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ION PAIR EXTRACTION IN PREPARATIVE ORGANIC CHEMISTRY

VIII. ALKYLATION OF SOME WEAK ACIDS

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In a series of papers the present authors have shown that tetrabutylammonium salts of anions of some compounds containing an active methylene group such as methyl acetoacetate (1), methyl cyanoacetate (2), acetylacetone (3) and dimethyl benzoylmalonate (4) can be extracted into an aprotic solvent such as chloroform or methylene chloride in the form of ion pairs. The carbanion can be readily alkylated by adding an alkyl halide to these solutions. If a solution of a still weaker acid, such as benzyl cyanide, in chloroform or methylene chloride is shaken with an aqueous solution or a suspension of tetrabutylammonium hydroxide, the carbanion is present to such a low extent that very little of the ion pair is extracted into the organic solvent. The reactivity in these solvents, however, is high enough to permit a rapid alkylation of the carbanion, or ion pair, even when present in a small concentration. When an alkyl halide is added to such a suspension, a rapid alkylation occurs until the weak acid, base or alkylating agent has been consumed. We will now report that this procedure, for which we suggested the name Extractive Alkylation (1), is a highly useful method for the alkylation of a variety of weak acids. The results obtained using benzyl cyanide, diethyl malonate and benzyl methyl ketone are given in the table.

It is readily seen that both mono- and dimethylation can be performed. The dimethylation product, however, is rather difficult to obtain free from the monoethylation product even when an excess of base is used. When ethyl or higher alkyl iodides are used, however, it is possible to choose the amount of tetrabutylammonium hydroxide so that only the pure monoalkylated product is obtained. When α, ω-dibromo butane is used in the alkylation of benzyl cyanide, a nearly quantitative yield of the corresponding cyclic compound is obtained.

The quantitative analyses of the mixtures were carried out by VPC using a 2 m x 1/8" column containing Carbowax 20 M (5 %) and the identity was proved by NMR.

Alkylation of 0.1 mol of the substrate. Percentage composition of monoalkylation (M), dialkylation (D) and starting material (S). Mol of QOH per mole of substrate (x).

Substrate		Benzyl cyanide			Diethyl malonate			Benzyl methyl ketone		
Alkylation agent	x	M	D	S	M	D	S	M	D	S
Methyl iodide	1	72	14	14	86	3	11	92	0	8
" "	2	32	68	0	-	-	-	-	-	-
" "	3	8	92	0	4	96	0	60	40	0
Ethyl iodide	1	90	0	10	88	0	12	-	-	-
" "	1,2	100	0	0	100	0	0	-	-	-
Isopropyl iodide	1	75	0	25	45	0	55	-	-	-
Butyl iodide	1	-	-	-	85	0	15	-	-	-
1,4-dibromo butane	3	0	97	3	-	-	-	-	-	-

Extractive alkylation. A mixture of x · 0.1 mol of tetrabutylammonium hydrogen sulphate and x · 0.2 mol of sodium hydroxide in x · 100 ml of water was prepared. A solution containing 0.1 mol of the substrate and x · 0.2 mol of the alkyl iodide in 100 ml of methylene chloride was added to the stirred tetrabutylammonium hydroxide mixture. When methyl iodide was used the reaction was exothermic and complete after about 10 minutes. With butyl iodide or isopropyl iodide the stirred mixture was refluxed for 30 minutes. The layers were then separated, the methylene chloride evaporated, and the tetrabutylammonium iodide was precipitated by adding ether to the residue. The iodide was filtered off and the ether evaporated. The alkylated products were analyzed, and the yields obtained are given in the table.

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