POLYMETHYLATIONS OF BIS(CYANOMETHYL)BENZENES

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Abstract—o-, m- and p-bis(cyanomethyl)benzene were reacted with various quantities of methyllithium and methyliodide. Di and tetra methylations can be easily obtained in the cases of the meta and para isomers. Di and tri methylations were obtained in the reactions of the ortho isomer. The product from tri methylation of the ortho isomer cyclizes under the reaction conditions to a 3-indanone derivative.

Metalation of activated nitriles by methyllithium (MeLi), in ether/THF solution and subsequent treatment of the resulting monoanions with methyliodide (MeI) leads to the formation of various products depending on the nature and the relative amounts of the reactants.¹ The relatively slow reaction between MeLi and MeI permits the use of an excess of MeLi in the initial metalation step, so that after the addition of the methylating agent, MeLi can still function in more metalation reactions, addition to a CN triple bond or participate in a nucleophilic displacement process of a cyano group.¹

In the alkylation reactions of monoanions derived from primary nitriles the dialkyl derivatives are usually formed² and only under special conditions the products from monoalkylation can sometimes be obtained.3a-d Even though there are two acidic hydrogens on the carbon α to the cyano group in primary nitriles, vigorous conditions are required to obtain dimetalation⁴ compared to the rather easy dimetalation at a propargylic position.⁵ Das and Wilke⁶ have studied the IR spectra of the monolithio derivatives of acetonitrile and phenylacetonitrile and observed absorptions due to both lithium-carbon and lithium-nitrogen interactions. Gornowicz and West suggested earlier the existence of several tautomeric forms in the solution of monolithio acetonitrile.⁴ It is assumed that the negative charge in the monoanion is located mostly on the electronegative nitrogen, thus rendering the remaining hydrogen allenic in its nature and reducing its acidity and tendency to undergo metalation.⁴

During the alkylation reaction this hydrogen regains the capability to undergo metalation although it is now a part of a secondary nitrile. The remetalation process⁸ is very fast and starts even before the monoalkylation is completed; excess base, or in its absence molecules of the monoanion, serve as the metalating agents. As a result no monoalkylation derivatives are usually observed among the products and when the ratio of the primary nitrile to the base is 1:1, a mixture consisting of equal amounts of the starting material and the dialkyl derivative is formed.⁸

The nature of the substituent attached to the cyanomethylene group plays an important role in determining the course of the reaction after the dimethylation α to the cyano group is completed.¹ For example the different synthetic possibilities in the reactions of phenylacetonitrile (1) and α -naphthylacetonitrile (2) with MeLi and MeI are summarized in Scheme 1. The six products described in Scheme 1 can be obtained in high yields.¹

In the present study the reactions of o-, m- and pbis(cyanomethyl)benzene (3, 4 and 5) with MeLi and MeI were investigated. In each substrate there are four acidic hydrogens available for metalation and therefore various degress of methylation were expected. Our aim was to find out whether by controlling the amounts of the reactants it is possible to direct the course of the reactions towards the formation of specific products and to compare the results with those obtained in the reactions of monocyanomethylene compounds.



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RESULTS AND DISCUSSION

When 3, 4 and 5 were each reacted with 2 moles of MeLi in an ether/THF solution, the corresponding monoanions were formed quantitatively. In a subsequent treatment with 2 moles of MeI the dimethyl derivative of each isomer was produced in a high yield. The formation of the three bis(2 - cyanoethyl)benzenes (6, 7 and 8) is described in Scheme 2. The ortho and meta isomers 6 and 7 respectively, were obtained free from products of lower or higher degree of methylation, while a small amount of the tetra Me derivative 10 accompanied the para isomer 8. Inspection of the NMR spectra of 6, 7 and 8 revealed that in each case the two Me groups became attached to different carbons. Two equivalent chiral centers (designated by an asterisk in Scheme 2) exist in either 6, 7 or 8. Therefore, the ortho, meta and para isomers were probably obtained as diastereoisomeric mixtures of the dl and meso forms.

The presence of a diastereotoisomeric mixture was clearly seen in the NMR spectrum of 6 in which two absorptions (with relative intensity of 3:2) were observed for the proton on the carbon α to the cyano group. The large distance between the two chiral centers in 7 and 8 reduces the chemical difference between the diastereotoisomeric components of each mixture and this results in an identical NMR spectrum for both the *dl* and meso forms. No attempt has been made to separate the diastereotoisomers of 6, 7 and 8; each mixture had the same retention time for its components during GLC analysis.

IR spectra of 6, 7 and 8 showed a strong absorption at 2245 cm⁻¹ due to the presence of a CN group, and the main peak in their ms was at m/e 130 (M⁺-2HCN).

When 3, 4 and 5 were each subjected to a reaction with 4 moles of MeLi and subsequent treatment with 4 moles of MeI, different results were obtained for the first and the last two compounds. The reactions of 4 and 5 resulted in the formation of their tetra Me derivatives in an almost quantitative yield (Scheme 3). However, only trimethylation was obtained in the reaction of 3 (Scheme 4).

The two tetra Me derivatives *meta* and *para* bis(2 - cyanoisopropyl)benzene (9 and 10 respectively), had a strong absorption of a CN group at 2245 cm⁻¹ in their IR spectra. The main peak in their ms was at m/e 197 (M⁺-Me).

Steric interference is clearly the dominating factor which prevented the formation of a tetra Me derivative of 3. The tri Me derivative of 3, $o - (2 - \text{cyanoethyl}) - \alpha, \alpha$ dimethylphenylacetonitrile (11) had three different absorptions for three Me groups in its NMR spectrum. One is a doublet at $\delta 1.80$ (j = 6.2) and two singlets at $\delta 1.79$ and 1.73. The two singlets belong to the two Me groups



Scheme 3.

attached to the same carbon. However, because of restricted rotation around the bond connecting this carbon to the ring, the two Me's are different. The main peak in the ms of 11 was at m/e 156 (M⁺-HCN-Me). When the reaction mixture containing 11 was left overnight, the NMR spectrum of the product showed new signals in addition to those of 11. The new compound was purified by GLC analysis and its NMR spectrum revealed four aromatic protons at δ 7.14–7.54 and eight singlet signals divided into two sets with a relative intensity of 5:1. In each set there were four lines attributed to four different Me groups. In the first set (83%) absorptions were found at δ 3.74, 1.82, 1.42 and 1.35, while in the second set (17%) the corresponding absorptions were found at δ 3.62, 1.77, 1.63 and 1.54. The IR spectrum contained strong absorption of a CN group at 2240 cm⁻¹, and an absorption

of a C=N- bond at 1692 cm⁻¹. The ms pointed to a

molecular weight of 212. On the basis of the above data it was concluded that the new product was a mixture of two geometric isomers of 1,1,3 - trimethyl - 3 - cyano - 2 - N methylketiminoindanone (12a and 12b). The cause for the isomerism was the two different orientations of the N-Me group on the C=N bond.9 We assume that in the anti isomer 12a (83%) the Me is inclined towards the Me and the CN groups on carbon No. 3, while in the syn isomer 12b (17%) this Me is inclined towards the two Me groups on carbon No. 1. The anti form was favored over the syn because in the former case the N-Me group occupies a less hindered position. In 12a the N-Me group lies inside a deshielding zone developed by the CN group,¹⁰ therefore, is is expected to absorb in a lower field in the NMR than the N-Me group of 12b. This assumption is in agreement with the observed absorption of δ 3.74 for the N-Me group in the anti isomer 12a compared to δ 3.62 the corresponding absorption in the syn isomer 12b. Heating the mixture up to 70° didn't cause any coalescence of signals in the NMR spectrum. The steps leading to the formation of 12 are described in Scheme 4, and its detailed mass spectrum is given in Scheme 5.

Under normal reaction conditions the metalation of 11 by MeLi was relatively slow due to the existence of sterical interference. A competitive reaction of MeLi with MeI used most of the excess of MeLi and prevented complete metalation of 11; as a result only 28% yield of 12 was obtained after 20 hr of reaction. However, when 3 was reacted with 3 moles of MeLi and 3 moles of MeI, and only after 11 was formed (30 min) additional mole of MeLi was added, then a subsequent treatment with 1 mole of MeI gave 90% yield of 12. The mechanism for the formation of 12 is supported by an early report describing the cyclization of the parent compound 3 to 1 - cyano - 2 - iminoindane (13) by a reaction with sodium ethoxide in ethanol.^{11a}

The results show that it was not possible to combine the methylation reactions of the bis(cyanomethyl)benzenes with additions of MeLi to the CN bond, or with a nucleophilic displacement of CN groups. Apparently these reactions are slow and cannot be carried out in the presence of both MeLi and MeI. Contrary to the behavior of α, α - dimethylphenylacetonitrile' (Scheme 1), it seems that when two 2-cyanoisopropyl groups are attached to the phenyl ring, there is a mutual deactivation of these groups towards a nucleophilic attack by a methyl carbanion.

In the methylation reactions of the bis(cyanomethyl) benzenes, dimethylation was always obtained in the first stage in the form of monomethylation per each cyanomethyl group. Under similar conditions reactions of various mono cyanomethyl compounds proceeded directly to their dimethyl derivatives.¹ We assume that in the case of the materials having one cyanomethyl group, the acidity of the hydrogen abstracted in the first stage of the reaction is probably close enough to that of the hydrogen abstracted in the second stage of the reaction. Therefore, it is difficult to stop the reaction after monomethylation is accomplished. On the other hand the parallel differences in acidities existing between the bis(cyanomethyl)benzenes and their monomethyl derivatives are larger, thus enabling an easy monomethylation at







each cyanomethyl group. Tetra methylation was very smooth when there was no steric interference, in the later case trimethylation was obtained followed by a slow cyclization to an indanone derivative. The reactions of other aromatic compounds bearing more than one cyanomethyl group are now being investigated.

EXPERIMENTAL

The NMR spectra were recorded in CCl₄ or CDCl₃ on Virian T-60 instrument, chemical shifts are given in δ units relative to TMS. The IR spectra were taken on Perkin-Elmer Infracord 337 spectrometer, and UV spectra were recorded in EtOH soln on Unicam SP 800. Mass spectra were taken on Atlas Mat CH4. GLC analyses were preformed on a Hewlett Packard 7620A. Compounds 3^{11a-b} , 4^{12a-b} and 5^{13a-b} were prepared from the corresponding xylene dibromides by their reactions with sodium cyanide in water, ethanol and dioxane according to the method of Sandman and Garito.14 At the end of the reactions extraction with CH₂Cl₂ was used instead of filtration.¹

The general procedure for the metalation of nitriles by MeLi in THF/ether soln and the reactions of their monolithio derivatives with MeI was described in Ref. 1. The products were purified on 1.5 m, SE-30 15% on Chromosorb W. The experimental data is summarized in Table 1.

o-Bis(cyanoethyl)benzene (6) (dl + meso), NMR: 7.62-7.29/m, 4H (aromatic); 3.99/q (J = 6.4) 60% and 4.02/q (J = 6.4) 40%, 2H ,CN

(-CH); 1.73/d (J = 6.4), 6H (methyls). IR:
$$\bar{\nu}_{max} = 2245 \text{ cm}^{-1}$$

(C=N); 765 cm⁻¹ (ortho). UV: λ_{max} (nm) 275 (540). MS: M⁺ m/e184 (45%), m/e 169 (45%), m/e 157 (86%), m/e 156 (57%), m/e 142 (33%), m/e 130 (100%), m/e 115 (58%).

m-Bis(cyanoethyl)benzene (7) (dl + meso), NMR: 7.44-7.28/m, 4H (aromatic); 3.59/q (J = 7.0). 2H (_CH 1.63/d (I = 7.0)

$$5.59/4$$
 (J = 7.0), 2H (-C_H,); 1.65/4 (J = 7.0)
CH₃

6H (methyls). IR: $\hat{\nu}_{max} = 2245 \text{ cm}^{-1}$ (C=N); 800 cm⁻¹ (meta). UV: λ_{max} (nm) 250 (430), 260 (380), 267 sh (300). MS: M⁺ m/e 184 (28%), m/e 169 (48%), m/e 130 (100%).

Table 1. Products from reactions of bis(cvanomethyl)benzenes with MeLi and MeL*

Starting Material					
	CH ₃ Li moles per mole of starting material	CH ₃ I moles per mole of starting material	Time ^{b)} (min)	Major product (by GLC and NMR)	Yield %
3	2	2	15	6	94
4	2	2	30	7	92
5	2	2	30	8 10	80 10
4	4	4	30	9	99
5	4	4	30	10	99
3	4	4	15	11	90
3	4	4	20 hrs.	11 12a + 12b	72 28
11 ^{c)}	1	1	8 hrs.	12a + 12b	90

Satisfactory spectrochemical analyses were obtained for all the new compound except for 8 which was always accompanied by a small quantity of 10. Time = at room temp, after the addition of MeI. In this experiment 11 was obtained in situ from 3 and 3 moles of MeLi and 3 moles of MeI. a)

c)

p-Bis(cyanoethyl)benzene (8) (dl + meso), NMR: 7.38/s, 4H

(aromatic); 3.88/q (J = 7.0), 2H(-CH CN); 1.60/d (J = 7.0), 6H CH_3

(methyls). IR: $\bar{\nu}_{max} = 2245 \text{ cm}^{-1} \text{ (C=N)}; 835 \text{ cm}^{-1} \text{ (para)}. \text{ UV: } \lambda_{max}$ (nm) 254, 260, 266. MS: M⁺ m/e 184.

m-Bis(2-cyanoisopropyl)benzene (9), NMR: 7.56-7.40/m, 4H (aromatic); 1.64/s, 12H (methyls). IR: $\bar{\nu}_{max} = 2245 \text{ cm}^{-1}$ (C=N); 800 cm⁻¹ (meta). UV: λ_{max} (nm) 260 (240), MS: M⁺ m/e 212 (19%), m/e 197 (100%), m/e 183 (15%), m/e 170 (14%), m/e 130 $(15\%), m/e \ 103 \ (22\%).$

p-Bis(2-cyanoisopropyl)benzene (10), NMR: 7.50/s, 4H (aromatic); 1.65/s, 12H (methyls). IR: $\bar{\nu}_{max} = 2245 \text{ cm}^{-1}$ (C=N); 835 cm $^{-1}$ (para). UV: λ_{max} (nm) 255 (250), 262 (280), 267 (240). MS: M⁺ m/e 212 (16%), m/e 197 (100%), m/e 183 (67%), m/e 130 (20%), m/e 103 (16%).

 $o-(2-Cyanoethyl)-\alpha,\alpha$ -dimethylphenylacetonitrile (11), NMR:

7.65-7.29/m, 4H (aromatic); 4.64/q (J = 6.2), 1H (-CH < N);

1.79/s, 3H (Me); 1.73/s, 3H (Me); 1.80/d (J = 6.2), 3H (-

CH(). IR: $\bar{\nu}_{max} = 2245 \text{ cm}^{-1}$ (C=N); 763 cm⁻¹ (ortho). UV:

 λ_{max} (nm) 259 (310), 266 (300), 271 (220). MS: M⁺ m/e 198 (26%), m/e 183 (30%), m/e 171 (24%), m/e 156 (100%), m/e 144 (35%), m/e 29 (66%).

1.1.3 - Trimethyl - 3 - cyano - 2 - N - methylketiminoindanone (12a anti and 12b syn), NMR (anti): 7.54-7.14/m, 4H (aromatic);

3.74/s, 3H (=N-CH₃); 1.82/s, 3H (CC CH₃); 1.42/s, 3H (Me); CH₃

1.35/s, 3H (Me). NMR (syn): 7.54-7.14/m, 4H (aromatic); 3.62/s,

 $3H (=N-CH_3); 1.77/s, 3H (CH_3); 1.63/s, 3H (Me); 1.54/s, 3H (Me);$

(Me). IR: $\bar{\nu}_{max} = 2240 \text{ cm}^{-1} \text{ (C=N)}; 1692 \text{ cm}^{-1} \text{ (C=N)}. \text{ UV: } \lambda_{max}$

(nm) 256 (640), 263 (830), 270 (1000). MS: M* m/e 212 (62%), m/e 197 (13%), m/e 171 (55%), m/e 156 (100%), m/e 144 (71%), m/e 129 (70%).

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