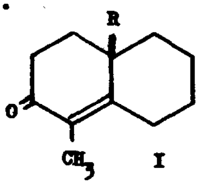
Tetrahedron Letters No.21, pp. 1975-1978, 1967. Pergamon Press Ltd. Printed in Great Britain.

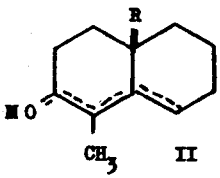
SELECTIVITY IN ALKYLATION WITH BENZYLOXYMETHYL HALIDES: THE INFLUENCE OF HETEROGENEITY AND OTHER FACTORS.

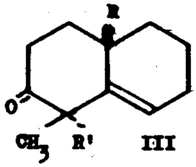
F.H. Bottom and F.J. McQuillin
Department of Organic Chemistry, The University of Newcastle upon Tyne.

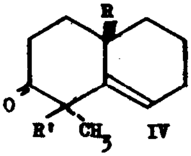
(Received 10 February 1967; in revised form 22 March 1967)

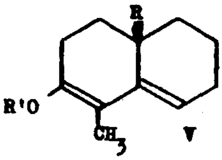
In the alkylation of substances of the type (I) with benzyloxymethyl chloride (1) the proportions of products, (III), (IV) and (V) was found to depend on the substituent R, vis R = CH_3, (III) > (IV); R = CO_2Et, (IV) > (III).


I


II


III


IV


V

R' = $PhCH_2OCH_2^-$

Closer study of this reaction, and in particular of the influence of the enolate cation, M, and of the particular halide employed has thrown valuable light on the mechanism of the alkylation process.

TABLE 1

Relative percentages(1) of products (III), (IV) and (V) from the Enolate (II) + $PhCH_2OCH_2$ halide in dioxan.

	(a) $R = CH_3$			(b) $R = CO_2Et$		
Halide(2)	III	IV	V	III	IV	V
F	52	7	41	14	25	61
Cl	59	11	30	14	24	62
Br	64	9	27	14	23	58
I	70	15	15	16	38	46
Cation(3)						
Li	53	7	40	13	44	43
Na	59	11	30	17	35	48
K	67	10	23	18	20	62
Mg	43	12	45	-	-	-

(1) C-alkyl products estimated from the intensity of the 4α- and 4β- CH_3 proton resonance: $R = CH_3$, 4α- CH_3 8.74τ, 4β- CH_3 8.92τ; $R = CO_2H$, 4α- CH_3 8.68τ, 4β- CH_3 8.82τ, at 60 Mc.

(2) M = Na, (3) halide = Cl.

In the solvent employed the metal enolate may be rather insoluble and the representation (II) may denote an essentially unsolvated close ion pair in the solid state, or a range of variously solvated ion aggregates in solution. Cation screening of the enolate oxygen will fall: M = Li > Na > K, and O-alkylation should consequently increase in the order M = Li < Na < K as is observed when $R = CO_2Et$, and for many instances in the literature (2). Cation solvation will, however, be a major factor in determining the relative amount of enolate in solution. In the case where $R = CH_3$ the enolate is noticably insoluble and the proportion of O-alkylation is found to fall: M = Li > Na > K which is the probable order of enolate solubility. This order is reasonably attributed to a heterogeneous alkylation of the unsolvated solid enolate which should favour C-alkylation as in other instances (3). Conversely the more soluble solvated enolate when R = CO_2Et leads to a high proportion of O-alkylation. We were in fact able to increase the C-alkylation in this case by use of a more concentrated solution, viz, 0.8 molar: (V), 62; (IV), 24; (III), 14%; 1.4 molar: (V), 48; (IV), 35; (III), 17%.

Since the transition state for C-alkylation presumably involves a considerable degree of bond formation the alkylation of (I, R = CH_3) is more sensitive to the halide employed than in the case (I, R = CO_2Et).

The ratio of the C-alkyl products (III)/(IV) varies, and is evidently not simply determined by the relative kinetic accessibility of the enolate from the α- and β-face. The proportion of the minor C-alkyl product is remarkably constant, whilst, in both series, the major C-alkyl derivatives is clearly formed at the expense of O-alkylation. We infer that the major C-alkyl product arises via a reaction complex involving the enolate oxygen atom. Specific ortho-carboxylation (4), or alkylation of phenols (5) are precedents. It is suggested that the metal enolate and alkyl halide form a type of pre-reaction complex: M enolate + R'hal $\rightleftharpoons$ (M enolate/R'hal)pair, possibly by dipole association. Such a complex may be formed on the α- or β- side of the enolate. Preferential α-alkylation of (I, R = CH_3) agrees with precedent (6). β-Alkylation of (I, R = CO_2Et) may therefore derive from a purely polar contribution of the ester substituent towards formation of the reaction complex on the β-face of the enolate.

1. (a) C.L. Graham and F.J. McQuillin, *J.Chem.Soc.*, 1963, 4634;
   (b) F.J. McQuillin and P.L. Simpson, *ibid*., 1963, 4726.
2. D.Y. Curtin, R.J. Crawford and M. Wilhelm, *J.Amer.Chem.Soc*., 1958, **80**, 1391; A. Brandstrom and I. Forsblad, *Acta Chem.Scand*., 1957, **11**, 904; A. Chatterjee, D. Banerjee and S. Banerjee, *Tetrahedron Letters*, 1965, No. 43, 3851; G. Brieger and W.M. Pelletier, *ibid*., 1965, No. 40, 3555; W.J. LeNoble and J.E. Rierta, *ibid*., 1966, No. 10, 1087; C.F. Hobbs, C.K. McMillin, E. Papadopoulos, and C.A. Van der werf, *J.Amer.Chem.Soc*., 1962, **84**, 43.
3. N. Kornblum and A.P. Lurie, *J.Amer.Chem.Soc*., 1959, **81**, 2705; J.P. Ferris, C.E. Sullivan and B.G. Wright, *J.Org.Chem*., 1964, **29**, 87.
4. Cf. J.R. Johnson, *J.Amer.Chem.Soc.*, 1933, **55**, 3029.
5. Cf. R. Barner and H. Schmid, *Helv.Chim.Acta*, 1960, **43**, 1393.
6. Cf. Wenkert, A. Afonso, J.B. Bredenberg, C. Kaneko and A. Tahara, *J.Amer. Chem.Soc*., 1964, **86**, 2038; C.L. Graham and F.J. McQuillin, *J.Chem.Soc.*, 1964, 4521.