Regioselectivity of the Alkylation of Ambident Anionic Species on Alumina or in the Presence of 'Solid Hexamethylphosphoric Triamide'

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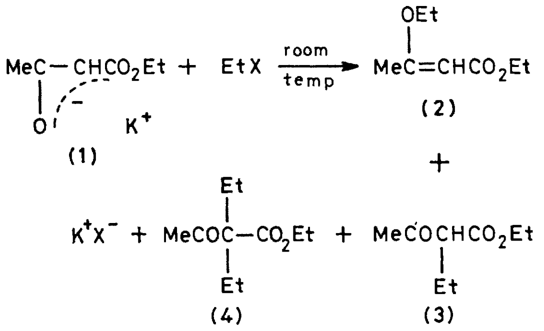
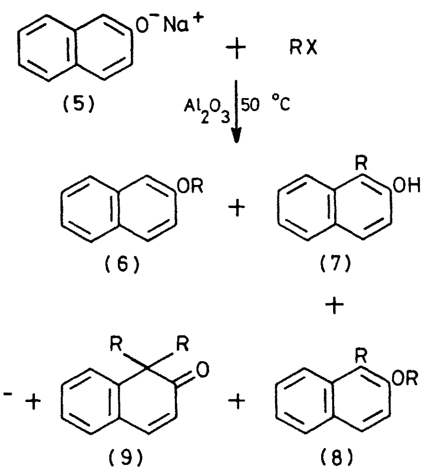
Summary C-Alkylation of the acetoacetate anions and of sodium naphthoxide is highly favoured on alumina, while O-alkylation of the acetoacetate anion predominates in tetrahydrofuran in the presence of solid hexamethylphosphoric triamide.

THE use of inorganic supports[1,2] and also of some solid organic supports such as solid HMPA[3] (polystyrene resin-supported hexamethylphosphoric triamide) has recently been attracting widespread interest in organic synthesis. As the regioselectivity of alkylation of ambident anions is strongly solvent-dependent,[4] it seemed worthwhile to examine the influence of such media on the C/O ratio in the alkylation of potassium acetoacetate (**1**) and sodium naphthoxide (**5**).

For acetoacetate, the observed products [enol ethers (**2**) and *C*-alkylated products (**3**) and (**4**)] were those expected. In the case of the naphthoxide, *O*-alkylated (**6**), mono-*C*-alkylated (**7**), di-*O,C*-alkylated (**8**), and di-*C*-alkylated products (**9**) were obtained. In this latter case, no experiments were carried out with solid HMPA as it had been shown previously[4] that in the case of naphthoxides, there is only a small change in regioselectivity on going from tetrahydrofuran (THF) to polar aprotic solvents.

Alumina (Merck 90 neutral, 70—230 mesh) was treated with sodium methoxide and then with ethyl acetoacetate or 2-naphthol, as described previously.[5] Solid HMPA, kindly provided by Dr. Y. Leroux, was used in suspension in THF[3a] in which solid, preformed potassium ethyl acetoacetate enolate was dissolved. In all cases, equimolar amounts of alkylating agents were used and the results are shown in Tables 1 and 2.





In the alkylation of acetoacetate, sodium methoxide-impregnated alumina and solid HMPA have opposite effects. *C*-Alkylation predominates on alumina; the effect is more pronounced than in ethanol, but is similar to that observed in Bu^tOH.[4] In the case of solid HMPA in THF, *O*-alkylation is preferred when there is more than 0·5 equiv. of $HMPA/K^+$. The observed selectivity is less than that for pure HMPA (83% *O*-alkylation) but is comparable with that obtained with *NN*-dimethylformamide or dimethyl sulphoxide. This selectivity, and the fact that there is no substantial improvement if more than 0·5 equiv. of solid HMPA is used, argue strongly for the intervention of a K^+ (polymer associated) acetoacetate species.

Although the fact that a high proportion of *C*-alkylated product is obtained when naphthoxides react with alkyl halides on sodium methoxide-impregnated alumina is similar to results obtained in protic solvents such as EtOH and CF_3CO_2H,[6] the high amount of di-*C*-alkylated product

TABLE 1

Alkylating agent	Medium	Time /days	Yield /%	% (**2**)	% (**3**)	% (**4**)
Et_2SO_4	Al_2O_3	5	76[a]	2	96	2
EtBr	Al_2O_3	5	53[a]	1	97	2
EtI	Al_2O_3	5	52[a]	<1	97	3
Et_2SO_4	THF	3	85[b]	5	93	2
Et_2SO_4	THF + 0·2 equiv. of solid HMPA	3	>95[b]	58	42	<1
Et_2SO_4	THF + 0·5 or 1 equiv. of solid HMPA	3	>95[b]	69	31	<1
Et_2SO_4	THF + 1·5 equiv. of solid HMPA	3	>95[b]	72	28	<1

[a] The yields are of isolated products. [b] The yields were determined by g.l.c. and are based on the amount of Et_2SO_4 remaining in the reaction mixture.

TABLE 2

Alkylating agent	Time /days	Yields /%[a]	% (**6**)[b]	% (**7**)[b]	% (**8**)[b]	% (**9**)[b]
MeI	2	40	16	33	17	33
Me_2SO_4	2	30	>98	—	—	—
$PhCH_2Cl$	2	53	1·5	40	3	56

[a] Yields were determined by n.m.r. spectroscopy and are of alkylated products. Unchanged 2-naphthol may be recovered.
[b] Relative yields of alkylated products.

is not typical of these solvents. Compound (**9**) has been obtained in small yield with $PhCH_2Cl$ as alkylating agent, but was not observed when MeI was used.[6,7] Interestingly it has been obtained[8] in small yield from the alumina catalysed reaction of 2-naphthol with methanol at high temperature.

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