

## SYNTHESIS OF CYANO-[D<sub>11</sub>]-CYCLOHEXANE

D. Abenheim<sup>1</sup>, A. Loupy\*<sup>1</sup>, A. Petit<sup>1</sup>, A. Gonthier-Vassal<sup>2</sup> and H. Szwarc<sup>2</sup>

<sup>1</sup>Laboratoire des Réactions Sélectives sur Supports, UA 478 CNRS, Bâtiment 410, Université Paris-Sud, F-91405 Orsay

<sup>2</sup>Laboratoire de Chimie Physique des Matériaux Amorphes, URA D 1104 CNRS, Université Paris-Sud, F-91405 Orsay

### SUMMARY

Cyano-[D<sub>11</sub>]-cyclohexane was prepared from commercial [D<sub>12</sub>]-cyclohexanol via the sequence alcohol-chloride-acid-nitrile in an overall yield of 33 % after purification. Isotopic purity was at least 98 %.

KEYWORDS : Glassy crystals ; Isotopic purity ; Safety ; [D<sub>11</sub>]-cyclohexyl magnesium chloride ; Dry-ice.

### INTRODUCTION

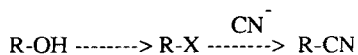
Differential scanning calorimetry experiments (1) have shown that phase I of cyanocyclohexane is a plastic crystal according to Timmermans criterion and that it can be supercooled to 100 K and below to give a glassy crystal. The supercooling is easy and complete and phase II was never observed in these initial experiments. So, cyanocyclohexane can be considered as a very "good" example of glassy crystal : no unwanted crystallization towards the more stable phase II was to be feared, and it was thought that the glass transition near 135 K could easily be studied by either cooling to or warming up to 135 K. Such opportunities are not frequent for glassy crystals and it was expected that it would be possible to trace the evolution of the dynamic and structural properties from the plastic phase to the glassy crystalline one.

A study of the crystal by neutron diffraction necessitates the obtention of a perdeuterated product in order to remove the important incoherent diffusion of hydrogen atoms. Subsequent thermodynamic measurements have shown that the phase diagrams for hydrogenated and deuterated compounds are analogous (2), so that it could be expected that their structural properties will be much the same : this motivates the present work.

## RESULTS AND DISCUSSION

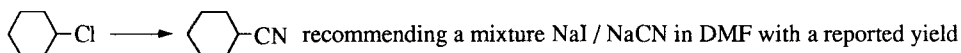
The synthesis of cyano-[D<sub>11</sub>]-cyclohexane has to be realized from commercially available [D<sub>12</sub>]-cyclohexanol [C<sub>6</sub>D<sub>11</sub>OD from Aldrich, isotopic purity ≥ 98 %]. All methods were tested and optimized starting from hydrogenated cyclohexanol C<sub>6</sub>H<sub>11</sub>OH and subsequently transposed to the perdeuterated products.

Several two-steps and one-pot methods have been described in the literature (3-7) for the direct conversion R-OH → R-CN. They involve transformation of the alcohol into potential electrophilic agents able to undergo subsequent substitution by CN<sup>-</sup> (i.e. halides, sulfonic esters, etc...).



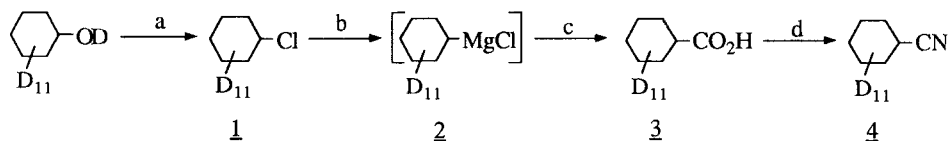
These procedures are essentially applied to primary alcohols, because with secondary substrates formation of nitriles are very often accompanied by elimination products. In the special case of R = cyclohexyl, the methods described are not applicable because it is well known that cyclohexyl derivatives are poor substrates for S<sub>N</sub>2 reactions (8). An elimination product (cyclohexene) is thus obtained almost exclusively (6,9).

However, in the literature, two types of conditions were described for the transformation



recommending a mixture NaI / NaCN in DMF with a reported yield of 16 % (7) or KCN/Polysorbate 80 in CH<sub>3</sub>CN under phase transfer catalysis conditions with 40 % yield (10). In our hands, for both cases, only traces of cyclohexane carbonitrile were recovered together with starting materials and cyclohexene.

Because of the failure of the direct transformation, we performed the synthesis of cyano-[D<sub>11</sub>]-cyclohexane according to the following easy steps starting from the alcohol :

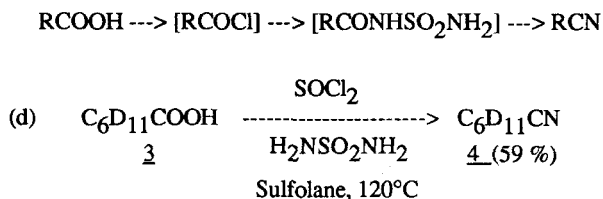


The first step (a) was performed in the presence of a solution of DCl in D<sub>2</sub>O with a large excess of anhydrous CaCl<sub>2</sub> (yield 73 %), according to a procedure described for C<sub>6</sub>H<sub>11</sub>OH + HCl/H<sub>2</sub>O (11). The present result is far better than those using a system of SOCl<sub>2</sub> + ZnCl<sub>2</sub> recommended for this case (12).

The transformation (step b) of the chloro derivative into the organomagnesium compound C<sub>6</sub>D<sub>11</sub>MgCl was realized as usual by reacting 1 with magnesium in diethyl ether. The carboxylic acid

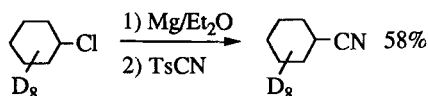
3 was consequently prepared (step c) by reacting 2 with CO<sub>2</sub> (13,14) (dry ice), followed by acid hydrolysis (total yield for these two steps 78 %).

Finally, acid 3 was directly transformed (step d) according to a one-pot method consisting of 3 steps and described by Hulkenberg and Troost (15) :



The required per-deuterated nitrile was obtained, after purification by distillation, with an overall yield of 33 % from 1 with an isotopic purity  $\geq 98$  %.

We have employed an efficient, cheap and mainly safe procedure for the transformation 1 --> 4 in order to avoid that previously published (16), which calls for the use of tosyl cyanide (17) :



Indeed, tosyl cyanide is an expensive, and hazardous product able to decompose in the contact of moisture or water and is known to seriously damage mucous membranes, breathing passages, eyes and skin ; its inhalation can even be lethal (18).

## EXPERIMENTAL

Commercial products were purchased from Aldrich or Janssen with chemical purity  $\geq 99$  %; C<sub>6</sub>D<sub>11</sub>OD : isotopic purity  $\geq 98$  %; 37 % solution of DCl in D<sub>2</sub>O : % D ~ 99 %.

### Step (a)

Into a flask fitted with a reflux condenser, was introduced 15 g of per-deuterated cyclohexanol (0.133 mol), 33.4 ml DCl (0.89 mol) in D<sub>2</sub>O solution and 12 g of finely ground anhydrous CaCl<sub>2</sub> (1.08 mol). The mixture was heated at 80° C for 24 hours with magnetic stirring. After cooling to room temperature, the mixture was extracted with ether. The organic layers were washed successively with saturated solutions of NaCl and NaHCO<sub>3</sub> before drying over MgSO<sub>4</sub>. Filtration and evaporation of the solvent gave 12.6 g of 1 (0.097 mole ; 73 %).

### NMR (62.5 MHz in CDCl<sub>3</sub>, <sup>13</sup>C coupled with D)

$\delta = 59.5\text{-}60$  ppm (triplet 1-1-1) : 1 C bearing Cl coupled with 1 D

$\delta = 35\text{-}36$  ppm (quint. 1-2-3-2-1) : 2 C coupled with 2 D,  $\alpha$  to Cl

$\delta = 23\text{-}24,5$  ppm (sext. 1-3-5-5-3-1) : 3 C coupled with 2 D,  $\beta$  and  $\gamma$  to Cl

Step (b)

In a dry three-necked flask equipped with a reflux condenser and a dropping funnel, 4.86 g of powdered magnesium and 20 ml of anhydrous diethyl ether were introduced under nitrogen and with magnetic stirring; 12.4 g of chloro-[D<sub>11</sub>]-cyclohexane in 80 ml of diethyl ether was then added dropwise. Stirring was maintained for two hours more at room temperature. The Grignard reagent was titrated in order to control the conversion of starting materials (iodine, sodium thiosulfate).

Step (c)

The above Grignard reagent solution was cooled to -40°C. Small pieces of dry ice (CO<sub>2</sub>) in a two-fold excess were introduced very slowly in order to avoid solidification. After CO<sub>2</sub> addition, the reaction was left to occur at room temperature under magnetic stirring. Hydrolysis was then carried out by means of 2N hydrochloric acid and ice (exothermic reaction). After washing with saturated NaCl solution, drying over magnesium sulfate and ether removal, 10.42 g (0.075 mole) of crude acid 3 were collected, i.e. with a 78 % yield for steps (b) + (c).

Step (d)

In a round-bottomed flask with a reflux condenser, was introduced 10.45 g of carboxylic acid 3 (0.075 mole), 9.39 g of thionyl chloride (0.079 mole), 8.65 g of H<sub>2</sub>NSO<sub>2</sub>NH<sub>2</sub> (0.090 mole), and 75 ml of sulfolane. The mixture was heated for 3 hours at 120° C under magnetic stirring. After cooling, it was poured into a 1 N NaOH solution and then extracted three times with diethyl ether-cyclohexane (1:1). The combined organic layers were washed three times with water to remove excess sulfolane. After drying over MgSO<sub>4</sub>, filtration and solvents removal, cyano[D<sub>11</sub>]-cyclohexane 4 is obtained and purified by distillation under reduced pressure (b<sub>18</sub> = 48-49° C). 5.3 g of pure product was collected (59 %). <sup>1</sup>H N.M.R. clearly shows that less than 2 % of hydrogen atom can be observed. They are mainly located on the carbon atom lying in a position with respect to the cyano group (2.6 ppm). Isotopic purity of 4 is consequently ≥ 98 %.

<sup>13</sup>C NMR (Bruker 100 MHz - CDCl<sub>3</sub>)

δ = 122 ppm (s) : CN ;

δ = 27.8 - 28.8 (quint) : 2 C coupled with 2 D, α to carbon bearing cyano group ;

δ = 26.7 - 27.7 (triplet) : 1 C bearing CN group, coupled with one D ;

δ = 23.4 - 24.3 (quint) : 1 C coupled to 2 D, γ to carbon bearing cyano group ;

δ = 22.2 - 23.2 (quint) : 2 C coupled with 2 D in position β to C-CN.

Mass spectra (electronic impact coupled with v.p.c-column CP Sil 5CB of 25 m length)

46 (intensity 43) : C<sub>3</sub>D<sub>5</sub> ; 58 (37) : C<sub>3</sub>D<sub>4</sub>N ; 64 (100) : C<sub>4</sub>D<sub>8</sub> ; 74 (26) : (M-C<sub>2</sub>D<sub>4</sub>N)<sup>+</sup> ;

86 (21) : (M-C<sub>2</sub>D<sub>5</sub>)<sup>+</sup> ; 88 (29) : (M-CD<sub>2</sub> = CD<sub>2</sub>)<sup>+</sup> ; 92 (18) : (M-DCN)<sup>+</sup> ; 100 (19) : (M-ND<sub>3</sub>)<sup>+</sup> ;

102 (23) : (M-CD<sub>3</sub>)<sup>+</sup> ; 118 (11) : (M-D)<sup>+</sup> ; 120 (8) : M<sup>+</sup>.

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