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# CONTROLLED REACTIONS OF ACTIVATED NITRILES WITH METHYLLITHIUM AND METHYLIODIDE

## A NEW DISPLACEMENT OF $CN^-$ FROM SATURATED CARBON

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**Abstract**—Disubstituted nitriles, ketones and N-methylketimines can be synthesized by controlled reactions of nitriles, having an α activated methylene group, with methyllithium and methyliodide. Cyanide anion can be displaced from a tertiery carbon attached to naphthalene in a radical anion process.

Primary nitriles can be metalated easily in the α position by various metalation reagents such as sodium amide,[1] sodiohexamethyldisilazane[2] and several organo-lithium compounds.[3-6] In some cases addition to the cyano triple bond could be observed,[7] but the extent of this reaction can be reduced by using the right experimental conditions.[8,9] Several attempts were made to accomplish the dimetalation of nitriles[3,10,11] but, as was shown by Gornowicz and West,[12] a direct study of the anions generated in the metalation reactions is sometimes necessary in order to make conclusions in regard to their structure. These authors[12] succeeded in the dimetalation of acetonitrile only when t-butyllithium was used as the base. The question as to the degree of metalation arises, because in many cases[1] disubstituted products were obtained, in high yields, when the carbanions resulting from reactions of nitriles with bases were alkylated. In fact, special procedures have to be used when monoalkylation of primary nitriles is the desired reaction.[13-15]

We have recently studied the metalation of 3-butenenitrile **1** by methyllithium (MeLi), in ether/THF solution where the monoanion **2** was produced in an almost quantitative yield.[16] NMR of the solution proved the presence of **2** even though derivatization with either benzyl bromide or trimethylsilyl chloride led to the formation, in high yields, of disubstituted nitriles. It was found[16] that the reaction between MeLi and the alkylating reagent is too slow to interfere with the remetalation of the monosubstituted product obtained in the first stage of derivatization, and therefore the disubstituted nitrile is generated via a multistage process.

Das and Wilkie[6] have reacted phenylacetonitrile **7** with n-butyllithium to prepare the monolithium derivative **8**; they have isolated the lithium compound and studied extensively its physical and chemical properties. In this case too, reaction of **8** with an alkylating agent led to the formation of the disubstituted nitrile.[11]

We now wish to report how both alkylation and addition to activated nitriles can be performed by the use of controlled amounts of MeLi and methyliodide (MeI), the products being disubstituted nitriles, ketones and N-methylketimines. Methylations and additions to 3-butenenitrile **1**, phenylacetonitrile **7** and α-naphthylacetonitrile **13** were studied, in the last case a new displacement reaction of a cyano group from a saturated carbon has been found.

### RESULTS AND DISCUSSION

When one mole of **1** reacted with 2 moles of MeLi in ether/THF at −100°, and the solution was allowed to reach room temperature, the formation of the monoanion **2** was completed within 30 min. Subsequent treatment with 2 moles of MeI resulted in the formation of 2,2-dimethyl-3-butenenitrile **3**. In another experiment the amount of MeLi was increased to 4 moles while the relative quantities of the other reactants (**1** and MeI) remained unchanged. The major product after decomposition with cold water was the ketone 3,3-dimethyl-1-penten-4-one **5**. When the relative amounts of the three components taking part in the reaction were 1 mole of **1**, 4 moles of MeLi and 4 moles of MeI, N-methyl-3,3-dimethyl-1-penten-4-ketimine **6** was obtained in 60% yield. The results of the above reactions are summarized in Table 1.

The formation of the disubstituted nitrile **3** can be explained by the same mechanism of repeated metalations and alkylations which was described before for this kind of substitution.[16] Whenever an excess of MeLi was present in the reaction mixture, addition to the C≡N bond occurred to produce the lithium derivative **4**, which was then either hydrolyzed to give the ketone **5**, or trapped by a mole of MeI to yield the methylketimine **6**.

When the same sequence of reactions was applied to phenylacetonitrile **7**, instead of **1**, the same pattern of behaviour was found. Thus the product from the reaction of **7** with 2 moles of MeLi was the monoanion **8**, which after treatment with 2 moles of MeI formed 2,2-dimethylphenylacetonitrile **9**. The other two reactions of **7** (see Table 1) gave 3-phenyl-3-methyl-butan-2-one **11** and N-methyl-3-phenyl-3-methyl-butan-2-ketimine **12** respectively as the major products. In the last two reactions it is

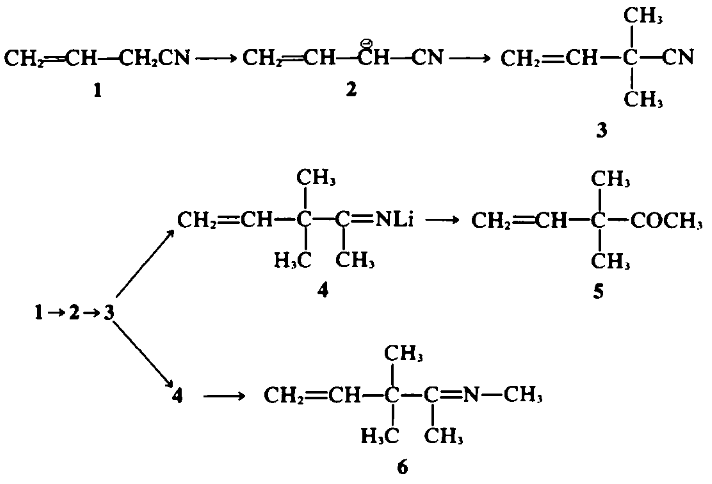


Table 1. Products from metalations and subsequent methylations of primary nitriles[a]

| Starting material | $CH_3Li$ moles per mole of starting material | $CH_3I$ moles per mole of starting material | Major product (by GLC and NMR) | Yield % | References |
|---|---|---|---|---|---|
| 1 | 2 | 2 | 3 | 64 | — |
| 1 | 4 | 2 | 5[b] | 41 | 24,25 |
| 1 | 4 | 4 | 6 | 60 | — |
| 7 | 2 | 2 | 9[c] | 95 | 26,27 |
| 7 | 4 | 2 | 11[d] | 81 | 8,29,30 |
| 7 | 4 | 4 | 12 | 95 | — |
| 13 | 2 | 2 | 15[e] | 95 | 31,32 |
| 13 | 4 | 2 | 17 | 96 | 23*a*,*b*,*c*,*d*,*e* |
| 13 | 4 | 4 | 18 | 75 | — |

[a] Satisfactory analyses were obtained for all the new compounds.

[b] No attempt has been made to optimize the yield of 5, b.p. 125·5°,[25] which was prepared before, in a low yield, by a sequence of several steps starting from acetylene, acetone and sodium in liquid ammonia,[24] and in a process involving the addition of a radical, generated from methylisopropyl ketone, to acetylene.[25]

[c] 9 was prepared by the action of $P_2O_5$ on the amide of α-phenylisobutyric acid[26] and from 7 by reaction with sodamide in ether and MeI.[27]

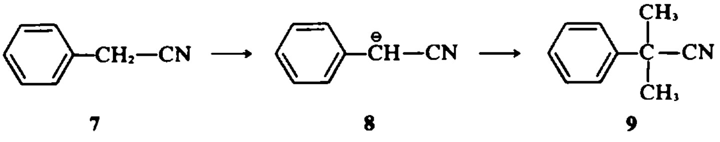
[d] 11 was synthesized by the addition of MeMgI to 9[28] and several other methods; ref. 29 and 30 are given as examples.

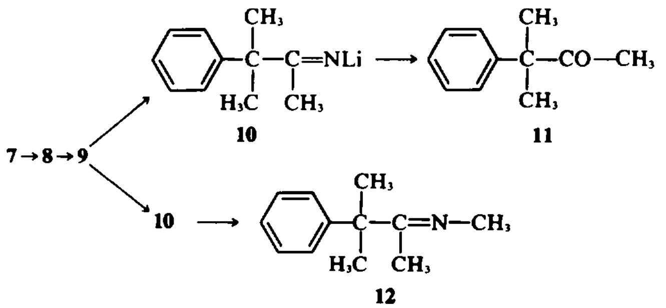
[e] 15 was synthesized from 13 either by the action of sodamide followed by MeI,[31] or by the action of $EtMe_2CONa$ and MeI.[32]

assumed that 9 was generated initially, then excess of MeLi was added to the C≡N bond to form 10, hydrolysis of which led to the obtention of 11, while its methylation led to 12.

In all cases investigated, addition of MeLi to the C≡N group started only after the dialkylation of the primary nitrile was complete. An easy differentiation between nitriles, ketones and N-methyl ketimines was based on IR spectra; $\nu_{C\equiv N}$ 2235–2240 $cm^{-1}$, $\nu_{C=O}$ 1710 $cm^{-1}$, $\nu_{C=N}$ 1655–1660 $cm^{-1}$. A peak of *m/e* 56 due to $[CH_3-\overset{|}{C}=N-CH_3]^+$ appeared in the mass spectra of the N-methyl ketimines.

The reaction of α-naphthylacetonitrile 13 with 2 moles of MeLi and the subsequent treatment of the resulting anion 14 with 2 moles of MeI gave the expected product



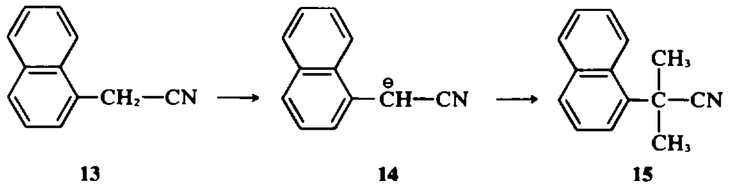


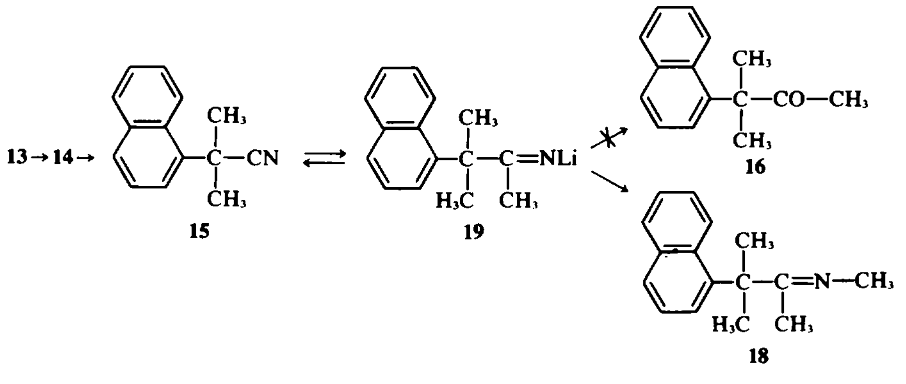
2,2-dimethyl-α-naphthylacetonenitrile **15**. However, when we have tried to react **13** with 4 moles of MeLi and 2 moles of MeI in order to synthesize the ketone **16**, no **16** was produced, but instead, α-isopropylnaphthalene **17** was obtained in an excellent yield. "Normal" behavior was observed in the reaction **13** with 4 moles of MeLi and 4 moles of MeI, where N-methyl-3-α-naphthyl-3-methylbutan-2-ketimine **18** was produced, again in high yield (Table 1).

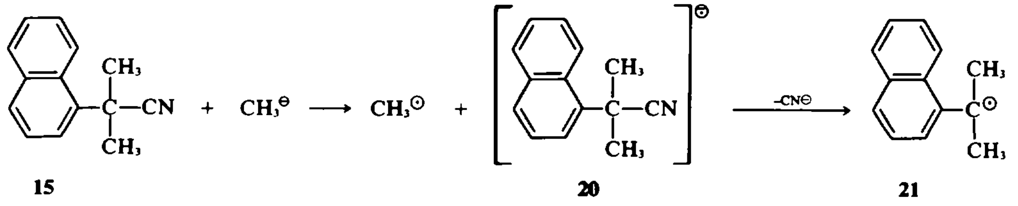
We assume that a state of equilibrium exists between **15** and the addition compound **19**,[17] in which the equilibrium lies to the left under the conditions designated to produce **16**, however, in the presence of an excess of MeI the equilibrium is shifted to the right and **18** is being formed in an irreversible reaction.

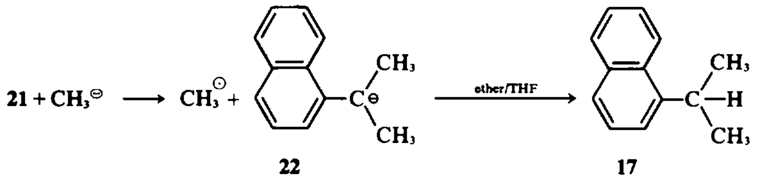
A radical anion process, which begins by donation of an electron by the methyl carbanion to **15**, is responsible for the formation of isopropylnaphthalene **17**. The radical anion **20** stabilizes itself by an expulsion of $CN^-$ to yield the radical **21**, which then reacts with a second methyl carbanion to give the anion **22**.

**22** is a tertiary carbanion and basic enough to abstract a proton from the solvent to give **17** as the final product. The last conclusion was based on the fact that **17** was already present in the reaction mixture prior to the work up; treatment of the solution with $D_2O$ did not lead to any incorporation of deuterium into the product. A similar result was also obtained from the reaction of the solution with trimethylsilyl chloride. Only few reactions describing the displacement of a cyano group from a saturated









carbon were reported, and no discussion of the mechanism given.[18-20] The cyano group which was attached to at least one phenyl was replaced by a hydrogen due to the action of sodium amide in boiling toluene,[18] xylene[18,19] or benzene.[20] We did not find any evidence for the existence of such a reaction between **9** and MeLi, in which addition to the C≡N bond was preferred; however, displacement of CN$^-$ occurred in the reaction of **15** in what we suggest to be a radical anion process. Support for the radical anion mechanism can be found in the studies of Kornblum and his coworkers,[21] who found that a facile displacement of a nitro group from the saturated carbon atom of **23** occurred in its reaction with sodiumthiophenoxide in DMF or DMSO.[21b] In another experiment a better leaving group, a chloride anion, was involved.[21a]

The initial step was an electron transfer to the unhindered $\pi$ system of **23**, and then the radical anion lost NO$_2^-$ to yield a free radical which in turn reacted with the base to form the final product **24**. In our system a similar behaviour is observed and a highly delocalized radical anion is produced in the first step by the electron transfer from the methyl carbanion to the naphthalene $\pi$ system. We have here an interesting case of a cyano group acting as a leaving group, the driving force for this unusual phenomenon being probably the generation of the planar radical **21**. In the transformation of **25** to **26** Kornblum and Boyd[22] have shown that under exactly the same experimental conditions NO$_2^-$ is a better leaving group than CN$^-$, in a process of chain reactions involving radical anion. In our study we have found a system where even a weak leaving group such as CN$^-$ can be easily displaced. After the formation of **21** the reaction proceeds in somewhat different pathway than what was found in the reaction of **23**; in a second electron transfer the carbanion **22** is being formed, which then very rapidly picks a proton from the solvent to give **17** in a high yield.

Several methods to prepare $\alpha$-isopropylnaphthalene **17** have been reported in the literature,[23] direct alkylation of naphthalene always resulted in the formation of mixture of the $\alpha$ and $\beta$ isomers,[23a,b] while in other procedures several steps were needed in order to synthesize **17**.[23c,d,e] We therefore suggest that $\alpha$-naphthylacetonetrile **13**, can serve as a good precursor to synthesize, in a high yield, pure $\alpha$-isopropylnaphthalene **17**. We are now investigating other systems where CN$^-$ can be displaced from a saturated carbon in a radical anion process.

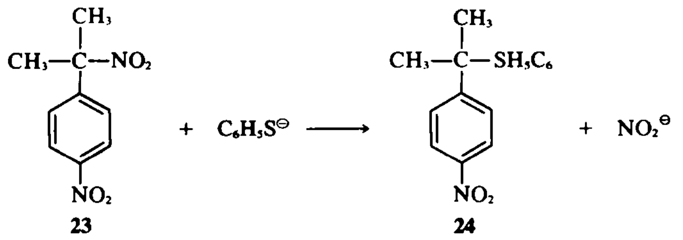
## EXPERIMENTAL

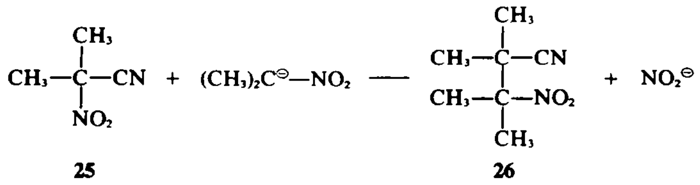
*Equipment and Materials.* The NMR spectra were recorded in CCl$_4$ on Varian HA-100 or T60 instruments, chemical shifts are given in $\delta$ units relative to TMS. The IR spectra were taken on a Perkin-Elmer Infracord 337 spectrometer, and UV spectra were recorded in ethanol solutions on a Unicam SP 800. GLC analyses were performed on a Aerograph Autoprep A90-P3 or Hewlett Packard 7620A. Mass spectra were taken on Atlas Mat CH4.

Phenylacetonitrile, $\alpha$-naphthylacetonitrile and methyliodide are commercial materials, 3-butenenitrile was obtained from allylbromide and cuprous cyanide.[33] All solvents were dried and distilled prior to their use.

### *General procedure for the metalation of the primary nitriles*

The reactions were carried out under an inert atmosphere in a round bottomed flask with a side arm stoppered by a septum. The solution of MeLi in ether (ca. 1·9M) was cooled to −100° and an equal volume of dry THF was added. The nitrile, dissolved in a little THF, was introduced slowly by way of a syringe while the mixture was shaken frequently. The solution was then allowed to reach room temperature. The metalations of 3-butenenitrile **1** and phenylacetonitrile **7** were completed within 30 min (yellow





solutions), while the metalation of α-naphthylacetonitrile **13** was completed after 120 min (dark red solution).

### *Reactions with MeI*

Before the addition of MeI the reaction mixtures were cooled in dry ice/acetone to −78°. After the introduction of MeI the solutions were left, below −40°, for 30 min. to allow the disubstitution reaction to occur and to prevent as much as possible the reaction between MeLi and MeI. Whenever addition of MeLi to the C≡N triple bond was desired the solution was allowed to reach room temperature and then stirred for another 2 h. Decomposition on cold water was followed by an extraction of the aqueous phase with ether and the organic layer was then washed with very dilute HCl solution and 2 times with water. After drying over $MgSO_4$ the organic phase was filtered and the solvent removed under vacuum. The products were purified by GLC on 1·5m, SE-30 15% on Chromosorb W, except **6** which was purified on 1·5m, DEGS 15% on Chromosorb W.

2,2-*Dimethyl*-3-*butenenitrile* **3**. NMR: 5·69/q ($J_1$ = 10) ($J_2$ = 18), 1H (vinyl); 5·35/d (J = 18), 1H (terminal methylene); 5·12/d (J = 10), 1H (terminal methylene); 1·4/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 2240\ cm^{-1}$ (C≡N), MS: $M^+$ *m/e* 95 (50%), *m/e* 80 (100%).

3,3-*Dimethyl*-1-*penten*-4-*one* **5**. NMR: 5·89/q ($J_1$ = 17) ($J_2$ = 10), 1H (vinyl); 5·08/d (J = 17), 1H (terminal methylene); 5·08/d (J = 10), 1H (terminal methylene); 2·01/s, 3H $(CH_3-\overset{|}{C}{=}O)$; 1·13/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 1710\ cm^{-1}$ $(\rangle C{=}O)$; MS: $M^+$ *m/e* 112 (13%), *m/e* 97 (28%), *m/e* 69 (100%).

*N-Methyl*-3,3-*dimethyl*-1-*penten*-4-*ketimine* **6**. NMR: 5·95/q ($J_1$ = 10) ($J_2$ = 17·5), 1H (vinyl); 5·15/d (J = 17·5), 1H (terminal methylene); 5·14/d (J = 10), 1H (terminal methylene); 3·18/s, 3H $(=N-CH_3)$; 1·27/s, 3H $(CH_3-\overset{|}{C}{=}N)$; 1·27/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 1660\ cm^{-1}$ $(\rangle C{=}N-)$. MS: $M^+$ (absent), *m/e* 110 (very small), *m/e* 56.

2,2-*Dimethylphenylacetonitrile* **9**. NMR: 7·15–7·45/m, 5H (phenyl); 1·59/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 2235\ cm^{-1}$ (C≡N). UV: $\lambda_{max}$ (nm) 253 (160), 260 (200), 266 (160). MS: $M^+$ *m/e* 145 (35%), *m/e* 140 (100%), *m/e* 103 (48%).

3-*Phenyl*-3-*methyl*-*butan*-2-*one* **11**. NMR: 7·24/s, 5H (phenyl); 1·83/s, 3H $(CH_3-\overset{|}{C}{=}O)$; 1·45/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 1710\ cm^{-1}$ $\rangle C{=}O$. UV: $\lambda_{max}$ (nm) 255 (260), 269 (290), 268 (250). MS: $M^+$ *m/e* 162 (3%), *m/e* 147 (5%), *m/e* 119 (100%).

*N-Methyl*-3-*phenyl*-3-*methyl*-*butan*-2-*ketimine* **12**. NMR: 7·14/s, 5H (phenyl); 3·06/s, 3H $(=N-CH_3)$; 1·43/s, 3H $(CH_3-\overset{|}{C}{=}N)$; 1·32/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max}$ 1658 $cm^{-1}$ $(\rangle C{=}N)$. UV: $\lambda_{max}$ (nm) 255 (360), 261 (326), 267 (227). MS: $M^+$ *m/e* 175 (3%), *m/e* 160 (1%), *m/e* 119 (8%), *m/e* 56 (100%).

2,2-*Dimethyl*-α-*naphthylacetonitrile* **15**. NMR: 8·1–7·3/m, 7H (aromatic); 2·01/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$. IR: $\bar{\nu}_{max} = 2240\ cm^{-1}$ (C≡N). UV: $\lambda_{max}$ (nm) 273 (5,700), 283 (6,900), 290 (4,550), 293 (4,550). MS: $M^+$ *m/e* 195 (60%), *m/e* 180 (100%), *m/e* 153 (73%).

α-*Isopropylnaphthalene* **17**. NMR: 8·18–7·2/m, 7H (aromatic), 3·68/7 (J = 6·8), 1H $(-C\underline{H}(CH_3)_2)$; 1·5/d (J = 6·8), 6H $((C\underline{H}_3)_2CH-)$. UV: $\lambda_{max}$ (nm) 275 (5,700), 285 (6,650), 292 (4,600), 295 (4,400). MS: $M^+$ *m/e* 170 (40%), *m/e* 155 (100%).

*N-Methyl*-3-α-*naphthyl*-3-*methyl*-*butan*-2-*ketimine* **18**. NMR: 8·5–7·35/m, 7H (aromatic); 3·4/s, 3H $(=N-CH_3)$; 1·82/s, 6H $(CH_3-\overset{|}{\underset{|}{C}}-CH_3)$; 1·65/s, 3H $(CH_3-\overset{|}{C}{=}N)$. IR: $\bar{\nu}_{max} = 1655\ cm^{-1}$ $(\rangle C{=}N)$. UV: $\lambda_{max}$ (nm) 274 (3,500), 284 (4,180), 292 (2,950), 295 (3,000). MS: $M^+$ *m/e* 225 (40%), *m/e* 210 (15%), *m/e* 56 (100%).

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