⁶ has also been employed, but sodium has apparently not been used. The conditions described are different from those employed⁸ for the related preparations of trifluoroacetylacetone and hexafluoroacetylacetone from acetone and trifluoroacetone, respectively, and ethyl trifluoroacetate. Swarts⁵ mentions that a mixture of ethyl acetate and ethyl trifluoroacetate react violently with sodium, but the investigation was not continued. We have found that this reaction, although violent, can be controlled to provide a simple and rapid preparation of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate in 75–80% yield, no ethyl acetoacetate being produced, even though ethyl acetate is used in a two-fold excess. Hydrolysis *in situ* of the sodio-derivative of the keto-ester (the primary product) with dilute sulphuric acid leads to a 75–80% yield of 1,1,1-trifluoroacetone, based on the ethyl trifluoroacetate used. Not only is this reaction rapid but it is our experience and that of others,^{4,7} that yields of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate obtained

¹ A. Sykes, J. C. Tatlow and C. R. Thomas, *J. Chem. Soc.* 835 (1956); K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.* 78, 2268 (1956).

² E. T. McBee, O. R. Pierce and D. D. Meyer, *J. Amer. Chem. Soc.* 77, 917 (1955); D. A. Rausch, A. M. Lovelace and L. E. Coleman, *J. Org. Chem.* 21, 1328 (1956).

³ F. Swarts, *Bull. Acad. Roy., Belg.* 13, 175 (1927).

⁴ A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, *J. Amer. Chem. Soc.* 69, 1819 (1947).

⁵ F. Swarts, *Bull. Acad. Roy., Belg.* 12, 679 (1926).

⁶ E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, *J. Amer. Chem. Soc.* 75, 3152 (1953).

⁷ G. M. Wyman, Ph.D. Thesis, Cornell (1944); presented at the 124th Meeting of the American Chemical Society, p. 37M. Chicago, Sept. (1953).

⁸ R. N. Haszeldine, W. K. R. Musgrave, F. Smith and L. M. Turton, *J. Chem. Soc.* 609 (1951).

from the reaction promoted by sodium ethoxide are only about 55–60%, although 78% has been claimed.⁵

We have also used sodium for effecting the condensations of ethyl propionate and ethyl butyrate with ethyl trifluoroacetate, and, although the yields are low (34% and 27%, respectively), they are higher than those obtained by the sodium ethoxide method (10%⁷ and 33%⁸ for the propionate and 2%⁷ for the butyrate); again the non-fluorinated esters were in considerable excess, but no self-condensation products were detected. Alkylation⁷ of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate with methyl and ethyl iodides also gives lower yields (26% and 24%, respectively).

Ethyl heptafluorobutyrate and ethyl acetate give the expected β -keto-ester in 29% yield by the sodium method; but in this case the ethoxide route is better.¹⁰ Another product, produced in the sodium reaction but not investigated, may be the unidentified compound which Hauptschein and Braun¹⁰ obtained by the action of sodium on ethyl heptafluorobutyrate.

The sodium method is comparable with the ethoxide¹¹ for the condensation of ethyl trifluoroacetate with ethyl ethoxyacetate (42% yield in both cases).

In a previous paper,¹² we reported the condensation of diethyl succinate with ethyl trifluoroacetate to give diethyl trifluoroacetosuccinate; in this case the sodium is superior to the ethoxide method (72% and 16% yields, respectively).

No reaction occurs between either diethyl malonate or ethyl difluoroacetate and ethyl trifluoroacetate in the presence of sodium; with ethyl bromoacetate, the bromide ion is liberated.

The sodium route, although advantageous for the preparation of some fluorine-containing β -keto-esters, is probably of little general value if the objective is the synthesis of simple ketones by acidic hydrolysis—with the notable exception of 1,1,1-trifluoroacetone. Grignard reagents usually give superior yields. These, however, may be ruled out if the desired ketone has other functional groups, e.g. trifluoro-laevulic acid.¹²

The higher yields obtained in these sodium-promoted reactions as compared with the ethoxide method is not surprising. The equilibria involved¹³ in these condensations will proceed further in the direction of the β -keto-ester anion, the less ethanol there is in the reaction mixture; there is obviously less ethanol in the sodium than in the ethoxide reaction. This consideration may be upset when side-reactions occur. On the basis of these equilibria, the lack of reaction of ethyl difluoroacetate with ethyl trifluoro-acetate is understandable.¹³

Another feature of the sodium (and the ethoxide) reactions is the absence of alkanecarboxylate self-condensation products. First, as ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate, for example, is presumably a stronger acid than ethyl acetoacetate, its anion should be favoured thermodynamically in the equilibria involved.¹³ Secondly, ethyl trifluoroacetate would be expected to be attacked more rapidly by $^-\text{CH}_2\text{CO}_2\text{Et}$ than is ethyl acetate. The fluoro- β -keto-esters should therefore be the major products

⁵ E. T. McBee, C. E. Hathaway and C. W. Roberts, *J. Amer. Chem. Soc.* **78**, 4053 (1956).

¹⁰ M. Hauptschein and R. A. Braun, *J. Amer. Chem. Soc.* **77**, 4930 (1955).

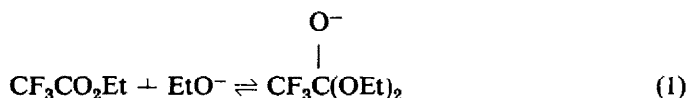
¹¹ J. Burdon, V. C. R. McLoughlin and J. C. Tatlow, *J. Chem. Soc.* 4644 (1960).

¹² P. Brown, J. Burdon, T. J. Smith and J. C. Tatlow, *Tetrahedron* **10**, 164 (1960).

¹³ Ingold, *Structure and Mechanism in Organic Chemistry* p. 788 *et seq.* G. Bell and Sons, London (1953).

whether the condensations are controlled by thermodynamic or kinetic factors. However, thermodynamic considerations alone do not offer a complete explanation for the absence of self-condensation products. When the sodium salt of ethyl acetoacetate is treated with ethyl trifluoroacetate, no ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate is formed; instead high-boiling materials, presumably further condensation products, are isolated. The two β -keto-esters are therefore not in equilibrium.

Secondly, ethyl trifluoroacetate and other polyfluoro-esters, unlike non-fluorinated esters, are known^{14,16} to form adducts with sodium ethoxide:



This reaction, presumably reversible, lies at least 99% to the right. Such adduct formation, since equimolar quantities of ethoxide or sodium and ethyl trifluoroacetate are employed, removes almost all the base and one of the esters from the reaction. Since condensations involving polyfluoro-esters take place at comparable rates with those that do not, and since no self-condensation products are formed, we conclude that the adduct equilibrium (1) must reverse sufficiently rapidly as the reaction proceeds to give sufficient quantities of base and ethyl trifluoroacetate at all times, and also that the amount of ethyl trifluoroacetate in the reaction mixture, in spite of equilibrium (1), is still sufficient to compete effectively with the much greater excess of ethyl acetate for the anion $^-\text{CH}_2\text{CO}_2\text{Et}$. Alternatively, and less likely, the adduct itself may act as base and reactant. Quantitative kinetic and thermodynamic measurements are obviously necessary in order to clarify the matter.

Although it is commonly stated that sodium ethoxide is the actual active species in sodium-promoted Claisen condensations, this has never been proved, the investigations¹⁶ usually cited (e.g. Ref. 13) as evidence being inconclusive. If sodium itself does promote the reaction, sodium ethoxide must also participate since ethanol is liberated and reacts with sodium to give the ethoxide. The well-known acceleration of sodium-promoted condensations as the reaction proceeds is often assumed to be due to the build-up of ethoxide; this is not necessarily true—it could equally well be due to some physical effect, such as removal of a protective layer from the surface of the sodium.

EXPERIMENTAL

Ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate. A flask fitted with two water-cooled reflux condensers and a solid CO_2 -ethanol-cooled condenser was charged with Na wire (16.5 g). A mixture of ethyl trifluoroacetate (101.5 g, 1.0 mole) and ethyl acetate (130 g, 2.1 mole) was rapidly added to the Na wire. A very vigorous exothermic reaction which continued for about ten min until all the Na had dissolved makes it dangerous to carry out the experiment on a scale much larger than that given here. After cooling the dark-coloured reaction mixture was diluted to 500 ml with dry ether, and then refluxed for 14 hr. Evaporation *in vacuo* left the crude sodio-derivative as a dark brown tar; this was dissolved in ether (400 ml) and washed with 15% H_2SO_4 (200 ml). The aqueous layer was extracted with ether, and the combined ether layer and extracts were dried (MgSO_4) and distilled to give ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate (101 g), b.p. 128–132° (cited⁸ b.p. 131.5°), characterized as its blue Cu salt, m.p. 189° (from benzene) alone and on admixture with an authentic specimen (cited⁴ m.p. 189°).

¹⁴ Bender, *J. Amer. Chem. Soc.* **75**, 5986 (1953).

¹⁵ F. Swarts, *Bull. Soc. Chim., Belg.* **35**, 412 (1926).

¹⁶ Snell and McElvain, *J. Amer. Chem. Soc.* **53**, 2310 (1931).

No ethyl acetoacetate could be detected in the product or in the higher-boiling residues by analytical vapour-phase chromatography.

When the reaction mixture was worked up immediately after the exothermic reaction had subsided, a 61% yield of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate was obtained.

Preparation of other fluorine-containing β -keto-esters. Ethyl trifluoroacetate (22.8 g), ethyl propionate (37 g, 2.3 moles) and Na wire (3.69 g, 1.0 mole) were caused to react as in the previous experiment to give ethyl $\gamma\gamma\gamma$ -trifluoro- α -methylacetoacetate (10.8 g), b.p. 137–140° (cited⁹ b.p. 57.8°/26 mm) (Found: C, 42.5; H, 4.9. Calc. for $C_7H_8F_3O_3$: C, 42.4; H, 4.6%). The ester gave a 2,4-dinitrophenylhydrazone, m.p. 70.5–71.5° from aqueous ethanol. (Found: C, 41.2; H, 3.3 $C_{12}H_{13}F_3N_4O_6$ requires: C, 41.3; H, 3.5%) and a Cu salt, m.p. 131°, which could not be purified owing to its great solubility in the common organic solvents.

The following were prepared in a similar manner: ethyl α -ethyl- $\gamma\gamma\gamma$ -trifluoroacetoacetate (27%), b.p. 150–154° (Found: C, 45.1; H, 5.4. $C_8H_{11}F_3O_3$ requires: C, 45.3; H, 5.2%), 2,4-dinitrophenylhydrazone, m.p. 89.5–90° from aqueous ethanol. (Found: C, 42.8; H, 3.8. $C_{14}H_{16}F_3N_4O_6$ requires: C, 42.9; H, 3.8%), Cu salt (green), m.p. 204°: ethyl α -ethoxy- $\gamma\gamma\gamma$ -trifluoroacetoacetate (42%), b.p. 110–115°/100 mm (slight dec.), identical by IR spectroscopy with an authentic specimen.¹¹

Ethyl 4,4,5,5,6,6,6-heptafluorobutyrylacetate. Ethyl heptafluorobutyrate (34.0 g), ethyl acetate (30 g, 2.4 moles) and Na wire (3.20 g, 1.0 mole) were caused to react as in previous experiments. Distillation of the ethereal extracts gave a liquid (22.0 g), b.p. 94–152°/105 mm, which was redistilled at atm. press. to give (i) a mixture (10.5 g), b.p. 140–152°, which contained, according to analytical vapour-phase chromatography, approximately equal parts of the ester product and another, apparently lower-boiling material; and (ii) ethyl 4,4,5,5,6,6,6-heptafluorobutyrylacetate (11.5 g), b.p. 152–155° (cited¹⁰ b.p. ca. 150°) (Found: C, 33.4; H, 2.5. Calc. for $C_8H_7F_7O_3$: C, 33.8; H, 2.5%). This ester gave a turquoise Cu salt, m.p. 117–118° from aqueous ethanol. (Found: C, 30.5; H, 1.8. Calc. for $C_{10}H_{12}F_{10}O_6Cu$: C, 30.5; H, 1.9%). Hauptschein and Braun¹⁰ gave m.p. 105–105.5° for this Cu salt.

1,1,1-Trifluoroacetone. The crude sodio-derivative of ethyl $\gamma\gamma\gamma$ -trifluoroacetoacetate, prepared as in the first experiment from ethyl trifluoroacetate (106 g), was refluxed with 20% H_2SO_4 (250 ml) for 10 hr. The volatile products were collected in a trap cooled to -78° and were distilled to give 1,1,1-trifluoroacetone (63.5 g), b.p. 20–22° (cited³ b.p. 22°), characterized as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. with an authentic specimen¹ 134–135° (cited⁴ m.p. 139°).

1,1,1-Trifluorobutan-2-one. The crude sodio-derivative of ethyl $\gamma\gamma\gamma$ -trifluoro- α -methylacetoacetate, prepared from ethyl trifluoroacetate (21.0 g) as in the earlier experiment, was refluxed with 30% H_2SO_4 (200 ml) for 28 hr. Extraction of the aqueous solution with di-*n*-butyl ether, followed by fractionation of the dried ($MgSO_4$) extracts through a 6" column packed with Dixon gauzes, gave 1,1,1-trifluorobutan-2-one (5.50 g), b.p. 45–46° (cited¹⁷ b.p. 44–45°). The 2,4-dinitrophenylhydrazone had m.p. 89–91° alone and on admixture with an authentic specimen¹ (cited¹⁷ m.p. 91–92°).

1,1,1-Trifluoropentan-2-one. Ethyl α -ethyl- $\gamma\gamma\gamma$ -trifluoroacetoacetate (11.2 g) was refluxed with 10% H_2SO_4 (60 ml) for 24 hr. Isolation as in the previous experiment gave 1,1,1-trifluoropentan-2-one (3.10 g), b.p. 64–67° (cited¹⁷ 65–67°); this gave a 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. with an authentic specimen, 75–75.5° (cited¹⁷ m.p. 73–73.5°).

Hydrolysis of the crude sodio-derivative, as in the two previous experiments, gave about a 5% yield of ketone, based on the ethyl trifluoroacetate used.

3,3,4,4,5,5,5-Heptafluoropentan-2-one. Ethyl 4,4,5,5,6,6,6-heptafluorobutyrylacetate (10.5 g) was hydrolysed with 10% H_2SO_4 (60 ml) as in the previous experiment to give 3,3,4,4,5,5,5-heptafluoropentan-2-one (4.10 g), b.p. 63–63.5° (cited¹⁸ 63.5°): the ketone gave a 2,4-dinitrophenylhydrazone, m.p. 76–77° alone and on admixture with an authentic specimen¹ (cited¹⁸ m.p. 76–76.5°).

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¹¹ L. B. Barkley and R. Levine, *J. Amer. Chem. Soc.* **75**, 2059 (1953).

¹⁸ E. T. McBee, O. R. Pierce and W. F. Marzluff, *J. Amer. Chem. Soc.* **75**, 1609 (1953).