Tetrahedron Letters No.40, pp. 3555-3558, 1965. Pergamon Press Ltd.
Printed in Great Britain.

OXYGEN ALKYLATION IN THE ETHYL ACETOACETATE SYNTHESIS

G. Brieger and W. M. Pelletier
Chemistry Department
Oakland University, Rochester, Michigan

(Received 19 July 1965)

In a search for convenient preparative techniques, we have investigated the effect of solvent, halide, base, and temperature on the alkylation of the ambident anion derived from ethyl acetoacetate. Our attention has focused on the use of dipolar aprotic solvents. A recent report (1) describing oxygen alkylation in small yield using the standard synthesis (2) prompts us to report our findings.

Using dipolar aprotic solvents, and anhydrous potassium carbonate as base, it was found that extensive oxygen alkylation may occur. The findings are summarized in Table I. The solvents used, with the exception of acetonitrile and acetone, were dried by azeotropic distillation with benzene followed by vacuum distillation. Acetonitrile and acetone were purified by standard techniques. In some cases, the commercially available solvents were used directly. The reactions were conducted in sealed tubes, under the indicated conditions. The analyses were done directly with the filtered reaction mixture on a 5' x 1/4" column packed with 20% Apiezon L/Chrom. W. at 170°C, with 45 ml. min He flow.

The n-butyl ethyl acetoacetate used in this study was prepared by the standard technique (3). The β-butoxy ethyl crotonate was prepared by refluxing n-butyl chloride with ethyl acetoacetate and potassium carbonate in dimethyl sulfoxide. After purification by vapor phase chromatography, its infrared spectrum showed two strong bands at 1710 and 1620 cm^{-1} respectively. Spectral data for β-alkoxy crotonates has been reported (1).

TABLE I[a]

Purified Solvent	Base	Temperature	Time	% O-Alkylation[b]
N-methyl pyrrolidone	K_2CO_3	100°C	1 hr	51
Dimethyl acetamide	"	"	"	49
Dimethyl formamide	"	"	"	46
Dimethyl sulfoxide	"	"	"	47
Acetonitrile	"	"	"	19
Acetone	"	"	"	10

a. n-butyl chloride used throughout, all reagents 1.4 molar

b. Relative yield

It may be seen that the use of dipolar aprotic solvents gives as much as 50% oxygen alkylation. The use of dimethylformamide and alkali hydroxides has been recommended for the alkylation of ethyl acetoacetate (4). In view of the present results, it appears likely that a mixture of C- and O-alkylated products is also obtained in this procedure.

We have also studied the effect of varying the leaving group in the alkyl halide. The results are indicated in Table II.

TABLE II

Halide	Solvent	Base	Temperature	Time	% O-Alkylation
R-Cl	DMF	K_2CO_3	100°C	1 hr	46
R-Br	"	"	"	"	33
R-I	"	"	"	"	0 ± .5%
(R = n-butyl)					

It appears that the nature of the leaving group profoundly affects the extent of O-alkylation, permitting a complete return to C-alkylation in the case of the n-butyl iodide.

The extent of O-alkylation also varies with temperature. Interestingly, the effect of temperature on the reaction in dimethyl sulfoxide <u>increases</u> the proportion of O-alkylation considerably, whereas in N-methyl pyrrolidone, the proportion of O-alkylation decreases as seen in Table III.

TABLE III[a]

Temperature	Time	Base	% O-Alkylation in Dimethyl Sulfoxide	% O-Alkylation in N-methyl Pyrrolidone
50°C	1 hr	K_2CO_3	41	-
100°C	"	"	47	57
146°C	"	"	57	51
Reflux	"	"	69	43

[a] n-butyl chloride was used.

When the base cation is varied, there is also a change in oxygen alkylation, suggesting that the anion is not entirely free in solution, but remains somewhat associated. The results are given in Table IV.

TABLE IV[a]

Base	Time	Temperature	Solvent	% O-Alkylation
Li_2CO_3	2 hrs.	130°C	Dimethylformamide	19
Na_2CO_3	"	"	"	61
K_2CO_3	"	"	"	53

A practical consequence of this work is that O-alkylated ethyl acetoacetate may be obtained in fair yield by a convenient preparative technique, i.e. refluxing halide and ethyl acetoacetate with anhydrous potassium carbonate in dimethylsulfoxide.

While the observations herein reported generally agree with those reported by Kornblum (5) and others (6,7) for the alkylation of ambident anions, a theoretical discussion is deferred until further studies on the nature of leaving groups and cations have been made.

REFERENCES

1. S. T. Yoffe, K. V. Vatsuro, E. E. Kugutcheva, and M. I. Kabachnik, Tetrahedron Letters **10**, 593 (1965)
2. E. C. Horning, ed., Organic Syntheses Coll. Vol. III, p. 405 J. Wiley, New York
3. H. Gilman, A. G. Blatt, eds., Organic Syntheses Coll. Vol. I, p. 248 J. Wiley, New York
4. H. E. Zaugg et al, J. Org. Chem. **26**, 644 (1961)
5. N. Kornblum, R. Seltzer, and P. Haberfield, J. Am. Chem. Soc. **85**, 1148 (1963)
6. H. E. Zaugg, J. Am. Chem. Soc. **82**, 2903 (1960)
7. H. E. Zaugg, J. Am. Chem. Soc. **83**, 837 (1961)