Mono-C-Alkylation of β-Dicarbonyl Compounds Using Tetraethylammonium Fluoride

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Summary The hydrogen-bonded solvates formed between tetraethylammonium fluoride and a number of β-dicarbonyl compounds react at about room temperature with alkyl iodides to provide high yields of the mono-*C*-alkylated β-dicarbonyl products with no apparent contamination due to the formation of *O*-alkyl, dialkyl, or polymerisation products.

A DIFFICULTY that frequently arises in the alkylation of β-dicarbonyl compounds is the concurrent formation of both *C*-alkylated and *O*-alkylated products.[1] In general, *O*-alkylation competes significantly with *C*-alkylation when the equilibrium concentration of the enol tautomer is relatively high as is often the case with β-diketones and β-keto-esters. Thus attempted monoalkylation of β-dicarbonyl anions at carbon often provides low yields owing to competing *O*-alkylation as well as dialkylation, β-diketone cleavage, and coupling resulting from air oxidation of the enol salts of both starting material and monoalkylation product. Careful fractional distillation is usually necessary therefore, in order to isolate the desired monoalkylation product.

Several attempts have been made to optimize the yields of mono-*C*-alkylated products and these have usually employed conditions where the oxygen atom is shielded by association with a metal cation or a hydrogen-bonding solvent.[2] Of such procedures one of the most successful has been the utilisation of thallium(I) enolates[3] which apparently exist as tightly associated ion-pairs favouring *C*-alkylation. However, this is accompanied by a distinct loss of reactivity of these enolates as nucleophiles in reactions with alkyl halides.

We now report rapid and efficient mono-*C*-alkylation of a number of enolisable β-dicarbonyl compounds using the strongly H-bonded monosolvates formed between the enolised β-dicarbonyl compound and the powerful H-bond electron donor tetraethylammonium fluoride. These solvates do not show any appreciable amount of free enolate anion character. Hence, *O*-alkylation is inhibited and other side-reactions due to the presence of enolate salts do not occur. Reaction of these solvates with alkyl iodides† at 30 °C in chloroform (in which the solvates are very soluble) for 2 h‡ followed by ether extraction and distillation or recrystallisation gave the mono-*C*-alkylated product (>90%) with no apparent contamination due to *O*-alkylated or other side-products. The tetraethylammonium iodide§ which precipitated on addition of ether may be recovered and reconverted into the fluoride *via* an ion-exchange column. The solvates are formed when a concentrated solution of the fluoride in water,¶ in the presence of a quantitative amount of the β-dicarbonyl compound, is evaporated under reduced pressure.** It is normally difficult to render tetra-alkylammonium fluorides totally anhydrous without decomposition but in the presence of an enolisable β-dicarbonyl compound they preferentially H-bond to the enol hydroxy group and the water readily escapes providing the anhydrous solvate. These solvates are stable and non-hygroscopic and may usually be rendered crystalline by continuous washing with ether. Thus, the H-bonded monosolvate tetrabutylammonium fluoride–pentane-2,4-dione was prepared as described above and recrystallised unchanged from $CHCl_3$. The ^{19}F n.m.r. spectrum of this solvate in $CDCl_3$ solution shows a doublet (*J* 2·27 Hz) at −50 °C similar to that observed for the very strongly H-bonded bifluoride anion[4] and the ^1H n.m.r. spectrum shows that the β-diketone is totally enolised. Details of these and other spectra and those of related solvates will be published independently.

TABLE. Mono-*C*-alkylation of β-dicarbonyl compounds using tetraethylammonium fluoride.

β-Dicarbonyl compound	Yield % With MeI	With EtI
Pentane-2,4-dione[a]	95	94
1-Phenylbutane-1,3-dione[a]	92	91
1,3-Diphenylpropane-1,3-dione[a]	94	92
Methyl acetoacetate[b]	91	91
Ethyl acetoacetate[b]	95	91

[a] Mono-*C*-alkylations of these β-diketones were also carried out using Pr^iI giving yields of >90%. All reactions involving these β-diketones were carried out using the pre-prepared solvates and showed 100% reaction by ^1H n.m.r. analysis within 1 h at 30° C.
[b] These reactions were carried out using the anhydrous fluoride and showed 100% reaction by ^1H n.m.r. analysis after 2—2·5 h at 30 °C.

An alternative procedure to that requiring the evaporation of the aqueous fluoride in the presence of the β-dicarbonyl compound is available for those compounds which may undergo intermolecular self-condensation in the presence of tetra-alkylammonium fluorides at elevated temperatures. The β-keto-esters investigated here were found to undergo intermolecular self-condensation on heating to *ca.* 90 °C in the presence of tetraethyl- or tetrabutyl-ammonium fluorides. In these cases mono-*C*-alkylation was achieved by first rendering the fluoride anhydrous and stirring at 30 °C with a quantitative amount of the β-keto-ester and an excess of the alkyl iodide in $CHCl_3$ solution. This method was found to give complete conversion into the mono-*C*-alkylated ester in *ca.* 2 h. No self-condensation is observed when equimolar mixtures of tetraethyl- or tetrabutyl-ammonium fluorides and simple β-diketones are evaporated at 90—100 °C and here the former method of mono-*C*-alkylation is preferred. The former method surmounts the difficulty of rendering these fluorides anhydrous and presumably the presence of small amounts of water in the reaction mixture, while not preventing reaction, may lower the rate and possibly the efficiency of the mono-*C*-alkylation owing to the ability of water to compete for the fluoride electron donor. Representative examples of both procedures and recovered yields are given in the Table.

An aqueous solution of tetraethylammonium fluoride containing 0·02 mol of the fluoride was added to a solution of 1,3-diphenylpropane-1,3-dione (0·02 mol) in tetrahydrofuran. On heating this mixture at *ca.* 90 °C under reduced pressure, the solvents rapidly escaped leaving the anhydrous solvate which was washed with ether, dissolved in $CHCl_3$, and stirred at 30 °C with an excess of methyl iodide (0·04 mol) for 1 h. The reaction mixture was then diluted with ether (50 ml), filtered, and evaporated to give a white solid which, on recrystallisation from ethanol, provided crystals of 2-methyl-1,3-diphenylpropane-1,3-dione, m.p. 81—82 °C (4·48 g, 0·0188 mol, 94%).

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† Alkyl bromides may also be used though longer periods of reaction and/or high reaction temperatures may be required.

‡ Most reactions are complete in <1 h.

§ The iodide may contain solvated hydrogen fluoride.

¶ Prepared by neutralisation of the aqueous hydroxide with hydrofluoric acid followed by brief evaporation at 90—100 °C under reduced pressure.

** Where the β-dicarbonyl compound is relatively low boiling (*e.g.*, pentane-2,4-dione) a slight excess is preferred, the excess readily escaping with the water on evaporation.

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