

## Hydrogen Bonding in Organic Synthesis. Part 6.<sup>1</sup> C-Alkylation of $\beta$ -Dicarbonyl Compounds using Tetra-alkylammonium Fluorides

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Mono-C-alkylation of a number of  $\beta$ -dicarbonyl compounds using alkyl iodides and tetra-alkylammonium fluorides is described. Yields are high with primary iodides and isopropyl iodide, but much lower with *s*-butyl and *t*-butyl iodides. The reactions occur under mild conditions with no apparent *O*-alkylation or other competing reactions.

A DIFFICULTY that frequently arises in the alkylation of  $\beta$ -dicarbonyl compounds is the concurrent formation of both *C*- and *O*-alkylated products as well as, in some cases, products from competing Claisen condensations,  $\beta$ -diketone cleavage, and coupling of the air-oxidised enol salts of both starting material and its monoalkylation product. In general, *O*-alkylation is especially favoured when the equilibrium concentration of the enol tautomer is relatively high (e.g. in  $\beta$ -oxo-esters and  $\beta$ -diketones), and alkylation may tend to occur at the more electronegative atom of the ambident anion.<sup>2</sup>

Numerous attempts have been made to improve the efficiency of the *C*-alkylation of  $\beta$ -dicarbonyl compounds; however, they have usually met with limited success. Various observations<sup>2</sup> suggest that *O*-alkylation may be inhibited by preventing the existence of large amounts of free enolate anion, which may be achieved by careful control of conditions or by shielding the oxygen atom by association with a metal cation or with a hydrogen-bonding solvent.<sup>3</sup> One of the most successful procedures for such *C*-alkylations employs the crystalline thallium(I) enolates which appear to give exclusively the *C*-alkylated product on treatment with short-chain alkyl iodides.<sup>4</sup> Presumably the oxygen atom of the enolate anion is shielded by the associated metal atom even in solution. However, these enolates appear to suffer a distinct loss of reactivity as nucleophiles, and reactions require periods of several hours of reflux temperatures.

We have found that treatment of a number of  $\beta$ -dicarbonyl compounds with short-chain alkyl iodides in the presence of tetra-alkylammonium fluorides gives high yields of mono-*C*-alkylated derivatives with no apparent *O*-alkylation or other side reactions. These reactions usually occur at or about room temperature in reasonably short periods of time. In the presence of the powerful hydrogen-bond electron donor fluoride anion, the  $\beta$ -dicarbonyl compound should behave as a hydrogen-bond electron acceptor and thereby form a tightly bonded complex anion with fluoride. Presumably, the

oxygen atom is shielded not only by the large cation but also by the enol hydroxy-fluoride hydrogen bond. Fluoride undoubtedly prefers the enol hydroxy-group to the keto  $\alpha$ -CH group for hydrogen-bonding purposes, and although the situation is less clear with  $\beta$ -oxo-esters and dialkyl malonates,  $\beta$ -diketones containing at least one  $\alpha$ -hydrogen atom are totally enolised in the presence of fluoride.<sup>5</sup> The enhanced reactivity of the  $\beta$ -dicarbonyl compound on hydrogen bonding to fluoride is in keeping with previous observations on the effect of hydrogen bonding on the reactivity of the organic electron acceptor.<sup>6-10</sup> This enhanced reactivity presumably arises by transfer of electron density from the fluoride anion *via* the hydrogen bond.<sup>7,8</sup> The overall result is therefore, to shield the oxygen atom of the  $\beta$ -dicarbonyl compound, hence inhibiting *O*-alkylation while at the same time increasing the effectiveness of the compound as a nucleophile. The most serious possible drawback with our procedure is that fluoride has been shown to be a potentially powerful initiator of aldol condensations and Michael reactions of ketones. Pentane-2,4-dione has been found to undergo intermolecular self-condensation in the presence of potassium fluoride,<sup>5</sup> and many other ketones undergo similar condensations in the presence of fluoride.<sup>11</sup> However, no self-condensation occurs on treatment of  $\beta$ -diketones with the tetra-alkylammonium fluorides used here, even at temperatures approaching 100 °C; presumably the solvates are too stable to permit dehydration leading to condensation. Similarly,  $\beta$ -oxo-esters and dialkyl malonates do not undergo intermolecular self-condensation under the conditions required for *C*-alkylation; however,  $\beta$ -oxo-esters will self-condense on heating with these fluorides under reduced pressure (see later).

Although tetra-alkylammonium fluorides offer the advantage over their alkali metal counterparts of considerably greater solubility in a number of organic solvents, their use in synthesis has been limited owing to their extreme hygroscopic nature. However, their versatility in organic synthesis has become increasingly

<sup>1</sup> Preliminary communication, J. H. Clark and J. M. Miller, *J.C.S. Chem. Comm.*, 1977, 64.

<sup>2</sup> H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, Menlo Park, 1972.

<sup>3</sup> N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Amer. Chem. Soc.*, 1963, **85**, 1141.

<sup>4</sup> E. C. Taylor, G. H. Hawkes, and A. McKillop, *J. Amer. Chem. Soc.*, 1968, **90**, 2421.

<sup>5</sup> J. H. Clark and J. M. Miller, *Tetrahedron Letters*, 1977, 139, 1422.

<sup>6</sup> J. H. Clark and J. Emsley, *J.C.S. Dalton*, 1975, 2129.

<sup>7</sup> J. H. Clark and J. M. Miller, *J.C.S. Chem. Comm.*, 1976, 229.

<sup>8</sup> J. H. Clark and J. M. Miller, *J. Amer. Chem. Soc.*, 1977, **99**, 498.

<sup>9</sup> J. H. Clark and J. M. Miller, *Tetrahedron Letters*, 1977, 599.

<sup>10</sup> J. H. Clark, H. L. Holland, and J. M. Miller, *Tetrahedron Letters*, 1976, 3361.

<sup>11</sup> J. H. Clark and J. M. Miller, *J.C.S. Perkin I*, in the press.

apparent in the last few years,<sup>11-16</sup> and a general method for overcoming this problem is therefore desirable.

We have suggested<sup>11</sup> that in addition to our own applications of tetra-alkylammonium fluorides, many reports on uses of these fluorides may be interpreted in terms of hydrogen-bond-assisted reactions, that is when reaction involves a potential hydrogen bond electron acceptor. In these cases it may be possible to render the fluoride anhydrous (normally a very difficult process) by evaporation of an aqueous solution in the presence of the appropriate protic organic compound. Both the

relative to pure pentane-2,4-dione. This suggests a considerable reduction in the amount of double-bond character, which is presumably due to delocalisation of the negative charge in the complex anion resulting in an appreciable amount of carbanion character.\* The details of these spectra and those of related solvates will be discussed in a later article.

Treatment of these  $\beta$ -diketone monosolvates with low molecular weight alkyl iodides in chloroform solution at or about room temperature provides quantitative yields of the mono-*C*-alkylated products. The corresponding

Mono-*C*-alkylation of  $\beta$ -dicarbonyl compounds with alkyl halides and tetra-alkylammonium fluorides

Fluoride	$\beta$ -Dicarbonyl compound	Solvent	Yield (%) / Time (h) / Temp. (°C) with						
			MeI	EtI	Pr <sup>n</sup> I	Pr <sup>n</sup> I	Bu <sup>t</sup> I	Bu <sup>t</sup> I	Me[CH <sub>2</sub> ] <sub>9</sub> Br
Bu <sup>n</sup> <sub>4</sub> NF	MeCO·CH <sub>2</sub> ·COMe <sup>a</sup>	CHCl <sub>3</sub>	95/2/25	94/2/25	91/2/25	88/2/25	32/3/20	7/2/20	93/1/60 <sup>b</sup>
Et <sub>4</sub> NF			93/2/25						
Me <sub>3</sub> BzNF			92/2/25						
Bu <sup>n</sup> <sub>4</sub> NF	PhCO·CH <sub>2</sub> ·COMe <sup>a</sup>	CHCl <sub>3</sub>	92/2/25	91/2/25	90/2/25	94/2/25			
Bu <sup>n</sup> <sub>4</sub> NF	PhCO·CH <sub>2</sub> ·COPh <sup>a</sup>	CHCl <sub>3</sub>	94/2/25	92/2/25	92/2/25	90/2/25			
Et <sub>4</sub> NF	EtO <sub>2</sub> C·CH <sub>2</sub> ·COMe <sup>c</sup>	Me <sub>2</sub> N·CHO	95/3/25	91/3/25	94/10 25	85/8/25			
Et <sub>4</sub> NF	MeO <sub>2</sub> C·CH <sub>2</sub> ·COMe <sup>c</sup>	Me <sub>2</sub> N·CHO	91/3/25	91/3/25					
Et <sub>4</sub> NF	EtO <sub>2</sub> C·CH <sub>2</sub> ·CO <sub>2</sub> Et <sup>c</sup>	Me <sub>2</sub> N·CHO	85/3/25	88/3/25	90/6/25	86/8/25			
Me <sub>3</sub> BzNF	EtO <sub>2</sub> C·CHEt·CO <sub>2</sub> Et <sup>c</sup>	Me <sub>2</sub> N·CHO	90/2/60	88/2/60	84/3/60				
Et <sub>4</sub> NF	EtO <sub>2</sub> C·CHPh·CO <sub>2</sub> Et <sup>c</sup>	Me <sub>2</sub> N·CHO	85/2/25	88/2/25	84/4/25				

<sup>a</sup> The reactions involving the  $\beta$ -diketones were carried out using the pre-prepared solvate (see text). <sup>b</sup> Tetrahydrofuran as solvent. <sup>c</sup> The reactions involving the  $\beta$ -oxo-esters and malonates were carried out using the 'anhydrous' fluoride (see text).

new electron acceptor and water should enter into competition for the fluoride anion and the success of the subsequent dehydration will depend on the relative strengths of the two protic compounds as hydrogen bond electron acceptors and on the difference in their b.p.s.

$\beta$ -Diketones are obvious candidates for such a procedure as they generally have significantly higher b.p.s than water and, through enolisation, offer an extremely good electron acceptor site for hydrogen bonding. In the presence of an enolisable  $\beta$ -diketone, aqueous solutions of tetra-alkylammonium fluorides may be readily rendered anhydrous, providing a stable, non-hygroscopic monosolvate (excess of  $\beta$ -diketone may be removed by washing with cold ether in which the monosolvates are insoluble). These solvates may often be rendered crystalline, although this is not necessary for the subsequent *C*-alkylation reaction. The preparation of one such crystalline monosolvate, Bu<sup>n</sup><sub>4</sub>N<sup>+</sup>[F···HO-CMe=CH·COMe]<sup>-</sup> is described in the Experimental section. This monosolvate is stable and non-hygroscopic; it may be recrystallised unchanged from dimethylformamide and stored indefinitely. Its <sup>19</sup>F n.m.r. spectrum shows a doublet (*J* 2.27 Hz) at -50 °C in CDCl<sub>3</sub> solution similar to that observed for the very strongly hydrogen-bonded hydrogen fluoride anion,<sup>17</sup> and the <sup>1</sup>H n.m.r. spectrum shows that the  $\beta$ -diketone is totally enolised. The <sup>13</sup>C n.m.r. spectrum shows the enolic olefinic carbon signals shifted *ca.* 20 p.p.m. upfield

\* There is no evidence from the <sup>1</sup>H n.m.r., <sup>19</sup>F n.m.r., or i.r. spectra for the existence of HF either in these solvates or in solutions of fluoride in  $\beta$ -diketones, which rules out the possibility of proton transfer.

<sup>12</sup> W. T. Miller, J. H. Fried, and H. Goldwhite, *J. Amer. Chem. Soc.*, 1960, **82**, 3091.

<sup>13</sup> J. Hayami, N. Ono, and A. Kaji, *Tetrahedron Letters*, 1968, 1385.

bromides may also be used, although these may require higher temperatures and/or longer reaction periods. It was found, however, that on using alkyl chlorides, the considerably longer reaction times required often led to significant amounts of *O*-alkylation. Tertiary iodides such as 2-iodo-2-methylpropane and higher molecular weight secondary iodides such as 2-iodobutane give reduced yields of mono-*C*-alkylated products owing to competing dehydrohalogenation. With regard to the choice of fluoride, only tetramethylammonium fluoride was found to be largely ineffective, and this is undoubtedly due to the considerably reduced solubility of its solvates and of the fluoride itself in chloroform, dimethylformamide, or tetrahydrofuran. Little difference was found in the effectiveness of the fluorides listed in the Table, although should crystalline solvates of the  $\beta$ -diketones be required, those of tetra-*n*-butylammonium fluoride were found to be the easiest to prepare.

The process described for rendering these fluorides anhydrous is only appropriate for those organic electron acceptors which are stable to the conditions required for dehydration (see Experimental section). As mentioned before,  $\beta$ -oxo-esters are prone to self-condensation under such conditions and dialkyl malonates do not usually form a sufficiently strong hydrogen-bonded solvate with fluoride to enable efficient dehydration to be achieved. In these cases it is best first to render a relatively low molecular weight fluoride (see Table) partially anhydrous by brief evaporation (*i.e.* until a solid is formed). The

<sup>14</sup> R. F. Cunico and E. M. Dexheimer, *J. Amer. Chem. Soc.*, 1972, **94**, 2868.

<sup>15</sup> E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.

<sup>16</sup> J. Pless, *J. Org. Chem.*, 1974, **39**, 2644.

<sup>17</sup> J. S. Martin and F. Y. Fujiwara, *Canad. J. Chem.*, 1971, **49**, 3071.

fluoride is then extracted in an appropriate solvent (usually dimethylformamide) and a quantitative amount of the  $\beta$ -dicarbonyl compound is added. Although such fluorides are only partially soluble in dimethylformamide, they are very soluble in dimethylformamide containing an organic electron acceptor such as a  $\beta$ -dicarbonyl compound. The solution is then treated with molecular sieves to remove as much water as possible and finally with an excess of alkyl iodide to give the mono-*C*-alkylated product. The presence of small amounts of water does not seem to affect the reaction seriously. The reactions of  $\beta$ -oxoesters and dialkyl malonates required conditions little different from those needed for the  $\beta$ -diketones, with the exception of the mono-*C*-alkylated dialkyl malonates which required higher reaction temperatures in order to introduce the second *C*-alkyl group.

#### EXPERIMENTAL

$^1\text{H}$  N.m.r. spectra were recorded with a Varian A-60 (60 MHz) spectrometer. The  $^{13}\text{C}$  n.m.r. spectrum was recorded with a Brüker WP-60FT (15.08 MHz) spectrometer by using broad band off-resonance proton decoupling facilities. The  $^{19}\text{F}$  n.m.r. spectrum was recorded with a Brüker WP-60FT (56.4 MHz) spectrometer with  $\text{C}_6\text{F}_6$  as internal reference at  $-50^\circ\text{C}$ . Mass spectra were obtained with A.E.I. MS-30 double-beam spectrometer; both the direct probe and interfaced (Watson-Bieman) g.l.c. were used as inlets.

Tetraethyl-, benzyltrimethyl-, and tetra-*n*-butyl-ammonium fluorides were prepared by neutralisation of the individual commercial hydroxides (aqueous 20 or 40% solutions) with 52% hydrofluoric acid. The aqueous solutions were concentrated by evaporation for *ca.* 10 min at  $80$ – $90^\circ\text{C}$  under reduced pressure (aspirator) before use. The  $\beta$ -dicarbonyl compounds were commercial samples used as obtained.

Reactions were carried out at room temperature except where stated otherwise (Table). All reactions involving the  $\beta$ -diketones were carried out using the pre-prepared solvates; all other reactions involved the formation of the  $\beta$ -dicarbonyl-fluoride solvate in the reaction solution. Most of the  $\beta$ -diketone reactions were complete after 1 h; however all reactions were allowed to continue for a minimum of 2 h. Products were isolated by standard work-up procedures usually requiring initial precipitation of the tetra-alkylammonium iodide (or bromide) with ether. These iodides (or bromides) could be purified and reconverted into fluorides with an ion-exchange column. Experimental details for two representative preparations of mono-*C*-alkylated  $\beta$ -dicarbonyl compounds and one representative preparation of a tetra-*n*-butylammonium fluoride- $\beta$ -diketone monosolvate are given below. All

reaction products listed in the Table gave satisfactory mass and  $^1\text{H}$  n.m.r. spectra and b.p.s or m.p.s consistent with those reported.

*2-Methyl-1,3-diphenylpropane-1,3-dione*.—An aqueous solution of tetra-*n*-butylammonium fluoride (0.02 mol) was added to a solution of 1,3-diphenylpropane-1,3-dione (0.02 mol) in tetrahydrofuran. On heating this mixture at  $80$ – $90^\circ\text{C}$  under reduced pressure (aspirator), the solvents rapidly escaped, leaving the anhydrous solvate. The solvate was washed with cold ether, dissolved in chloroform and stirred at  $25^\circ\text{C}$  with an excess of methyl iodide (0.04 mol) for 2 h. The mixture was then diluted with ether (50 ml), filtered, and evaporated, giving a white solid which provided crystals of 2-methyl-1,3-diphenylpropane-1,3-dione (4.48 g, 0.0188 mol, 94%), m.p.  $81$ – $82^\circ\text{C}$  (from ethanol) (lit.,<sup>18</sup>  $82$ – $83^\circ\text{C}$ ),  $\delta$  7.9 (4 H, m, Ph), 7.4 (6 H, m, Ph), 5.23 (1 H, q, CH), and 1.58 (3 H, d, Me), *m/e* 238.

*Diethyl Ethylmalonate*.—An aqueous solution of tetra-ethylammonium fluoride (0.02 mol) was evaporated at  $80$ – $90^\circ\text{C}$  under reduced pressure until a solid had been formed. The solid was dissolved in dimethylformamide (20 g) containing diethyl malonate (0.02 mol), and the resulting solution was shaken briefly with 4 Å molecular sieves. The solution was decanted and stirred at room temperature ( $25^\circ\text{C}$ ) with an excess of ethyl iodide (0.03 mol) for 3 h. The mixture was then diluted with ether (50 ml) and filtered, and the filtrate was shaken with equal volumes of water ( $2 \times$ ) to remove the dimethylformamide. The ethereal extracts were removed, dried ( $\text{MgSO}_4$ ), filtered, and evaporated, and the residue was distilled to give diethyl ethylmalonate (3.3 g, 0.0176 mol, 88%), b.p.  $206$ – $208^\circ\text{C}$  at 760 mmHg (lit.,  $207$ – $209^\circ\text{C}$ );  $n_D^{22}$  1.4163 (lit.,  $n_D^{20}$  1.4170),  $\delta$  4.17 (4 H, q,  $\text{CH}_2\text{O}$ ), 3.21 (1 H, t, CH), 1.89 (2 H, m,  $\text{CH}_2$ ), 1.25 (6 H, t,  $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{O}$ ), and 0.94 (3 H, t,  $\text{CH}_3$ ), *m/e* 188.

*Tetra-*n*-butylammonium Fluoride-Pentane-2,4-dione Monosolvate*.—Pentane-2,4-dione (0.1 mol) was added to an aqueous solution of tetra-*n*-butylammonium fluoride (0.05 mol) and the mixture was evaporated at *ca.*  $80^\circ\text{C}$  under reduced pressure (aspirator) with shaking until no further ebullition occurred. The mixture was then cooled to provide a solid which was washed with cold ether and recrystallised from dimethylformamide and then from tetrahydrofuran to give white crystals of the monosolvate (10.8 g, 0.03 mol, 60%), m.p.  $128$ – $130^\circ\text{C}$  (Found: C, 70.1; H, 12.3; F, 5.0; N, 3.85.  $\text{C}_{21}\text{H}_{44}\text{FNO}_2$  requires C, 69.8; H, 12.2; F, 5.25; N, 3.9%),  $\delta_H$  3.2br (8 H, m,  $\text{CH}_2\text{N}$ ), 2.04 (6 H, s, Me), 1.5br (16 H, m,  $\text{CH}_2$ ), and 1.0br (12 H, t,  $\text{MeCH}_2$ ) [CH and OH coalesced at  $\delta$  6–7 (very broad)];  $\delta_F$  7.252 p.p.m. from  $\text{C}_6\text{F}_6$  (d, *J* 2.27 Hz);  $\delta_C$  191.111 and 190.868 (C=O), 78.939 (C–OH), 77.686 (d, CH), 59.159 (t,  $\text{CH}_2\text{N}$ ), 24.730 (Me), 24.345 (t,  $\text{CH}_2$ ), 19.963 (t,  $\text{CH}_2\text{Me}$ ), and 13.785 (q,  $\text{MeCH}_2$ ).

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<sup>18</sup> C. Weygand, H. Forkel, and C. Bischoff, *Ber.*, 1928, **61B**, 687.