

Ion Pair Extraction in Preparative Organic Chemistry

III. Alkylation of Methyl Cyanoacetate and Related Compounds

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It has been found that a variety of anions can be extracted in a chloroform or a methylene chloride layer as ion pairs with a large quaternary cation such as tetrabutylammonium.¹ When the weak acid, methyl cyanoacetate, HA, dissolved in chloroform, is shaken with a concentrated aqueous solution of tetrabutylammonium hydroxide, Q^+OH^- , the ion pair Q^+A^- appears in the chloroform layer. If the layers are separated and the chloroform evaporated, QA is readily obtained in crystalline form and can be recrystallized.

Brändström^{2,3} has presented evidence that an ion pair of some ambident anions can be alkylated on the carbon atom. Since chloroform and methylene chloride can be expected to solvate cations much better than anions and the tetrabutylammonium cation is a large one it can be predicted^{2,3} that the ion pair Q^+A^- will

be rapidly alkylated on the carbon atom when its solution in chloroform is treated with an alkyl halide. This has been found to be the case; for example using methyl iodide, the alkylation of the tetrabutylammonium salt of methyl cyanoacetate QA is complete in a few seconds.

The products obtained were those formed by mono- and dialkylation on the carbon atom. The identity of the products was established by NMR analysis and their relative amounts were estimated by VPC using a thermal conductivity detector chromatograph. The 2 m × 1/8" column was packed with Carbowax 20 M (5%). The column temperature was 120°C and the helium carrier gas flow rate was 40 ml/min.

The identity of the dimethyl-, diethyl-, and diisopropyl-alkylated products was confirmed by alkylation of the methyl α -cyanopropionate, the methyl α -cyanobutyrate, and methyl α -cyanoisovalerate by the same method as that used for methyl cyanoacetate. Only C-alkylation was obtained in each case as can be concluded from NMR analysis. The relative yields of the different products are given in Table 1.

Experimental. The tetrabutylammonium hydrogen sulphate, methyl cyanoacetate and alkyl halides were commercial products.

Tetrabutylammonium salt of methyl cyanoacetate. 38.4 g (0.11 mole) of tetrabutylammonium hydrogen sulphate (Astra Meditec) was

Table 1. Percentage composition of alkylation mixtures.

Alkylation agent	NC-CH ₂ COOCH ₃	NC- $\overset{\text{R}}{\text{C}}$ COOCH ₃	NC- $\overset{(\text{R})_2}{\text{C}}$ COOCH ₃	Time of reaction (min)
Methyl iodide	26.0	48.5	25.5	10
Ethyl iodide	14	72	14 ^a	20
Isopropyl iodide	3	94	3	120
Butyl iodide	7	86	7	60

^a A shoulder is observed on the front side of the main peak in VPC. This is the dialkylated product since it has the same retention time as methyl α -cyano- α -ethyl butyrate. Since the reaction mixture became neutral a stoichiometric consideration indicates that the amount of di-substituted product must be equivalent to that of the starting material recovered. The figures obtained in methylation and butylation indicate that such a quantitative consideration is correct. In these cases all peaks were well separated.

added to a solution of 8.4 g (0.21 mole) of sodium hydroxide in 100 ml of water cooled in ice water. This mixture was shaken in a separatory funnel with 9.9 g (0.1 mole) of methyl cyanoacetate in 100 ml of chloroform until the water layer became neutral (3 min). The layers were separated, the chloroform was evaporated, and the residue recrystallized from ethyl acetate. The yield was 23.8 g (70 %) melting at 83°C.

Alkylation procedure. 0.1 mole of the alkyl iodide was added to a stirred solution containing 17 g (0.05 mole) of the tetrabutylammonium salt of methyl cyanoacetate in 75 ml of chloroform. The reaction was exothermic and ended (neutral) after a few minutes. The chloroform was evaporated. Ether was added whereupon the tetrabutylammonium iodide crystallized. The iodide was filtered off. The yield of the salt was 97 %. The ether solution was evaporated and the residue analysed as described above. The relative yields of mono- and dialkylated products are given in Table 1.

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IV. Alkylation of Methyl Acetoacetate

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Carbon alkylation of alkyl esters of acetoacetic acid is a standard procedure in preparative organic synthesis.¹ With sodium ethoxide in alcohol the reaction is rather slow and the operation takes at least one day to perform. Using a base such as NaH or K₂CO₃ in an aprotic solvent such as DMF the reaction rate is higher than in alcohol but the product is contaminated by considerable quantities of *O*-alkylation products.²

We have recently demonstrated that tetrabutylammonium salts of alkyl cyanoacetates can be obtained by ion pair extraction.³ These salts were then alkylated in chloroform solution by a very rapid reaction. For preparative purposes, however, it is not necessary to prepare the pure salt separately. Instead we have found that the extraction and alkylation can be performed advantageously in one operation. This new unit operation is conveniently called extractive alkylation and can be used for many purposes. The obvious advantage of the extractive alkylation is that even compounds which are extracted as ion pair with chloroform only to a minor degree from an aqueous solution, can be quantitatively alkylated. It is thus possible to alkylate very weak acids by this procedure. Another advantage is that esters are often not hydrolysed during the conditions used in extractive alkylation.

The procedure is demonstrated by the alkylation of methyl acetoacetate. The methyl ester was chosen in order to obtain simple NMR spectra which facilitated the analysis of the products obtained. The quantitative analysis of the mixtures was carried out by VPC using a 2 m × 1/8" column containing Carbowax 20 M (5 %).

The composition of the products obtained in the extractive alkylation are given in Table 1. From this it can be seen that carbon alkylation is the main or