

# Investigation of the mechanism of decyanation of 2,2-diphenylpropionitrile induced by LiAlH<sub>4</sub>

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**ABSTRACT:** The LiAlH<sub>4</sub> reduction of 2,2-diphenylpropionitrile (**4**) in THF yields a mixture of the hydrocarbon **6** and the expected amine **5**. Medium effects and reduction with LiAlD<sub>4</sub> suggest a mechanism involving the attack of the hydride reagent on the cyano carbon atom followed by the fragmentation of the formed imine salt intermediate. Copyright © 2000 John Wiley & Sons, Ltd.

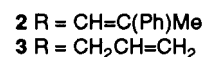
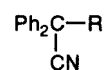
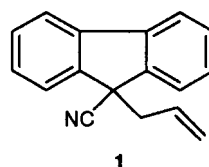
**KEYWORDS:** decyanation; diphenylacetonitriles; lithium aluminum hydride; medium effects; carbanions

## INTRODUCTION

The reductive decyanation of nitriles has been reported under a variety of conditions. Different mechanisms operate depending on the reducing agent used: electron transfer (alkali metals),<sup>1</sup> radical chain (Bu<sub>3</sub>SnH, SmI<sub>2</sub>)<sup>2,3</sup> and a polar mechanism (RLi, RMgX).<sup>4–6</sup> For the reductive decyanation of  $\alpha$ -aminonitriles with LiAlH<sub>4</sub>,<sup>7,8</sup> an S<sub>N</sub>1 mechanism with assistance of the amino group and formation of an iminium ion intermediate was proposed. The decyanation is also observed under more drastic conditions with KOH,<sup>9</sup> NaOH<sup>10</sup> or NaNH<sub>2</sub>.<sup>11</sup>

We previously reported, together with the usual formation of amine,<sup>12</sup> the first cleavage of an  $\alpha$ -sulfonyl nitrile induced by LiAlH<sub>4</sub> and presented evidence to support the participation of radical intermediates.<sup>13</sup> The  $\alpha$ -sulfonyl group is not compulsory to observe this type of reactivity<sup>14</sup> [in Ref. 14, the relative yields of amine and hydrocarbon (23 and 58%) should be inverted]. Black and Doyle found that the treatment of 9-allylfluorene-9-carbonitrile (**1**) and 2,2,4-triphenylpent-3-enitrile (**2**) with LiAlH<sub>4</sub> in Et<sub>2</sub>O yields the decyanation product together with the expected amine (Table 1, entries 1 and 2). In contrast, no decyanation was observed in reactions of 2,2-diphenylpent-4-enitrile (**3**) and similar compounds (Table 1, Entry 3).<sup>15</sup>

The authors proposed an attack on the cyano group followed by elimination of a hydrogen cyanide complex and formation of a carbanion: the nitriles yielding the decyanation product are usually precursors of the most stabilized carbanions (Scheme 1). In Scheme 1, the structure of the imine salt intermediate could be more



complex because its decomposition could occur after the nucleophilic attack by another hydride ion. Two of the four hydrides are readily available.<sup>16</sup>

**Table 1.** Reaction of nitriles 1–4 with LiAlH<sub>4</sub>

Entry	Nitrile	Conditions	Relative yield (%) <sup>b</sup>	
			Amine	Hydrocarbon
1	<b>1</b>	Slurry, Et <sub>2</sub> O <sup>a</sup>	33	67
2	<b>2</b>	Slurry, Et <sub>2</sub> O <sup>a</sup>	25	75
3	<b>3</b>	Slurry, Et <sub>2</sub> O <sup>a</sup>	100	
4	<b>4</b>	Slurry, THF <sup>c</sup>	71	29
5	<b>4</b>	Slurry, Et <sub>2</sub> O	100	
6	<b>4</b>	Solution, THF <sup>d</sup>	51	49
7	<b>4</b>	Slurry, Et <sub>2</sub> O–HMPA <sup>e</sup> (90:10, v/v)	48	52
8	<b>4</b>	LiAlD <sub>4</sub> , slurry, THF <sup>f</sup>	45	37 (100% D)
9	<b>4</b>	Slurry, THF, degassed <sup>g</sup>	69	31
10	<b>4</b>	Solution, THF, degassed <sup>d,g,h</sup>	57	43

<sup>a</sup> See Ref. 15.

<sup>b</sup> Estimated from <sup>1</sup>H NMR (200 or 400 MHz) of the crude product.

<sup>c</sup> All reductions carried out were 0.14–0.16 M in nitrile **4** using 3.5–3.8 equiv. of LiAlH<sub>4</sub>. The reaction time was 24 h.

<sup>d</sup> Solutions of LiAlH<sub>4</sub> prepared as described by Krishnamurthy and Brown<sup>24</sup> or purchased directly from Aldrich were used.

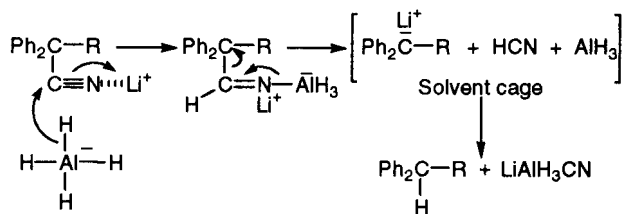
<sup>e</sup> The reaction time was 66 h, the excess of LiAlH<sub>4</sub> was 2.2 equiv. and 43% of the nitrile did not react.

<sup>f</sup> Isolated yields.

<sup>g</sup> Degassed by three or four freeze–pump–thaw cycles and using an atmosphere of purified argon.

<sup>h</sup> 4 equiv. of LiAlH<sub>4</sub> were used.

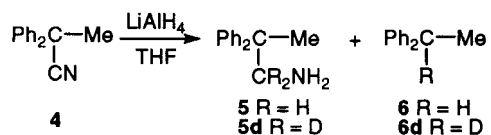
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Scheme 1

Such a mechanism was also proposed for the reductive decyanation promoted by Grignard reagents<sup>6</sup> and by alkali fusion.<sup>9</sup> Phenyl or alkyl cyanides and potassium cyanate, respectively, were trapped in these reductions. (The participation of an  $S_N2$  reaction at the  $sp$  carbon has also been proposed for these decyanations.<sup>17</sup> Gregory *et al.*<sup>4</sup> suggested a four-membered transition state for the decyanation of several 1-benzyl-1-cyano-1,2,3,4-tetrahydronaphthalenes with lithium reagents). In such decyanations the carbon atom bearing the cyano group is substituted by two phenyl groups. Thus, 2,2-diphenylpropionitrile and 2-methyl-2-phenylpropionitrile react with phenyldimethylsilyllithium to give the substitution product with 17% and 77% yields, respectively.<sup>18</sup> Although no mechanistic study was undertaken, the authors proposed an attack on the cyano group followed by the displacement of the cumyl anion and subsequent silylation by the silyl cyanide.

We observed that when 2,2-diphenylpropionitrile (**4**) was reduced with  $LiAlH_4$  in THF, a mixture of the amine **5** and hydrocarbon **6** was formed (Scheme 2; Table 1, entry 4). We discuss here, in addition to the pathway described in Scheme 1, the different mechanisms that could be involved in this transformation taking into account medium effects, experiments with  $LiAlD_4$  and the effect of dioxygen.



Scheme 2

## RESULTS AND DISCUSSION

### The polar pathway

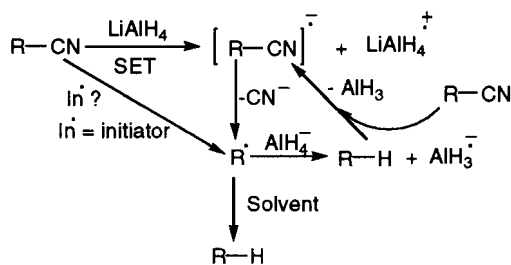
It is surprising that the nitrile **4** exhibits such a reactivity in THF whereas 2,2-diphenylpent-4-enitrile (**3**), a very closely related substrate, does not in  $Et_2O$ . A solvent effect seems to operate here. Indeed, when 2,2-diphenylpropionitrile (**4**) was reduced with  $LiAlH_4$  in  $Et_2O$ , no decyanation product was formed, in agreement with Black and Doyle's observations (Table 1, entry 5). In this field, Nagai and Hirata, using 0.3 equiv. of  $LiAlH_4$  in

refluxing  $Et_2O$  (clear solution), reduced **4** to 2,2-diphenylpropionaldehyde with a 72% isolated yield.<sup>19</sup> The reaction of nitrile **4** with 2.2 equiv. of  $LiAlH_4$  in  $Et_2O$ -HMPA (90:10, v/v) for 66 h gave similar yields of **5** and **6** (Table 1, entry 7). The conversion of **4** was about 57%. For comparison, **4** was totally consumed when the reaction was run in  $Et_2O$  with 1.5 equiv. of  $LiAlH_4$  for 42 h. Part of the crude product was treated with 2 M HCl for 1 h in order to convert the eventual imine into 2,2-diphenylpropionaldehyde. From GC and NMR analysis the relative yield of aldehyde was estimated to be <1%.

The  $LiAlD_4$  reduction of nitrile **4** in THF led to the formation of deuteriated hydrocarbon **6d** (Table 1, entry 8). The  $^1H$  NMR spectrum of the crude product shows a total absence of the quadruplet at  $\delta = 4.14$  ppm. Quantitative deuteration would agree with an  $S_N2$  pathway. Carbons bearing two or three aryl groups ( $Ar_2CHX$  or  $Ar_3CX$ ,  $X =$  leaving group) exhibit a great reactivity toward the  $S_N2$  and  $S_N1$  processes.<sup>20</sup> On the other hand, the cyano group can act as a leaving group. We mentioned above the reductive decyanation of  $\alpha$ -aminonitriles with the hydride ion via an  $S_N1$  polar pathway.<sup>7,8</sup> In the  $LiAlH_4$  reduction of nitrile **4**, an  $S_N2$  process seems unlikely, however, since (1) the cyano group has a poor leaving ability and (2) the attacked  $sp^3$  carbon would be sterically hindered both by the methyl and the two phenyl substituents.

Solvent and additive effects fit better with the mechanism described in Scheme 1. In ethereal solvents  $LiAlH_4$  is thought to react as an ion pair.<sup>21,22</sup> In  $Et_2O$ , the lithium ion is less solvated than in THF (steric effects) and could stabilize the imine salt intermediate, hence preventing the expulsion of a carbanion. Another way to modulate the participation of  $Li^+$  in the reaction is to add HMPA, a powerful dissociating and basic solvent.<sup>23</sup> With HMPA, the complexation of the nitrile group with the lithium ion would be diminished and the reactivity of **4** would decrease in the absence of electrophilic assistance. Moreover, the imine salt intermediate, not being stabilized by the lithium cation, would see its fragmentation favored. The steric hindrance of the nitrile group of **4** probably favors the first addition of hydride over the second, leading to an increased ability of the intermediate to expulse a carbanion.<sup>16</sup>

The observed deuterium incorporation is consistent with an internal hydride capture: as soon as the carbanion is formed, it could react with hydrogen cyanide (or deuterium cyanide) in a solvent cage leading to **6d**. Clear solutions of  $LiAlH_4$  favored the decyanation over the amine formation (Table 1, entries 6 and 10). Krishnamurthy and Brown<sup>24</sup> observed that clear solutions are more reactive than slurries toward the nucleophilic substitution of halides. They proposed that insoluble impurities might coat the undissolved  $LiAlH_4$  and hinder its reactivity. We suggest that some metallic impurities could complex the imine salt intermediate and prevent the formation of a carbanion.



Scheme 3

### The radical pathway

There are several precedents of reductions involving simultaneously radical and polar pathways. Ashby and Welder reported evidence suggesting the coexistence of the  $S_N2$  and SET routes in the reaction of alkyl iodides with  $\text{LiAlD}_4$ .<sup>25,26</sup> Such a proposition, applied to **4**, is described in Scheme 3. It is therefore necessary to examine more closely the characteristics of this reaction which could hint at a radical participation. If free radicals were involved, we would expect some hydrogen atom incorporation during the  $\text{LiAlD}_4$  reduction, the radical competitively abstracting a hydrogen atom from the metal hydride and from the solvent. Indeed, Newcomb suggested that hydrogen abstraction from  $\text{LiAlH}_4$  is at least one order of magnitude slower than that from THF.<sup>27</sup> In the reduction of **4**, no hydrogen atom incorporation was observed when only 1.3 equiv. of  $\text{LiAlD}_4$  was used.

Recently, a SET was proposed in an anomalous reductive decyanation of  $\alpha$ -tosyloxy- $\alpha$ -(trifluoromethyl)-phenylacetone nitrile with  $\text{NaBH}_4$ .<sup>28</sup> Ebersson estimated the standard potential of  $\text{AlH}_4^-/\text{AlH}_4$  redox couple as  $E^\circ_{\text{ox}} = -(0.1-0.3 \text{ V})$  vs NHE in THF.<sup>29</sup> House discussed possible electron transfer between carbanions and unsaturated carbonyl compounds in terms of the difference in standard electrode potentials. He concluded, that for  $E^\circ_{\text{red}} - E^\circ_{\text{ox}}$  more positive than  $-0.4 \text{ V}$  (equivalent to  $\Delta G^\circ < 9.2 \text{ kcal mol}^{-1}$ ) electron transfer would be feasible.<sup>30</sup> House's rule, applied to our system, taking  $E^\circ_{\text{ox}} = -0.3 \text{ V}$ , the electron transfer from the hydride ion to the nitrile **4** would be possible if  $E^\circ_{\text{red}}$  of **4** was more positive than  $-0.7 \text{ V}$ . The reduction potential of diphenylacetone nitrile, a substrate closely related to **4**, is  $E^\circ_{\text{red}} = -1.82 \text{ V}$  (vs SCE,  $\text{CH}_3\text{CN}$ ,  $-1.58 \text{ V}$  vs NHE).<sup>31</sup> Thus nitrile **4** is, by itself, not sufficiently oxidizing and participation of a SET route seems unlikely. One must underline, however, the limits of such a kind of argument because salts effects may drastically modify the redox relationship in the donor-acceptor couple.<sup>32,33</sup> An electron transfer could also occur from  $\text{AlH}_3^-$  formed in situ leading to a radical chain pathway (Scheme 3). We have calculated HOMO energies and ionization potentials of both  $\text{AlH}_4^-/\text{AlH}_4$  and  $\text{AlH}_3^-/\text{AlH}_3$  couples.  $\text{AlH}_3^-$  ( $E_{\text{HOMO}} = 2.028 \text{ eV}$ ,  $\text{IP} = 0.385 \text{ eV}$ ) appears to be

a better reducing agent than  $\text{AlH}_4^-$  ( $E_{\text{HOMO}} = -1.182 \text{ eV}$ ,  $\text{IP} = 4.225 \text{ eV}$ ).<sup>34</sup> We proposed such a possibility for the  $\text{LiAlH}_4$  reduction of a *gem*-disubstituted cyclopropyl bromide.<sup>35</sup> This reduction was observed only under strictly anaerobic conditions, dioxygen being an extremely efficient scavenger of the chain. We therefore carried out the reduction under strictly anaerobic conditions (entries 9 and 10). The yield of hydrocarbon **6** did not significantly change, hence the chain proposed for the disubstituted bromide does not seem to apply here. (We have noticed that when the reaction was performed in a Schlenk tube connected to a balloon filled with nitrogen, up to 19% of 1,1-diphenylethanol can be formed in the medium.<sup>36</sup> We verified that the alcohol was produced from dioxygen which can diffuse into the balloon. The origin of 1,1-diphenylethanol has not been clearly established but is consistent with the proposed mechanism since the reaction of carbanions with dioxygen is very fast<sup>37</sup>). In an attempt to trap a radical intermediate, we have introduced the hex-5-enyl group as radical probe and reduced 2,2-diphenylhept-6-enenitrile with  $\text{LiAlH}_4$  in THF under usual conditions. No cyclized hydrocarbon was formed (<1%).

### CONCLUSION

We suggest that the nucleophilic attack of the hydride reagent on the nitrile group followed by the formation of a carbanion is the major pathway for the decyanation of 2,2-diphenylpropionitrile induced by  $\text{LiAlH}_4$ . From literature data, nitriles bearing two phenyl groups on the  $\alpha$ -position readily give C—CN bond cleavage in the presence of  $\text{LiAlH}_4$  but also with Grignard reagents or sodium amide. These groups stabilize the carbanionic intermediate and weaken the C—C bond. Such a reactivity is reminiscent of the so-called 'cyanophilic' reaction which involves the reaction of tetracyanomethane with phenolates and thiophenolates to give aryl cyanates and thiocyanates, respectively.<sup>38,39</sup>

### EXPERIMENTAL

*General.*  $\text{Et}_2\text{O}$ , THF and HMPA were dried over sodium and then distilled. Glassware was oven-dried prior to use. Product mixtures were analyzed by gas chromatography (GC) and by integration of the  $^1\text{H}$  NMR spectrum (200 or 400 MHz). GC (30 m DB1 column or 25 m BPX5 column) was performed on a Fisons 8000 Series apparatus equipped with a flame ionization detector. Analysis by GC: column temperature,  $150^\circ\text{C}$  for 3 min, increased at  $5^\circ\text{C min}^{-1}$  to  $240^\circ\text{C}$ , held for 10 min; injector temperature,  $300^\circ\text{C}$ ; detector temperature,  $280^\circ\text{C}$ ; vector gas, helium. Gas chromatography coupled with mass spectrometry (GC-MS) was performed on a

Ribermag R 10.10C system (vector gas, helium; tension acceleration, 70 eV; injector, 300°C; interface, 300°C; source, 150°C).

*General procedure for heterogeneous LiAlH<sub>4</sub> reductions.* A Schlenk tube containing LiAlH<sub>4</sub> (Fluka, >97%, 0.483 g, 12.7 mmol) was purged with nitrogen and THF (16.2 ml) was added. The nitrile **4** (Aldrich, 97%, 0.760 g, 3.56 mmol) in THF (7.8 ml) was then transferred into this heterogeneous slurry. The mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. Then, with stirring and cooling, water (0.4 ml), a 20% solution of NaOH (0.4 ml), water (0.7 ml) and MgSO<sub>4</sub> were added in succession. After filtration the residue was washed with THF and the solvent carefully distilled. Chromatography on silica gel (elution: light petroleum) afforded **6** (27% isolated yield).<sup>40</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.63 (d, *J* = 7.2 Hz, 3 H), 4.14 (q, *J* = 7.2 Hz, 1 H), 7.10–7.34 (m, 10 H). GC–MS analysis was consistent with data described in the literature. C<sub>14</sub>H<sub>14</sub> (182.27): calculated C 92.26, H, 7.74; found: C 92.30, H 7.53%. Further elution with ethyl acetate and 20% ethanol in ethyl acetate gave **5** (52% isolated yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.53 (s, 2 H), 1.68 (s, 3H), 3.32 (s, 2 H), 7.13–7.36 (m, 10 H). GC–MS (70 eV): *m/z* (%) 211 (1.9) (M<sup>+</sup>), 181 (17.0), 103 (14.5), 44 (27.8), 30 (100.0). C<sub>15</sub>H<sub>17</sub>N (211.14): calculated C 85.26, H 8.11, N 6.63; found C 83.39, H 8.36, N 6.65%. Under these conditions, the conversion of nitrile **4** was always better than 95%. The mass balance was about 95%. The agreement between NMR analysis (relative yields **6:5** = 29:71) and yields of isolated products was within ±5%.

*1,1-Diphenyl-1-deuterioethane (6d) and 2,2-diphenyl-1,1-dideuteriopropylamine (5d).* The nitrile **4** (0.201 g, 0.94 mmol) in THF (2 ml) was added to an heterogeneous slurry of LiAlD<sub>4</sub> (Fluka, D ≥ 99%, 0.150 g, 3.57 mmol) in THF (4.2 ml). After the usual work-up and chromatography on silica gel (light petroleum as eluent), deuteriated hydrocarbon **6d** was isolated (37% yield). GC–MS (70 eV): *m/z* (%) 183 (42.1) (M<sup>+</sup>), 168 (100.0), 166 (29.9), 153 (13.7). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.63 (s, 3 H), 7.10–7.34 (m, 10 H). Further elution with 20% ethanol in ethyl acetate gave **5d** (45% isolated yield). GC–MS (70 eV): *m/z* (%) 213 (2.1) (M<sup>+</sup>), 181 (40.6), 165 (23.5), 103 (17.5), 77 (15.8), 32 (100.0). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 1.45 (s, 2H), 1.67 (s, 3 H), 7.05–7.36 (m, 10 H).

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