Alkylation of Ethyl 4,4,4-Trifluoroacetoacetate. First Example of a Reversible *O*-Alkylation Process leading to *C*-Alkylation

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In aprotic polar solvents the ratio of *O vs. C* alkylation products of ethyl 4,4,4-trifluoroacetoacetate (ETFAA) can be dependent on reaction time; in hexamethylphosphoric triamide (HMPA) or acetone, the S_N2 cleavage of enol ethers of ETFAA with sodium iodide was observed with concomitant formation of the sodium enolate and the corresponding iodides, and in the case of an activated iodide the mono- and di-alkylation products resulted quantitatively.

In order to find new versatile methods for the preparation of trifluoromethyl ketones, we have studied the alkylation of ethyl 4,4,4-trifluoroacetoacetonate (ETFAA) (**1**). Surprisingly, only two particular examples of this alkylation have been described: (i) methyl tosylate with enolate (**2**) (M = Cs) in hexamethylphosphoric triamide (HMPA) leads exclusively to the *O*-methyl enol ether,[1] (ii) chloroacetone on (**2**) (M = Na) in acetone, in the presence of a catalytic amount of KI leads exclusively to the corresponding *C*-alkylated product.[2]

Our studies have shown that enolates (**2**) derived from ETFAA (**1**) are very poor nucleophilic agents; therefore their alkylation has required the use of polar aprotic solvents with good cation solvating power, but with no ability to solvate the anions directly, *e.g.* HMPA or Me_2CO.[3]

Table 1 shows results concerned with the alkylation of ETFAA (**1**) using fluoride ions in tetrahydrofuran (THF)/HMPA (4 equiv.) It can be observed that: (i) a non-activated halide reacts quite slowly and preferably leads to *O*-alkylation, (ii) an activated halide (benzyl bromide) reacts faster and leads preferably to *C*-alkylation, (iii) in both cases the *C*:*O*-alkylation ratio increases with time.

To explain this last and quite unexpected observation, we propose that the salt X^-M^+ resulting from the alkylation was able to cleave enol ethers (**3**), *via* an S_N2 reaction leading to halide RX and enolate (**2**), which in turn can lead in part, by an irreversible process, to *C*-alkylated product (**4**). In order to test this hypothesis, the enol ethers (**3a**) and (**3b**) were prepared and treated with NaI in THF/HMPA (4 equiv.). For comparison, cleavages of enol ethers (**6a**) and (**6b**) were also attempted under the same conditions (Table 2).

The overall results have shown that NaI in THF/HMPA was able to cleave specifically the enol ethers of ETFAA (**3**), but not those of the non-fluorinated analogue (**6**) (run 7 and 8). The same reactivity was also observed in acetone but the

Table 1. Alkylation of ETFAA (**1**) in the presence of M^+F^- in THF/HMPA (4 equiv.) at 50 °C.[a]

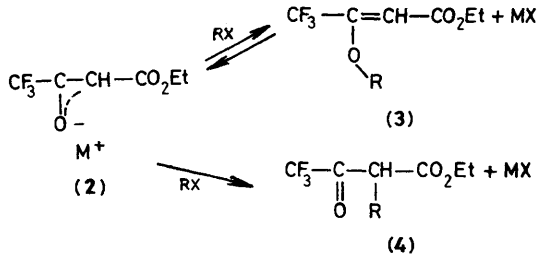
				% Yield				
Run	RX (equiv.)	M^+	*t*/h	Total alkylation	*C*-Alkylation (**4**)	Di-*C*-alkylation (**5**)	*O*-Alkylation (**3**)	Ratio *C*:*O*
1	Pr^nI (3)	K^+	2	13	3	—	10	0.34
	Pr^nI (3)	K^+	7	24	7	—	17	0.41
	Pr^nI (3)	K^+	24	52	21	—	31	0.68
2	$PhCH_2Br$ (1)	K^+	2	26	19	—	7	2.71
	$PhCH_2Br$ (1)	K^+	7	58	32	6	14	3.14
3	$PhCH_2Br$ (1)	Bu_4N^+	2	80	45	7	22	2.68
	$PhCH_2Br$ (1)	Bu_4N^+	3	88	52	9	18	3.89
	$PhCH_2Br$ (1)	Bu_4N^+	4	91	57	10	13	5.92

[a] The reactions were performed with 5.6 mmol of (**1**) in 8 ml of solvent; yields based on alkyl halide (1 equiv.) were determined by g.p.c. analysis using tetradecane as the internal standard. All new compounds were identified by mass spectroscopy and ^1H, ^{13}C, and ^{19}F n.m.r. spectroscopy.

Table 2. Cleavage of enol ethers (**3**) and (**6**) with NaI (1 equiv.) in THF/HMPA (4 equiv.).[a]

					Products, % yield[b]			
Run	Enol ether	*t*/h	*T*/°C	% Cleavage[b]	RI	(**2**)[c]	(**4**)	(**5**)
4	(**3a**)	2	20	39	22[d]	42	—	—
	(**3a**)	6	20	65	33[d]	59	—	—
	(**3a**)	24	20	88	28[d]	62	4	10
5	(**3a**)	1	80	100	—	—	40	30
6	(**3b**)	1	80	17	17	15	—	—
	(**3b**)	4	80	47	42	49	—	—
	(**3b**)	7	80	69	65	67	—	—
7	(**6a**)	72	80	0	—	—	—	—
8	(**6b**)	72	80	0	—	—	—	—

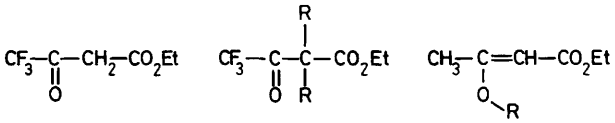
[a] The reactions were performed on 1.5 mmol of enol ethers (**3**) or (**6**) in 4 ml of solvent. [b] Yields were determined by g.p.c. analysis using tetradecane as the internal standard. [c] Yield of enolate (**2**) (M^+ = Na^+) was determined by ^{19}F n.m.r. spectroscopy using CF_3Ph as the internal standard. [d] The resultant benzyl iodide was unstable in the medium.



(3)

(2)

(4)



(1) (5) (6)

a; R = $PhCH_2$
b; R = octyl

reaction was slower. The more striking result was in run 5; here the cleavage reaction occurred with quantitative formation of mono- and di-*C*-alkylation products. This unexpected observation demonstrates that *C*-alkylation products, resulting from alkylation of (**2**) with benzyl bromide, can be thermodynamic and not kinetic products.

To our knowledge, this is the first example of a reversible *O*-alkylation process, which is due to the presence of the powerful electron-withdrawing CF_3 group.

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References

1 A. L. Kurts, A. Macias, I. P. Beletskaya, and D. A. Reutov, *Tetrahedron*, 1971, **27**, 4759.
2 R. E. Bambury, H. K. Yaktin, and K. K. Wyckoff, *J. Heterocycl. Chem.*, 1968, **5**, 95.
3 C. Aubert, J. P. Bégué, M. Charpentier-Morize, and G. Née, *J. Fluorine Chem.*, submitted for publication.