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DEPROTONATION-ALKYLATION OF ALKYL CYANIDES UNDER SONOCHEMICAL CONDITIONS.

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ABSTRACT: Deprotonation-alkylation of n-alkyl cyanides can be readily effected by an alkyl halide in the presence of sodium in a one pot procedure. Yields are generally better than in the usual methods, and the overall reaction conditions have important advantages in terms of ease and simplicity compatible with preparative scale-up.

Deprotonation of activated CH bonds on the α-positions of ketones, esters, nitriles is the first step leading to the alkylated derivatives.[1] It is generally effected at low temperature in the presence of alkoxides or amides, requiring a preparation step for these auxiliaries which can be expensive, inconvenient or

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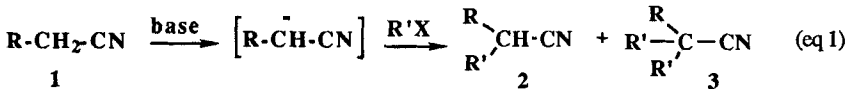
dangerous. The use of metals, easier to handle even if reactive, would constitute a simplification of the process but under normal conditions, no valuable result has yet been recorded.

Among these reactions of synthetic interest, the controlled intermolecular monoalkylation is frequently the more difficult to perform. In the case of nitriles, direct metallation with sodium or potassium was observed a long time ago,[2] but the yields of the alkylated products were too low for synthetic uses, and several undesired processes take place, among which the reductive decyanation.[3] More recently, attempts were made with less common forms of these metals such as the activated compounds with alumina [4] or graphite.[5] New approaches were found with the extension of sonochemical methods. Ultrasonically Dispersed Potassium (UDP) reacts with adiponitrile to induce the Thorpe-Ziegler cyclization in good yields at room temperature.[6] The in situ sonochemical generation of alkyl lithium reagents permits the easy deprotonation of a variety of substrates, avoiding the use of the potentially dangerous (on a preparative scale) and expensive alkyl lithium reagents.[7]

We became interested in the problem of the deprotonation-monoalkylation of n-alkyl cyanides, a reaction which seems sometimes difficult.



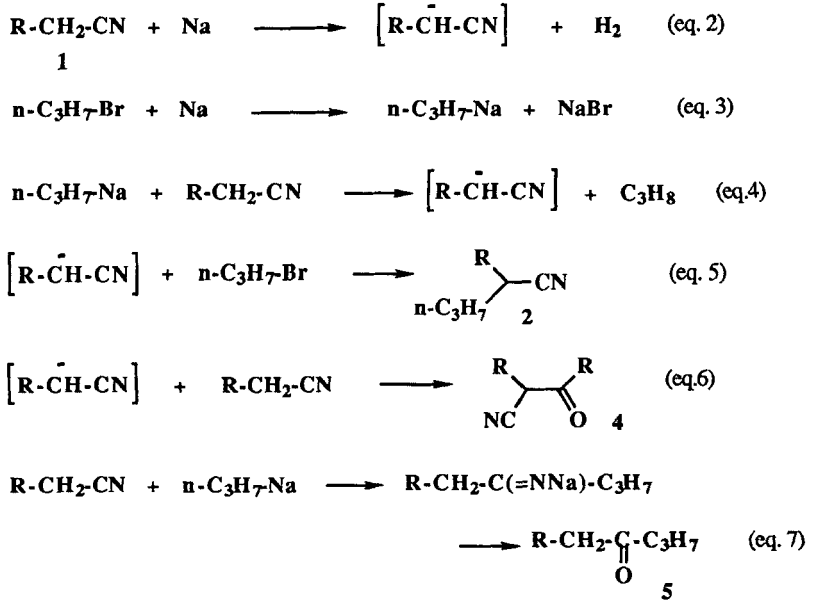
1 2 3 (eq 1)

R' = C_3H_7

The steric crowding provided by the small cyano group is weak, and the reaction goes easily to polyalkylation. The preparation of 2-propyl-pentanenitrile (**2**, R=R'= n-C_3H_7), precursor to the corresponding biologically active acid,[8] has been described using this approach, but it requires strict conditions of

solvent and temperature to reach convenient yields.[9] More generally, the common processes to introduce an alkyl substituent on the α-carbon of an n-alkyl cyanide, even under carefully controlled conditions (frequently low temperature deprotonation with LDA), give yields in the 40-70% range and the separation of monoalkyl from dialkyl products is not always simple.[10] Moreover, the general scope of these reactions make them unsuitable for large scale preparations. We found that a much more convenient procedure together with improved yields can be found with the sonochemical in situ generation of alkylsodium reagents. The general scheme of the reaction is shown in Scheme 1.

Scheme 1



In exploratory experiments, a mixture of pentanenitrile, propyl bromide and sodium (in the stoichiometry 1:1:1) was sonicated in toluene in a glass vessel equipped with a horn generator. The metal was immobilised under the emitter, and the double wall vessel was thermostated at 25 °C. Sonication was

effected for 2 h, then the mixture was analyzed by VPC, and the peaks identified by comparison with authentic samples.

In order to gain information on a system potentially extremely complex (eq. 2-7), experiments were first effected in two-steps. Pentanenitrile was sonicated with sodium in toluene then treated with 1-bromopropane. Low yields resulted for the expected compound, the major product being 6-cyano-5-octanone **4** (eq. 6, R= n-C_3H_7). This reaction should in principle be avoided in the one pot procedure. Under such conditions however, there is the possibility for propyl sodium formation (eq. 3), able to react in several manners with the nitrile substrate. In fact, it was shown that the initial rates of the reactions between sodium and the nitrile (eq. 2) or the alkyl halide (eq. 3) are similar. Adjustment of the stoichiometry and reaction time was thought to be able to solve this selectivity problem, with the objective of minimising dialkylation, even at the price of a lower conversion yield. After extensive experimentation[12], optimal conditions were determined. Sonications were effected for 2 h, and the favourable stoichiometry was found to be 1:1.5:2.0 for the nitrile, sodium and bromopropane respectively. The results are given in the Table 1.

Comparison with literature data lead to the following observations. Our lowest yield is observed for acetonitrile. In this case, polyalkylation is generally obtained from bromopropane in the presence of lithium diethylamide in benzene-HMPA at -60°C.[3] A case of clean monoalkylation is found with 1-t-Butyl-dimethylsilyloxy-ethyl bromide as the electrophile, in THF-HMPA at -78°C, as it occurs in 68% yield accompanied by 25% dialkylation.[11] Similar results are observed with other n-alkyl cyanides. With this respect, our results compete favourably in terms of yields and convenience, since all the process takes place

Table 1

Starting Material	Recovered **1**	**2** (%)	**3** (%)
CH_3CN	15	44	20
C_3H_7CN	16	65	3
C_4H_9CN	17	78	2
$C_5H_{11}CN$	25	68	2
$C_7H_{15}CN$	41	52	3

Yields refer to pure isolated products.

rapidly at room temperature using extremely simple reagents. for longer alkyl chains, the selectivity is high even if the conversion rate is slower, probably due to a decreased acidity of the proton to be abstracted. Dialkylation is minimal, making the purification step easy. Besides this undesired product, the only contaminant detected in amounts less than a few percents is the alkylsodium addition product on the CN bond **5** (eq. 7).

The reason for the sonochemical activation is still obscure. Comparative experiments have shown that under silent conditions, the yields and selectivity are much poorer. On the other hand, it is important to stress upon an interesting finding. Results of the same type can be obtained using a high speed stirrer with 18 indentations operated at 9000 rpm. At 15°C using the same stoichiometry, the

selectivity of the reaction is virtualy the same. In analogy with propellers which are well known to induce hydraulic cavitation, the stirring system used here generates a cavitating pressure wave of 2.7 kHz frequency, which makes this experiment a probable example of the influence of frequency on sonochemical processes. If our results have a preparative interest, especially because large scale preparations can be effected by this method, some fundamental aspects deserve further study in connection to the necessary improvement of the knowledge of sonochemical activation and the several methods to produce it.

Experimental

Nitriles, sodium, bromopropane were obtained from Aldrich, and used as received. Toluene was distillated over sodium. The sonochemical reactor was described in a previous work.(ref) The generator is a Sonic § Material Vibracell 600, operated at 20 kHz. Thermostatation is effected by circulating cold water in the jacketed reactor.

VPC analyses were effected with a Hewlet-Packard 3298 chromatograph, equiped with a 25 meters HP1 column (xylene internal standard).

Products were identified by IR, NMR, gc/ms techniques and compared to authentic samples given by Sanofi.

IR: $\nu_{CN} = 2245 - 2248\ cm^{-1}$

NMR : $[\ CH_3 - (CH_2)_n -]_x - CH_y - CN$

δ(ppm) ; J (Hz): t. O.9 / m. 1.5 - 1.7 / y = 2: t. 2.34 (J=7.5) ; y = 1: m. 1.7

Standard procedure.

The reactions have been carried out in a jacketed three necked flat bottom flask.

The central neck was fitted to the sonic horn or a high speed stirrer and the two side harms with septums to allow sampling, introduction of the temperature probe and of the pieces of metallic sodium (the toluenic dispersion of sodium sand was introduced through a funnel with a pressure equalizing tube). The solution of valeronitrile (0.146 mol, 15 cm^3), propyl bromide (0.292 mol, 26.4cm^3) and xylene (gc internal standard, 9 cm^3) in toluene (45 cm^3) is first introduced and cooled 5°C below the desired reaction temperature by circulating cooled water in the jacket. The mixture is sonicated and sodium is then added in three portions (1/3 at t=0, 1/3 at t=10 mn, 1/3 at t=20 mn). Heat was evolved and the initial temperature jump is generally of 5 °C.

After the required reaction time, the solid is filtered off and treated with ethanol to eliminate the unreacted sodium. Water (15 cm^3) is then added and the aqueous solution extracted with toluene. The toluenic solution is dried over magnesium sulfate and analysed by vpc. Toluene is then evacuated, and the residue fractionated under vacuum. Calculated yields of pure 2 and 3 are based on the starting nitrile. Yields determined by VPC are generally 5 % higher.

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