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THE ALKYL GROUP EFFECT IN THE ALKYLATIONS OF ETHYL ACETOACETATE IN DIMETHYL SULFOXIDE

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Recent insights (1) in the remarkable solvent properties of dimethyl sulfoxide (DMSO), and our own interest in the chemistry of isopropenyl ethers (2) led us to consider the possibility of direct O-alkylation of ethyl acetoacetate in that solvent. The connection is that Kornblum's work (3) suggests increased O-alkylation of ambident anions when the oxygen atom is strongly solvated, and that cations rather than anions are strongly solvated in DMSO (4); thus the oxygen atom of the ambident anion would be associated neither with solvent nor with the cation in that medium. An observation by Brower (5) fortified us in that belief. Brieger (6) has meanwhile shown that ethyl n-butoxycrotonate can be formed directly from ethyl acetoacetate in significant amounts, the yield depending on the leaving group, the cation and the temperature. Our own results fully confirm these observations, as detailed below; furthermore, we have noticed a remarkable alkyl group effect which seems to contradict trends predicted from current points of view.

When 0.2 mole of n-propyl chloride is slowly added to 200 cm^3 DMSO containing 0.2 mole of ethyl sodioacetoacetate in solution at 130°, the base is completely used up within about two hours. Extraction of the cooled reaction mixture with water and ether, followed by evaporation of the ether layer gives a 71% yield of a mixture shown by both N.M.R. and V.P.C. techniques to consist of the O- and C-alkylated products in a 43-57 ratio; of the 57% carbon alkylated product, 7% was dialkylated (almost exclusively "CC" rather than "OO"). Table I shows the effect of the alkali metal and the leaving group.

TABLE I

Metal and Halogen Effects on the Product Ratio

Halogen	Metal	Yield	% "O"	% "C"	% "CC"
Cl	K	73	47	25	28
Cl	Na	71	43	50	7
Cl	Li	65	26	44	10
Br	K	66	31	46	23
Br	Na	68	26	67	7
I	K	74	14	50	36
I	Na	71	6	84	10

Much less O-alkylation occurred in sulfolane, or in DMSO containing some methanol. Acetylacetone with i-propyl chloride gave a 67% yield of monoalkylated product with an "O"/"C" ratio of 85-15.*

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* For 2-i-propoxypent-2-en-4-one, ethyl β-benzoxycrotonate, ethyl β-n-propoxycrotonate and ethyl β-i-propoxycrotonate, n_D^{25} = 1.4624, 1.5222, 1.4496 and 1.4490, respectively. All of these materials were purified by V.P.C. and found to have C-and H-analyses agreeing to within 0.3% of the calculated values; some were synthesized by an alternative path as well (W. J. le Noble and P. J. Crean, J. Org. Chem., 27, 3875 (1962)). All other compounds referred to here were identified by means of N.M.R. and by comparison of their physical properties with those quoted in the literature. For further details, the M.S. thesis of J. E. P. should be consulted.

Perhaps the most interesting new results are shown in Table II. Although the metal atom affected the product ratio as expected from the known correlation of stability constants with atomic radii (7), the halogen and alkyl group effects are unexpected. Among the halides, the iodides are normally expected to give the most O-alkylation because they have relatively more S_N1 character (8); the exact opposite is found.

TABLE II

Product Ratio with Various Alkylating Agents

Alkyl halide	Yield, %	% "O"	% "C"	% "CC"
i-Propyl chloride	52	62	38	0
cy-Hexyl chloride[a]	10	55	45	0
n-Propyl chloride	73	47	25	28
n-Propyl bromide	66	31	46	23
Ethyl bromide	73	26	68	6
Methyl iodide	74	4	79	17
n-Propyl iodide	74	14	50	36
Methyl γ-chlorocrotonate	60	10[b]	90[c]	0
Benzyl chloride	60	5	45	50
Allyl chloride	30	0	100	0

(a) The low yield is due to elimination. In the case of tert-butyl chloride, isobutylene was the only product formed.
(b) Isolated as 2,5-dimethyl-3-carbomethoxyfuran. (c) Not purified.

The alkyl group effect can be partly accommodated by an S_N1 reactivity sequence; however, the benzyl and allyl groups then fall completely out of line. The difference in behavior between n-propyl and allyl chloride is particularly striking. It was demonstrated that the O-allyl and

O-benzyl derivatives prepared by an independent route, quantitatively survived the reaction conditions if small amounts were added at the start of the reaction, and hence that their absence is not due to secondary reactions.

On the other hand, both halogen and alkyl group effects are completely covered by the statement that increased S_N2 reactivity is correlated with a decreased "O"/"C" product ratio. Several additional examples can be found in the literature (9); however, neither the reason nor the range of validity of this statement are clear at this time (10).

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