

The reductive decyanation reaction : chemical methods and synthetic applications

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Dedicated to Prof. A. Lattes

Abstract

Several sequences involving the nitrile group require the removal of this function in a convenient and clean procedure. This transformation, called reductive decyanation, has received much attention over the years. In this review, we describe the chemical methods leading to reductive decyanation as well as the proposed mechanisms. Much of these methodologies proceed with good yields and stereoselectivities allowing their exploitation in organic synthesis.

Keywords : Nitrile, reductive decyanation, synthesis, alkali metals, metal hydrides

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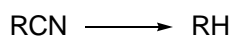
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Introduction

The use of the nitrile function for C-C bond formation reaction occupies an important position in organic chemistry.¹⁻⁴ Especially, deprotonation of the α -carbon and alkylation is an important reaction.⁵ The sequences involving the nitrile function usually requires the subsequent removal of the nitrile group in a convenient and clean manner. The reduction of the nitrile group (RCN) is observed with many reducing agents. Depending on the nature of the reducing agent and experimental conditions, the reaction can produce amines, aldehydes, primary alcohol, imines or alkanes (RCH₃ or RH).⁶ The latter transformation, described in Scheme 1, is called reductive decyanation.



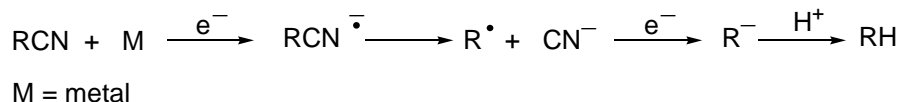
Scheme 1

In 1991, we discovered the anomalous reductive decyanation of a α -sulfonitrile induced by LiAlH₄.⁷ We were then interested in the great variety of procedures allowing this transformation. We realized that, despite a large use of this reduction in organic synthesis these last years, no recent review focused on this topic.

This paper provides an overview of the different routes leading to decyanation. For each of them, experimental conditions and mechanistic aspects will be described. We describe also recent applications in organic synthesis. The purpose of this work is to point out the utility of this reaction through a set of examples. We concentrate on reductive decyanation of nitriles and will not discuss dehydrocyanation,⁸ oxidative decyanation⁹ or reactivity of cyanamides.¹⁰

1. Metal dissolving conditions

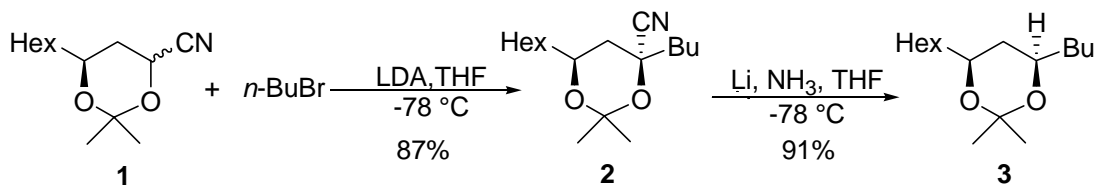
Arapakos *et al.* using sodium biphenyl radical anion, sodium in liquid ammonia or lithium-ethylamine solutions found that tertiary nitriles give reductive decyanation products in high yields.¹¹⁻¹³ The mechanism proposed involves a two electrons transfer with formation of a carbanion via a radical anion. The latter is then protonated by ammonia *in situ* or by another proton donor depending on the reaction conditions (Scheme 2).^{11,14-16}



Scheme 2

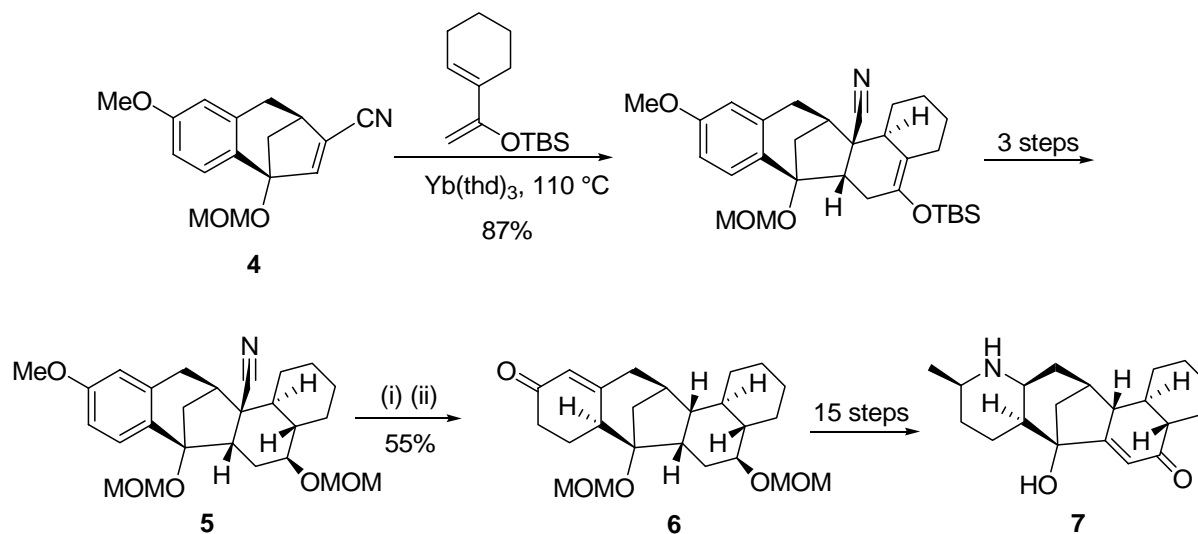
From the mechanism described above, the stereochemical outcome of these reductions should depend on the behavior of radical and carbanion intermediates as well as on the approach of the proton or, possibly, an hydrogen atom donor. More specific studies show that experimental conditions, additives, nature of the metal play an important role.^{14,15,17,18} Good stereoselectivities are obtained in many cases.

The Li or Na/NH₃ system has been widely used in organic synthesis.¹⁹⁻²⁷ Rychnovsky investigated the alkylation and reductive decyanation of cyanohydrin acetonides such as **1** (Scheme 3).²⁸ The latter are key intermediates in the synthesis of polyene macrolide antibiotics such as roflamycoin,²⁹ 17-deoxyroflamycoin³⁰ or filipin III.³¹ The observed stereochemistry reflects the configuration preference for an axial anomeric radical. The resulting axial carbanion is then protonated with retention of configuration.³² *Ab initio* calculations are consistent with this stereochemical outcome.³³



Scheme 3

During the synthesis of the Galbulimima alkaloid GB 13 **7**, the nitrile group appears as a dienophile activating group in **4** and is removed from **5** with lithium in NH₃/THF. Addition of ethanol resulted in the Birch reduction of the aromatic ring (Scheme 4).³⁴



(i) Li, NH₃, THF, -78 °C \longrightarrow -33 °C and then EtOH.

(ii) HCl, MeOH, THF.

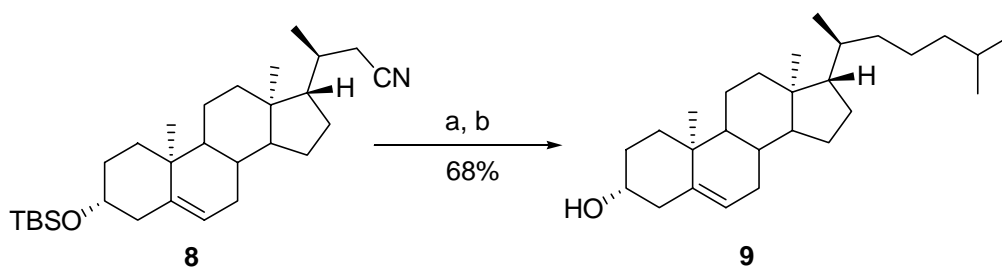
MOM = methoxymethyl;

Yb(thd)₃ = ytterbium tris(2,2,6,6-tetramethyl-3,5-heptane-dionate)

OTBS = *tert*-butyldimethylsilyloxy

Scheme 4

The drawback of such reaction conditions is that primary and secondary nitriles give the expected amine as well as decyanation products.^{11,12,35} Several methods were developed to improve the yields. It is possible to break the C-CN bond in good yields in HMPA (hexamethylphosphoramide) with K in the presence of *tert*-butyl alcohol as protic cosolvent³⁶⁻³⁸ or with high-surface-area potassium on neutral alumina (K/Al₂O₃) in hexane.³⁹ The radical anion generated from potassium metal/dicyclohexano-18-crown-6/toluene system is also highly effective for the reductive decyanation of primary, secondary and tertiary cyanides.^{40,41} This method was used in the preparation of *ent*-cholesterol **9** after alkylation at the α -carbon (Scheme 5).⁴²

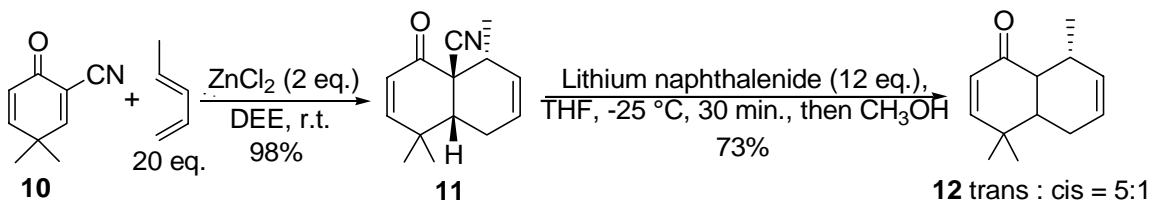


(a) LDA, THF, -78 °C; BrCH₂CH₂CH(CH₃)₂.

(b) (i) K, dicyclohexyl-18-crown-6, toluene, 5.5 h.; (ii) Bu₄NF, THF.

Scheme 5

The cyano group appears to be a good activating group for dienophiles like 4,4-disubstituted 2-cyano-2,5-cyclohexadienones. Lithium naphthalene was used as electron donor to remove the cyano group of Diels-Alder adducts providing an approach to the angularly substituted *cis*-decalin system.⁴³ Scheme 6 describes the reaction of cyclohexanone **10** with penta-1,3-diene. The reduction of adduct **11** with lithium naphthalene followed by protonation using methanol gives **12**.



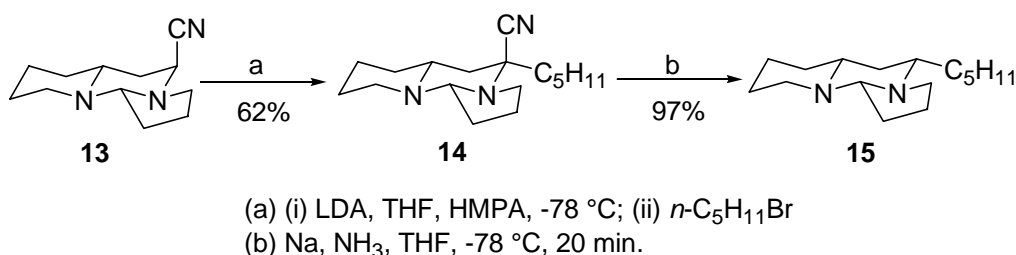
Scheme 6

It is noteworthy that the ensuing organolithium can be trapped, in the absence of a proton source, by an alkylating agent. In the same way, the reaction of different nitriles with lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (LiDBB : lithium di-*tert*-butylbiphenylide) in THF at low temperature (-30 or -78 °C) generates an organolithium intermediate resulting from a reductive decyanation. In the presence of an electrophile (Barbier-type reaction conditions), the coupling product is obtained.⁴⁴ A previous review focused on such non-deprotonating methodologies for obtaining organolithium reagents starting from non-halogenated materials.⁴⁵ Recently Rychnovsky *et al.* have investigated the reductive spiroannulation of nitriles using LiDBB in THF at low temperatures.⁴⁶⁻⁴⁸

The reduction of α -aminonitriles with metallic borohydrides leads to decyanation and proceeds through dissociation to iminium and cyanide ions (see section 2-1). Yamada *et al.* investigated the reductive decyanation of α -aminonitriles with sodium in liquid ammonia-THF.⁴⁹ In this case, the hydride reduction was unsuccessful probably due to the failure to form the corresponding iminium ion. The mechanism of decyanation of α -aminonitriles with alkali metals

is probably similar to the one described in Scheme 2 and does not involve an iminium ion. Initial electron transfer leads to a radical anion followed by C-CN bond cleavage and formation of a radical. Further reduction of the latter affords an α -amino carbanion.⁵⁰⁻⁵² Both α -amino radicals⁵³ and carbanions were trapped by intramolecular cyclisation.^{54,55}

Studies have shown that reductive decyanation of α -aminonitriles proceeds with retention of configuration⁵⁶⁻⁶⁰ or leads to the thermodynamically favored product.^{52,61} The decyanation of α -aminonitriles with the Na/NH₃ system was used to perform the decyanation of 2-oxoazetidine-4-carbonitriles⁶² or during the asymmetric synthesis of natural ant defense alkaloids.^{60,63,64} Scheme 7 describes the two last steps of the preparation of (+)-tetraponerine-8 **15**. Alkylation of the α -aminonitrile **13** leads to a single isomer **14**. The stereoselective decyanation using sodium in liquid ammonia yields exclusively *all-cis* tetraponerine-8 **15**.

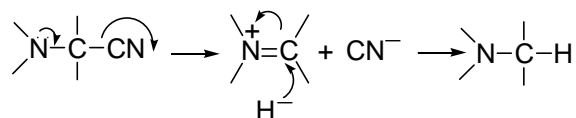


Scheme 7

2. Alumino- and borohydrides

2.1 α -Aminonitriles

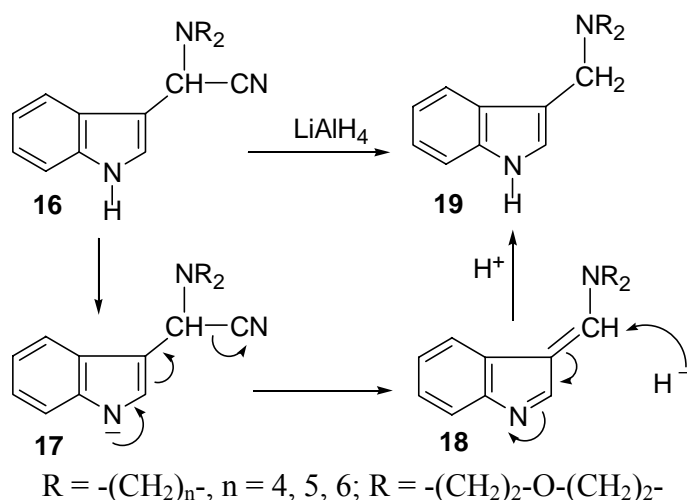
α -Aminonitriles are transformed into amino derivatives by reductive decyanation using alumino- and borohydrides.^{57,65-72} The mechanism is a S_N1 process with formation of an iminium ion followed by an addition of the hydride ion (Scheme 8).⁷³ Several facts support this mechanism. The LiAlD₄ reduction leads to the α -deuterated amine. Formation of the iminium ions favors also the decyanation over the reduction to primary amine. So Lewis acids, such as AlCl₃, are able to promote decyanation in unfavorable cases.⁷³ Moreover, the decyanation pathway is favored with disubstituted α -aminonitriles.⁷⁴



Scheme 8

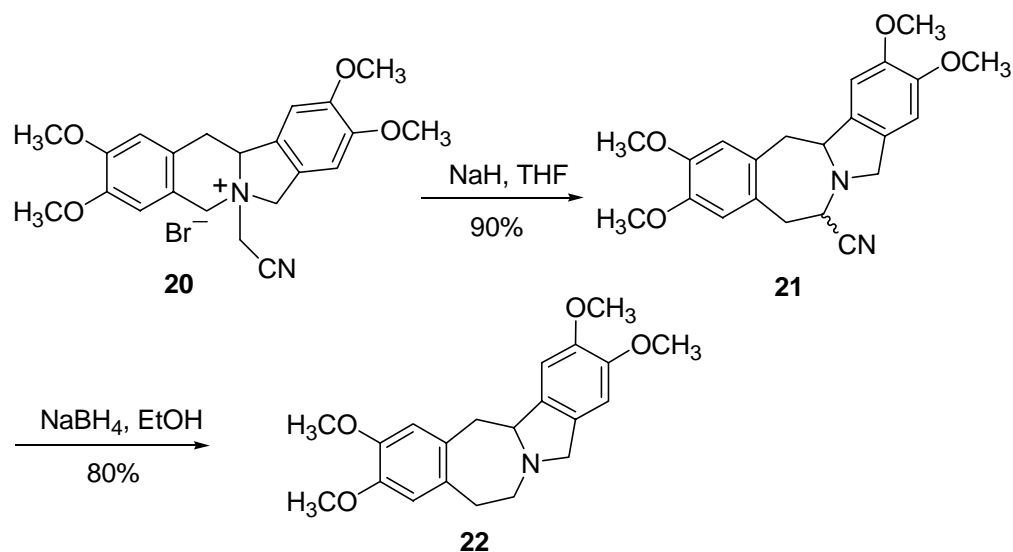
The reaction product also depends on the stereoelectronic effects and the strain of the molecule.^{73,75} So the stereoelectronic effects are expected to favor the decyanation process when the nitrile group is antiparallel to the lone-pair electrons of nitrogen.⁷⁶

An anomalous decyanation of monosubstituted nitrile **16** has been observed (Scheme 9).⁷⁷ Anion **17** is first formed and expels the cyanide ion. The resulting intermediate **18** is then reduced to the decyanation product **19**. Excellent yields are obtained. When the H atom borne by the nitrogen is replaced by a methyl group the expected primary amine is obtained.



Scheme 9

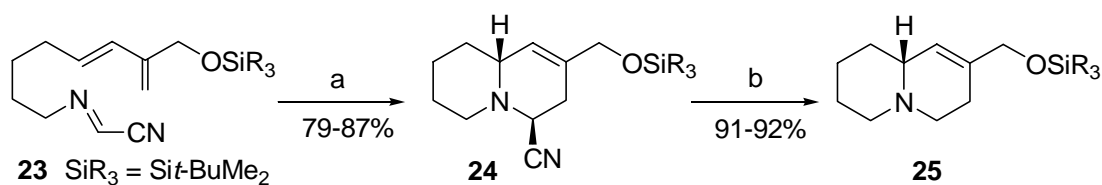
Liu and Liang used the Stevens rearrangement for ring enlargement and reductive decyanation to prepare benzazepine derivatives such as **22**.⁷⁸ Cyanomethyl quaternary ammonium salt **20** undergoes ring enlargement and affords **21** as a mixture of diastereoisomers (*syn* : *trans* = 9 : 1). They are then reduced with NaBH_4 in ethanol to give **22**.



Scheme 10

α -Aminonitriles can also be decyanated with other hydride donors such as $\text{AgBF}_4/\text{Zn}(\text{BH}_4)_2$,^{58,79,80} BH_3 ⁸¹ or NaBH_3CN .^{82,83} Sassaman used a system containing NaBH_3CN - $\text{Hg}(\text{TFA})_2$ - DABCO to prepare secondary and tertiary amines from α -aminonitriles. Here Hg^{2+} ions favor the formation of the iminium intermediate. DABCO decreases the rate of mercury II reduction and prevents polyalkylation of secondary amines.⁸⁴ Fe^{2+} ions are equally effective in accelerating the elimination of the cyano group in α -aminonitriles. They, therefore, promote the reduction with NaBH_3CN .⁸³

Amos *et al.* examined the Diels-Alder reaction of iminoacetone nitriles, a class of electron-deficient imines such as **23**. The reduction of cycloadduct **24** with NaBH_3CN affords quinolizidine **25** in a good yield (Scheme 11).⁸⁵



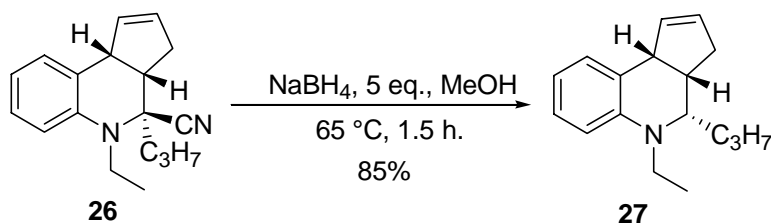
(a) Toluene, 120 °C, BHT (3 eq.), 14 h.

(b) NaBH_3CN (6 eq.), AcOH (12 eq.), CH_3CN , r.t., 22 h.

Scheme 11

The reductive decyanation of α -aminonitriles by hydrides is stereoelectronically controlled⁸⁶ and proceeds with a high stereoselectivity.^{58,79,80,87-89} For instance the reduction of

substituted α -aminonitrile **26** led exclusively to cyclopenta[*c*]quinoline derivative **27** (Scheme 12).⁹⁰

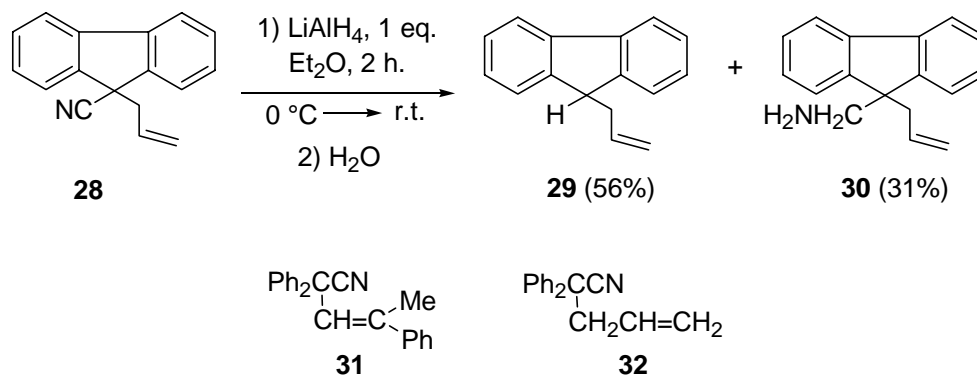


Scheme 12

It is important to notice that α -aminonitriles appears as “masked” iminium ions and the reaction of Grignard reagents appears as a valuable method for carbon – carbon bond formation (Bruylants reaction).⁹¹ This method has been widely used in organic synthesis.^{63,75,85,88,89}

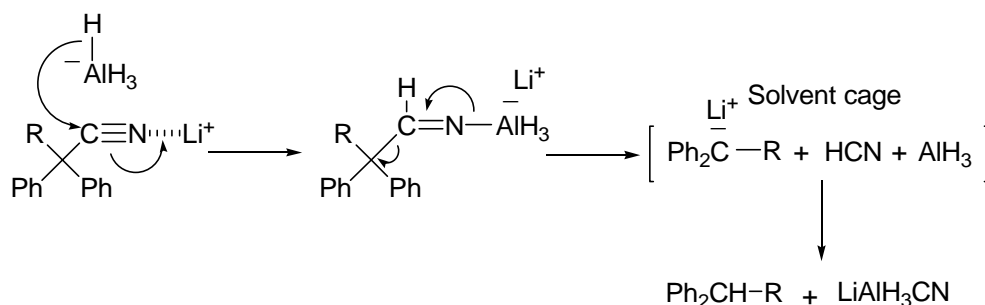
2.2 Other cases

Alumino- and borohydrides promote reductive decyanation for substrates other than α -aminonitriles. Potassium hydride was also described but the yield obtained was poor.⁹² Black and Doyle found that the treatment of 9-allylfluorene-9-carbonitrile **28** and 2,2,4-triphenylpent-3-enitrile **31** with LiAlH_4 in Et_2O (slurry) yield the decyanation product together with the expected amine (Scheme 13).



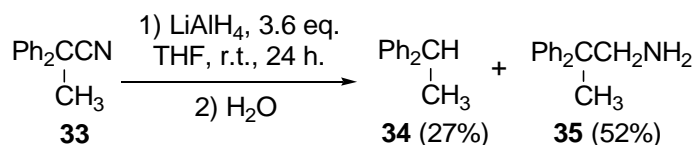
Scheme 13

In contrast, no decyanation was observed in reactions of 2,2-diphenylpent-4-enitrile **32** and similar compounds.⁹³ 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. No mechanism was proposed,⁹³ Scheme 14 could account for the reported products:



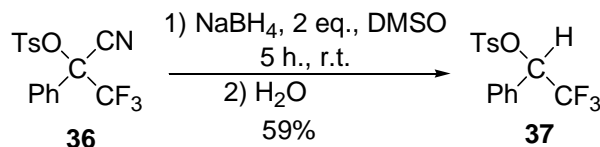
Scheme 14

We investigated the LiAlH_4 reduction of 2,2-diphenylpropionitrile **33** (Scheme 15).⁹⁴ The solvents THF or HMPA favor the decyanation process in comparison with Et_2O . We suggested that, in Et_2O , the imine salt intermediate is stabilized by the cation Li^+ while in more basic and dissociative medium the C-C bond cleavage is favored. The LiAlD_4 reduction leads to the deuterated hydrocarbon and could be consistent with an “internal” protonation in a solvent cage. There was no evidence for radical intermediates in this reaction. We deduced that our observations were consistent with the mechanism proposed by Black and Doyle. However a S_N pathway cannot be totally excluded since carbon atoms bearing two or three aryl groups exhibit a great reactivity toward the $\text{S}_\text{N}1$ and $\text{S}_\text{N}2$ processes.⁹⁵



Scheme 15

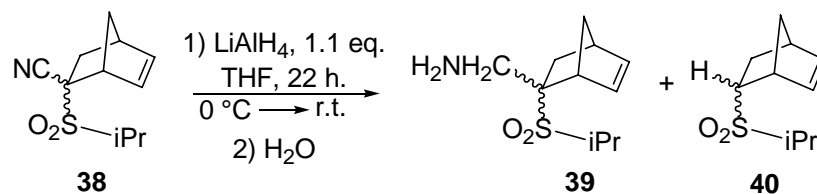
An anomalous reduction of α -tosyloxy- α -(trifluoromethyl)phenylacetonitrile **36** with NaBH_4 in DMSO was described by Németh *et al.*⁹⁶ Since S_N was disfavored by steric ($\text{S}_\text{N}2$) and electronic ($\text{S}_\text{N}1$) factors, the authors proposed a single electron-transfer (SET) process (Scheme 16).



Scheme 16

In 1991 we described the first experimental evidence for C-C bond cleavage of a α -sulfonitrile induced by LiAlH_4 in THF (slurry).⁷ Starting from 2-

(isopropylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile **38**, a mixture of the expected amine **39** and the decyanated product **40** was obtained in an approximate 1-1 ratio (Scheme 17). The mass balance was 88%. The stereochemical outcome of this reaction was uncertain since inconsistent results were obtained from this point of view.



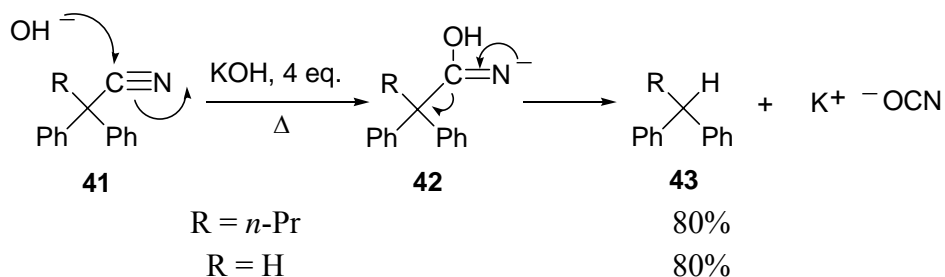
Scheme 17

Later, experiments based on a free radical-clock and isotopic labelling suggested the intervention of radical intermediates.⁹⁷ Electrochemical data were not consistent with an electron transfer from the hydride ($E_{\text{H}^\bullet/\text{H}^-}^\circ \approx -0.2 \text{ V vs NHE}$) to the nitrile **38** ($E_p < -1.96 \text{ V vs NHE}$ for **38**). We realized, however, that this kind of trapping experiment, performed in heterogeneous medium, was not compelling. Independently, Ashby studied the hydride reduction of hindered alkyl iodides. He concluded that unfiltered heterogeneous solutions of LiAlH_4 or LiAlD_4 lead to inconsistent results.⁹⁸ We are now working on a series of substituted 2-phenylsulfonylnitriles in order to obtain a better reproducibility.

The mechanism of the reductive decyanation promoted by LiAlH_4 for substrates other than α -aminonitriles remains a puzzle. Different pathways have been proposed depending on the nature of the substrate. It is noteworthy that all substrates undergoing the decyanation reaction are α -substituted by a carbanion stabilizing group. The addition-elimination process first proposed by Black and Doyle would be similar to the mechanism proposed for reductive decyanation induced by the hydroxide ion or organometallic reagents (see sections 3 and 5-1).

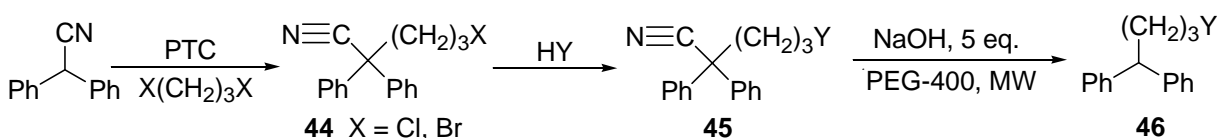
3. Acid or base promoted decyanation reactions

The decyanation reaction is also observed under harsh conditions. Old methods describe sodamide in boiling toluene⁹⁹ or polyphosphoric acid at 200 °C.¹⁰⁰ Berkoff *et al.* have developed the reductive decyanation of sufficiently activated tertiary and secondary nitriles using alkali fusion (150 °C, KOH 85%, 4 eq.).¹⁰¹ They proposed a process involving the initial attack of hydroxide ion on the nitrile carbon followed by a C-C bond cleavage. Trapping of potassium cyanate supports this mechanism (Scheme 18).



Scheme 18

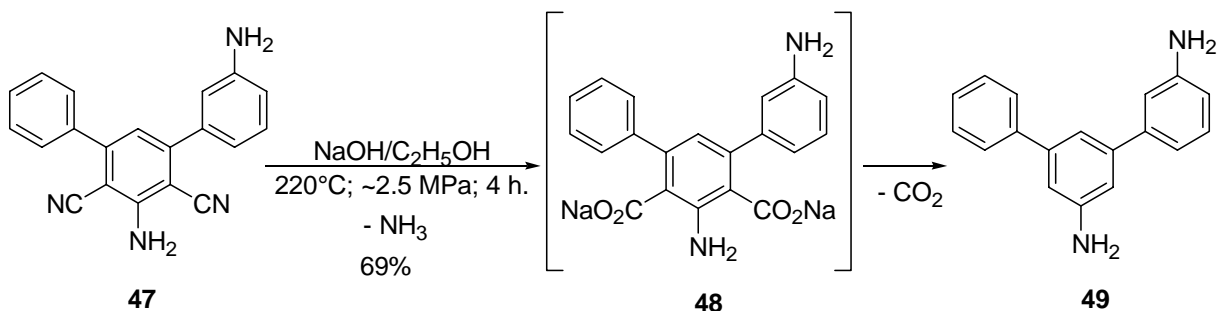
More recently, Bendale *et al.* reported the reductive decyanation of alkyldiphenylacetonitriles using sodium hydroxide-PEGs in a domestic microwave oven.¹⁰² PEGs exhibit a crown ether role by complexing Na^+ and with microwave irradiation high yields are obtained in just 2-3 minutes. The mechanism proposed was similar to that described by Berkoff. Using this methodology 4,4-diphenylbutylamines **46**, reported to be antilipidperoxidative, neuroleptic and antihypertensive agents, were prepared. Nitriles **44** are obtained from diphenylacetonitrile by alkylation under phase transfer catalysis conditions (PTC). The next step is the substitution of the remaining halogen atom by a secondary amine leading to **45** (Scheme 19).



sec. Amine = YH	Yield(%)
<i>N</i> -Phenylpiperazine	68
<i>N</i> -Methylpiperazine	71
Morpholine	81
Pyrrolidine	65
Piperidine	72

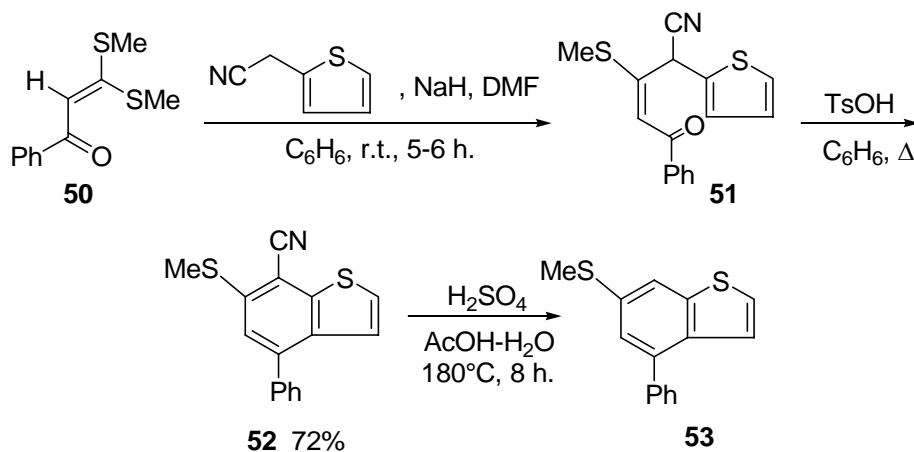
Scheme 19

Milart *et al.* prepared a series of di- or triamino-*m*-terphenyls as described in Scheme 20. Gewald's method was applied for the preparation of **47**.¹⁰³ The cyano groups were removed from **47** under harsh basic conditions. The authors consider that treatment with ethanolic sodium hydroxyde solution at high pressure (2.5 MPa) and temperature (220°C) may cause the conversion of the nitrile groups to anions of the corresponding carboxylic acids (**48**) which easily decarboxylate.¹⁰³



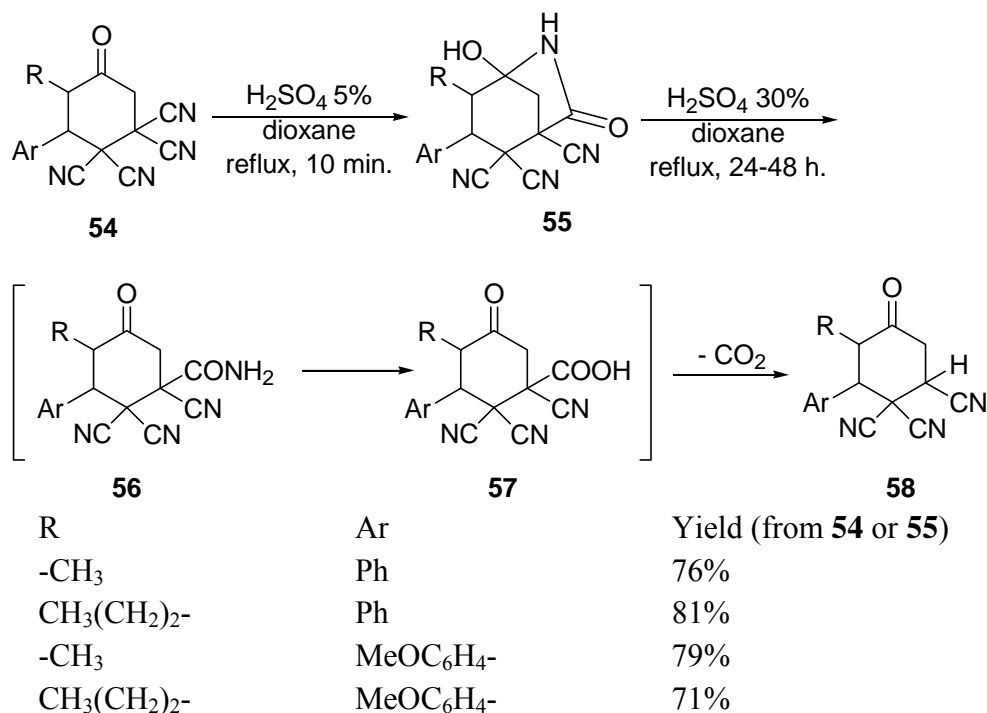
Scheme 20

Under severe acidic conditions, the reductive decyanation is equally observed with good yields.¹⁰⁴ The nitrile group is probably hydrolyzed and then decarboxylated. Such conditions have been employed in the course of the synthesis of benzo[*b*]thiophenes. The method is described in Scheme 21. Benzoannellation is developed via conjugate addition-displacement on β,β -(dimethylthio)ketone **50** by carbanion derived from 2-cyanomethylthiophene and is followed by acid induced cyclisation of **51**. The nitrile group is efficiently removed using a mixture of sulfuric acid, acetic acid and water at 180°C (Scheme 21).



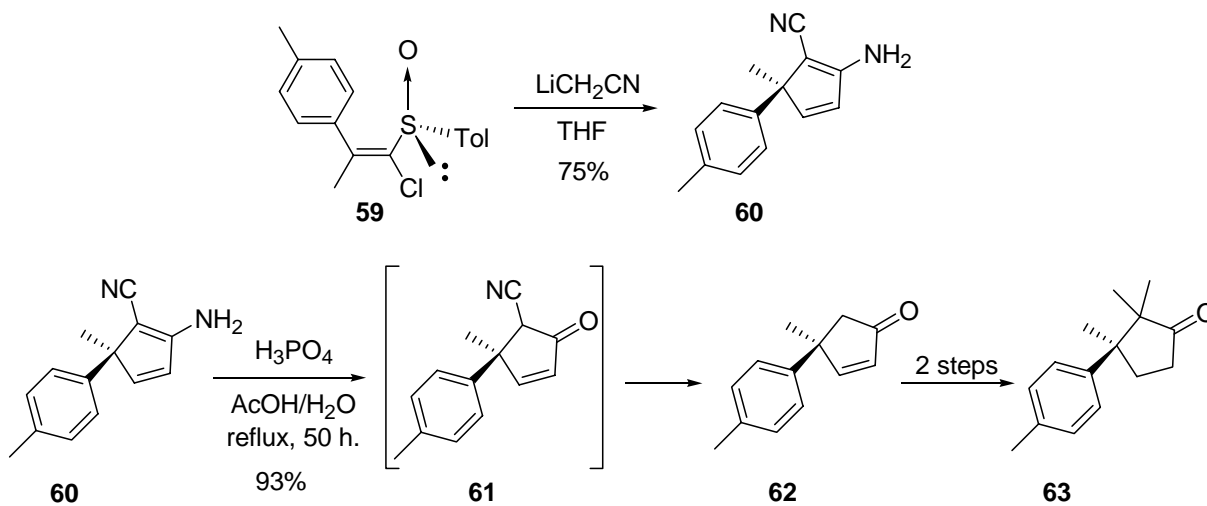
Scheme 21

Sheverdov *et al.* managed to reduce selectively one cyano group in position 2 of tetracyanocyclohexanones **54**. This reaction is explained by intramolecular interaction of the cyano group with the carbonyl group. On heating with 5% H_2SO_4 , hydroxy compounds **55** were isolated. More severe conditions (30% H_2SO_4) led to the formation of tricyanocyclohexanones **58**. Intermediates **56** are formed by retro-cyclisation of **55**. Hydrolysis of amides **56** and subsequent decarboxylation of the corresponding carboxylic acids would lead to the final products (Scheme 22).¹⁰⁵



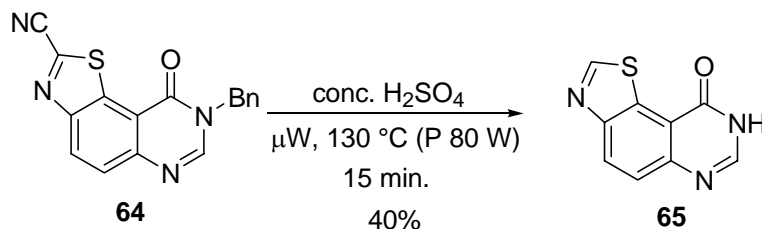
Scheme 22

Satoh *et al.* synthesized chiral 4,4-disubstituted-2-cyclopentenones¹⁰⁶ and elaborated a six step synthesis for enantiomerically pure (+)- α -Cuparenone **63**. They investigated the reaction of cyanomethyl lithium with optically active sulfoxide **59** and obtained enaminnitrile **60**. The latter is treated under reflux optimally with phosphoric acid in acetic acid, containing a small amount of water, to afford the decyanated compound **62** with 93% yield and over 99% ee (Scheme 23).



Scheme 23

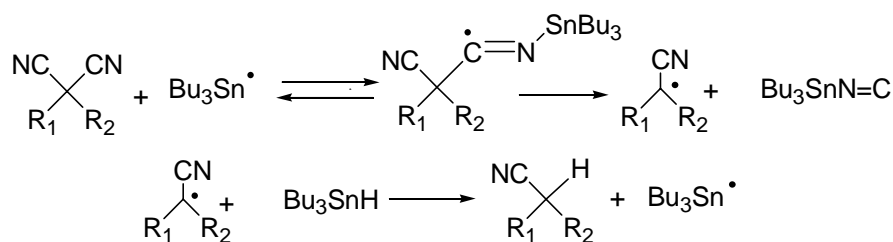
Alexandre *et al.* prepared thiazoloquinazolinones derivatives such as **65**. In the last step, they heat the precursor **64** in H_2SO_4 with a focused microwave reactor. The transformation involves deprotection of the nitrogen group and decyanation of the thiazole moiety (Scheme 24).¹⁰⁷



Scheme 24

4. Bu_3SnH or SmI_2 promoted decyanation reactions

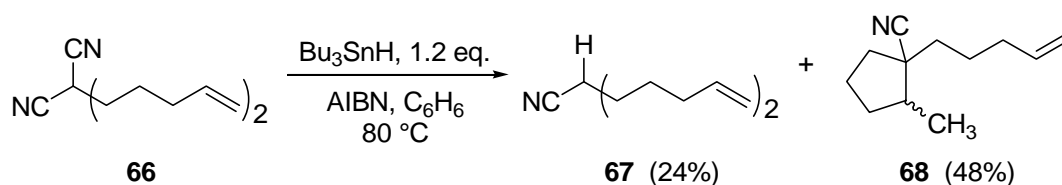
Curran and Seong discovered accidentally that mono- and dialkylated malonitriles (geminal dinitriles) are reductively decyanated to mononitriles on treatment with tributyltin hydride and a small amount of AIBN in refluxing benzene.¹⁰⁸ They proposed a chain mechanism to account for this reduction, the first step being the addition of the tin radical to the carbon-nitrogen triple bond to generate a carbon radical species (Scheme 25). So far, the reaction is limited to geminal dinitriles. Attempts to reduce 2-cyanoacetate under the same conditions gave no reaction. The first radical adduct is apparently generated, but its fragmentation is not fast enough with respect to the reverse addition to propagate the chain. Thus, the fragmentation of the carbon-carbon bond is facilitated by the ability of the nitrile group to labilize adjacent bonds.



Scheme 25

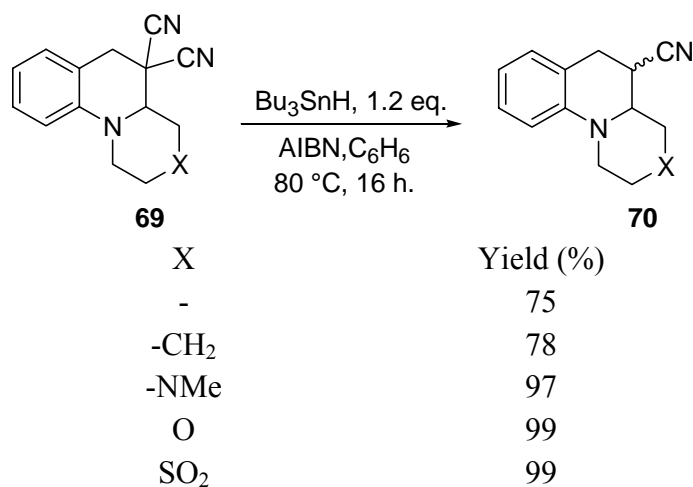
A variety of mono- and dialkylated malonitriles were reduced with good yields (75-94%) in this way. The α -nitrile radical was trapped by cyclization using the 5-hexenyl rearrangement. The rate constant of cyclization of the unsubstituted 5-hexenyl radical is $k = 2 \times 10^5 \text{ s}^{-1}$ at 20°C . Substitution of the radical with the cyano group should decrease this constant of approximately

two orders of magnitude.¹⁰⁹ When **66** is reduced, the cyclized product **68** is formed together with **67** (Scheme 26).



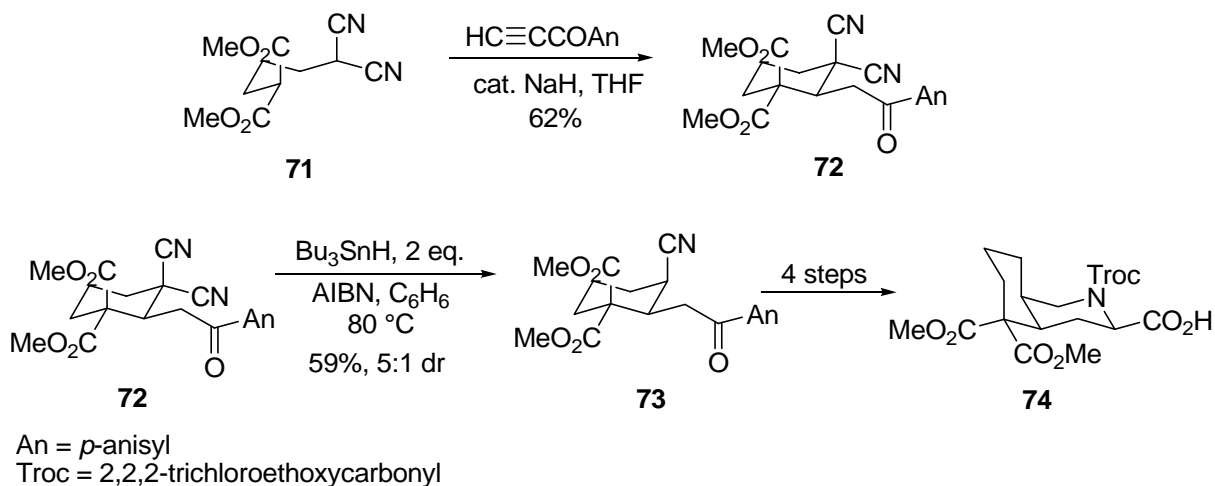
Scheme 26

Gerlach developed the synthesis of tricyclic cyano substituted tetrahydroquinolines **70** in good yields from the geminal dinitriles **69**¹¹⁰ by radical decyanation using Bu₃SnH (Scheme 27).



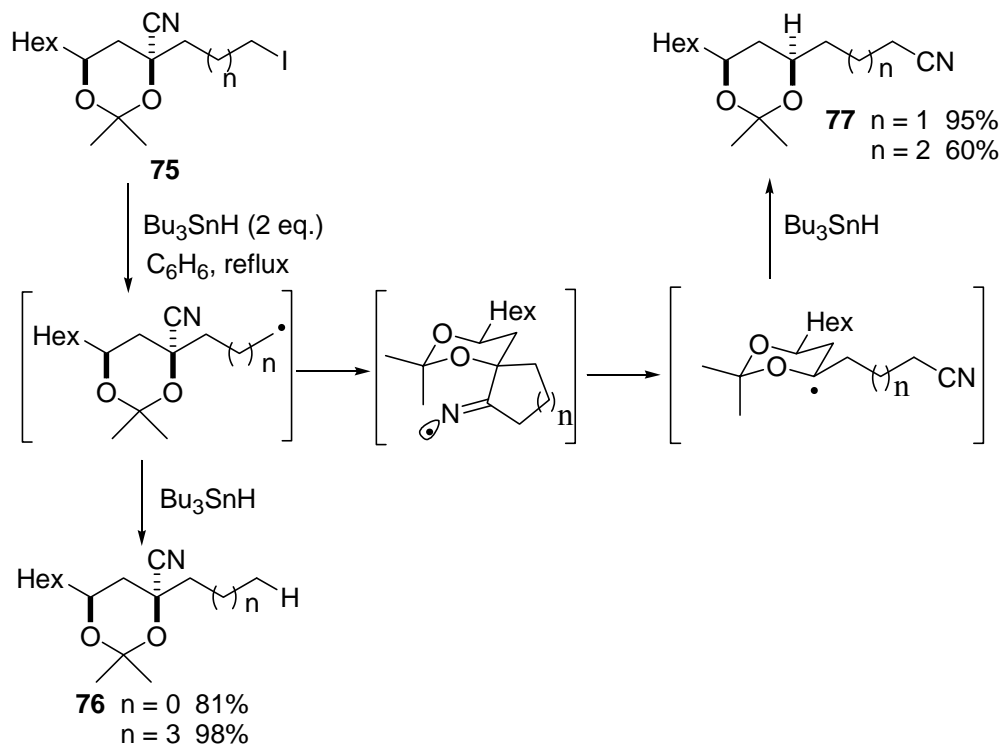
Scheme 27

Hattori and Grossman used this method to prepare the fused bicyclic α -amino acid **74** that lacked a quaternary center at the ring junction.¹¹¹ Tethered diacid **71** undergoes a double Michael addition with the alkynone and affords **72**. This cyclic geminal dinitrile was treated with tributyltin hydride to afford mononitrile **73** in 59% yield (5:1 mixture of diastereomers, Scheme 28). The reaction of the intermediate decyanated radical with tributyltin hydride apparently occurred predominantly from the less hindered face to give the higher energy *cis* isomer of the product.



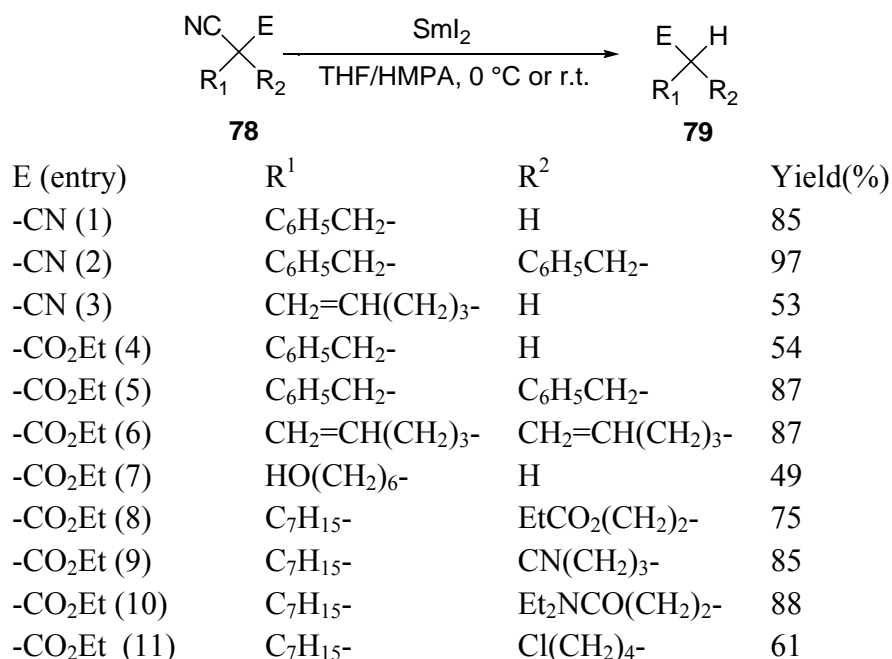
Scheme 28

It is worth noting that the reductive decyanation on mononitrile **75** promoted by tributyltin hydride proposed by Rychnovsky and Swenson is, in fact, a nitrile transfer reaction.¹¹² The reaction proceeds by a mechanism of cyclization followed by β -scission affording the 1,4- or 1,5-cyano transfer, when $n = 1, 2$, respectively (formation of **77**). When the cyclization is not allowed ($n = 0, 3$), the nitrile transfer reaction is not observed and the simple dehalogenation products **76** are formed (Scheme 29).



Scheme 29

Kang *et al.* proposed an alternative samarium (II) iodide (2-3 eq., in THF/HMPA, 5-10% v/v versus THF, 0°C) promoted reductive decyanation of malonitriles.^{113,114} Without HMPA no decyanation reaction was observed. The reaction was successfully applied to α -ethoxycarbonyl substituted nitriles at room temperature and extended to a range of substrates with an hydroxyl group or a carbon-carbon double bond located on the side chain (Scheme 30, entries 1-7). The mechanism could be similar to the tin hydride method, however, no cyclization products were observed when the side chain has a C=C bond.



Scheme 30

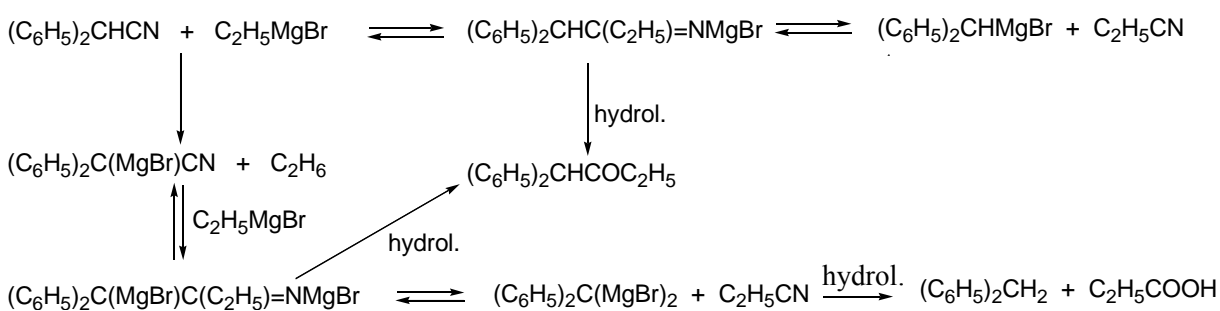
With this method, Molander and Wolfe reduced also a serie of α -cyano esters and show that nitriles, amides and chlorides are well-tolerated (Scheme 30, entries 8-11). The reaction conditions were similar to these described by Kang (two equivalents of ethanol were added).¹¹⁵

In a review, Kamochi and Kudo described the rapid reduction of a variety of organic functionalities including decyanation with SmI₂.¹¹⁶

5. Miscellaneous

5.1 Organometallic promoted decyanation reactions

There are literature reports on the decyanation of tertiary nitriles by organometallic reagents.^{117,118} In 1953, Blicke and Tsao studied the action of several Grignard reagents on nitriles.¹¹⁹ Diphenylacetone nitrile reacts with ethylmagnesium bromide in refluxing toluene giving the evolution of about one equivalent of ethane. After acid hydrolysis, 1,1-diphenyl-2-butanone (20%) and diphenylmethane (45%) were found. When the reaction mixture was carbonated, diphenylmalonic acid (55%) was found together with 1,1-diphenyl-2-butanone (5%). The nitriles were difficult to isolate but propionic acid was isolated after hydrolysis. Similar results were obtained with other Grignard reagents but the yield of diphenylmethane was much lower. The reaction scheme 31 may explain the formed products. The first step seems to be a nucleophilic addition of the Grignard reagent on the nitrile group, followed by the elimination of propionitrile and formation of diphenylmethylmagnesium bromide. The same process can occur after an initial deprotonation of diphenylacetone nitrile.

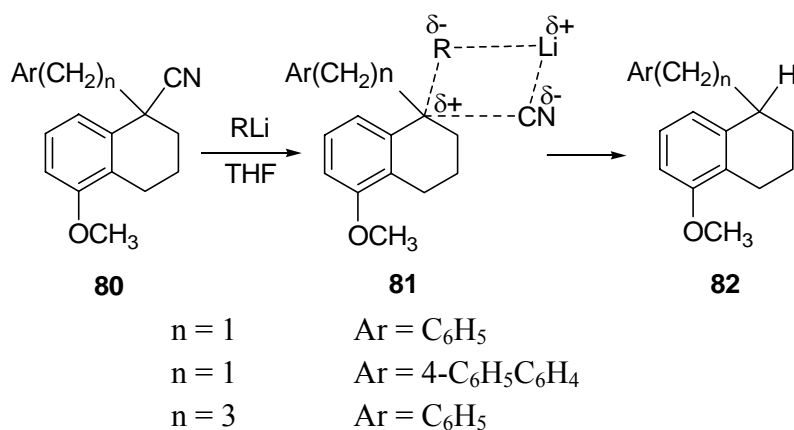


Scheme 31

King *et al.*, studying the decyanation of 9-cyanofluorenes promoted by ethylmagnesium bromide in refluxing xylene, proposed a simple general $\text{S}_{\text{N}}2$ mechanism to this reaction.¹²⁰

Kulp and Romanelli extended this method to alkyldiphenylacetonitriles and formed decyanation products using either methyllithium or phenyllithium as reagents.¹²¹ They also observed the formation of the decyanation product when treating butyldiphenylacetonitrile with phenylmagnesium bromide at a reaction temperature rising to 180°C.

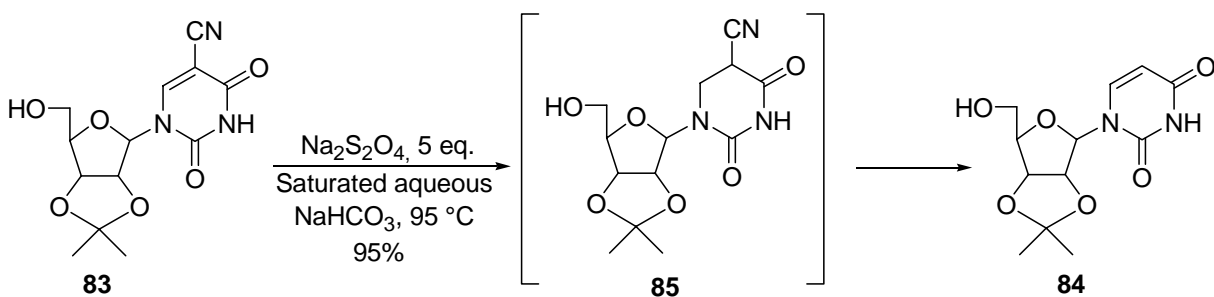
During the synthesis of imidazoles next to a quaternary carbon center, Gregory *et al.* treated tertiary nitriles **80** by methylmagnesium bromide and obtained the desired ketone. But when alkyllithiums in ether solvents were tried as an alternative to Grignard reagents, both ketone and decyanation product **82** were obtained. With methyllithium or butyllithium, in THF, yields of decyanation are quantitative.¹²² The authors explained the formation of decyanation products through a 4-membered transition state **81**, the collapse of which is accompanied by a hydride ion abstraction from the alkyl substituent R by the incipient benzylic carbonium ion at the 1-position of the tetrahydronaphthalene nucleus (Scheme 32). The formation of a monodeuterated compound as the sole decyanation product in an experiment with CD_3Li , but not when the reaction was quenched in THF with DCl supports this mechanism. Formation and fragmentation of a 4-centered transition state in THF probably occurs because THF is a stronger Lewis base than diethyl ether or benzene and is better to solvate the lithium cation. Marr *et al.* proposed a similar mechanism for decyanation of ferrocenyl- α,α -dibenzylmethylcyanide induced by *n*-BuLi.¹¹⁷ An electron transfer pathway was also proposed for this kind of decyanation.¹²³



Scheme 32

5.2 Sodium dithionite promoted decyanation reactions

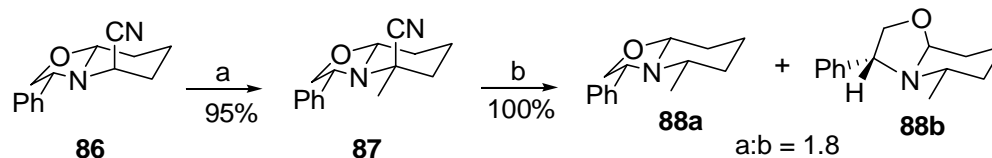
Uridine **84** was prepared in high yield from 5-cyanouridine **83** by the action of sodium dithionite in aqueous sodium hydrogen carbonate. The reaction presumably involves initial reduction of **83** into **85** followed by a base catalysed elimination of hydrogen cyanide (Scheme 33).¹²⁴ Similar conditions were used for the decyanation of a pyrazinecarbonitrile but the reaction was not entirely reliable.¹²⁵



Scheme 33

5.3 Raney nickel or hydrogenation promoted decyanation reactions

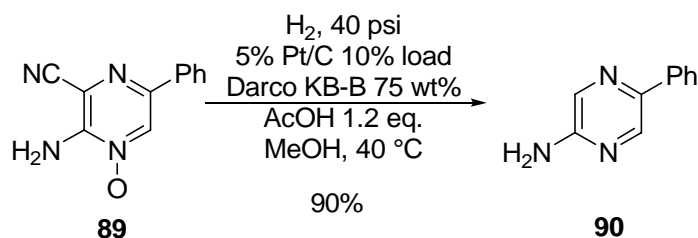
A Raney nickel mediated decyanation was used to modify piperidine scaffolds containing the chiral, non racemic *N*-(cyanomethyl)oxazolidine system. Alkylation of the commercially available **86** is followed by treatment with Raney nickel.^{126,127} Compounds **88** are obtained as a mixture of two epimers at the C-6 position without any racemisation at the C-2 methyl group. The authors proposed the formation of a prochiral iminium ion which could be explained in terms of a “push pull” mechanism. The delivery of the hydrogen present in Raney nickel is the result of a stereoelectronically controlled process.⁸⁶ The oxazolidine epimerization probably occurs during workup of the reaction mixture.



- (a) (i) LDA (3 eq.), THF, -78 °C, 20 min. (ii) MeI (2 eq.), -78 °C \longrightarrow r.t.
 (b) Raney nickel (excess), THF, r.t., 1.5 h.

Scheme 34

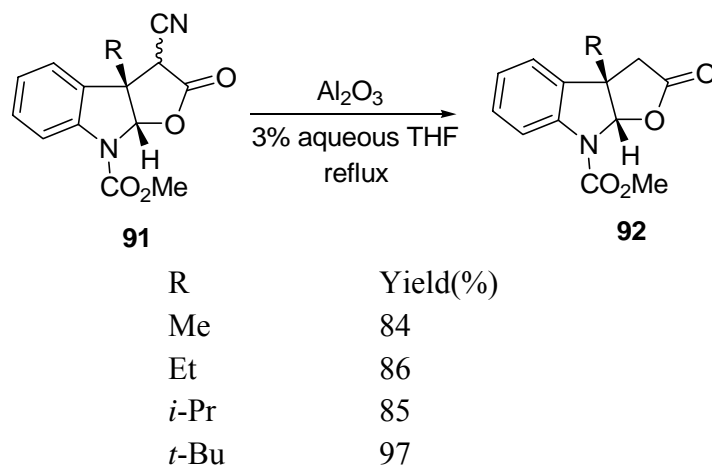
Albazeze-Walker *et al.* have developed a mild and robust protocol for the deoxygenation/decyanation of pyrazine carbonitrile-*N*-oxides such as **89**. These transformations occur by hydrogenation with platinum on carbon in the presence of activated carbon under acidic conditions.¹²⁵ The generality of this decyanation was explored and good yields were obtained (Scheme 35).



Scheme 35

5.4 Hydrolytic decyanation

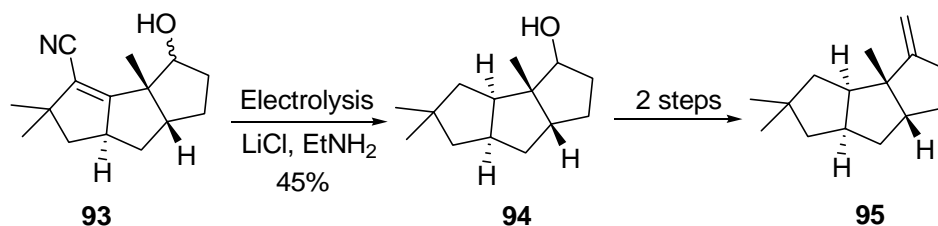
The hydrolytic decyanation of α -cyano- γ -lactones **91** with wet alumina in a variety of solvents affords the corresponding γ -lactones **92**. The transformation occurs under neutral conditions and without the need for an aqueous workup. We report here yields obtained in THF with 1.9 g of alumina per mmol of substrate. The proposed mechanism involves the initial formation of ketenimines which react with water to form successively ketenes and carboxylic acids. The later subsequently decarboxylate to yield γ -lactones (Scheme 36).¹²⁸



Scheme 36

5.5 Electrochemical cleavage of nitriles

The use of electrochemically generated electrons was first reported in 1968 by Arapakos and Scott.¹²⁹ Decyanation of dehydroabietonitrile, cycloheptyl nitrile and octanenitrile, in anhydrous amine media, produces dehydroabietene, cycloheptane and n-heptane, respectively, in 60-80% yields. They showed that the electrolytic generation of solvated electrons provides a reductive selectivity with sensitive nitriles and avoids the side reactions encountered with the chemical methods of generating solvated electrons, for example, the competitive reduction of some primary and secondary nitriles to their corresponding amines. This method was used to perform reductive decyanation during the total synthesis of (\pm)-Hirsutene **95** (Scheme 37).²²

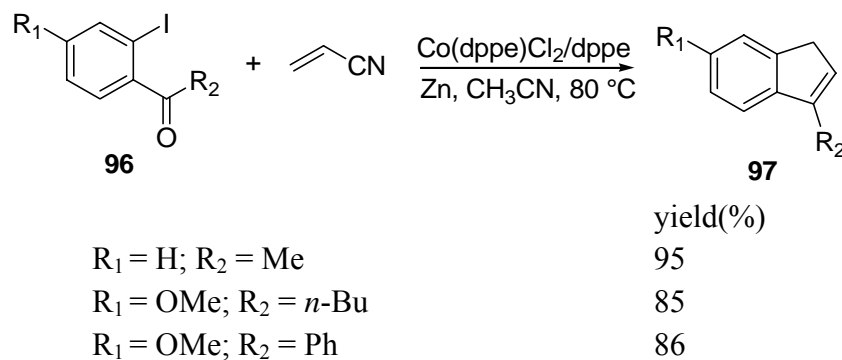


Scheme 37

Shono *et al.* reported the electroreductive decyanation of a great range of nitriles with a Zn cathode in DMF containing Et₄NOTs as a supporting electrolyte.¹³⁰ The yield of the reaction is highly influenced by electrolytes, electrode material and solvents but the method is applicable to epoxy, α -alkoxy or α -amino nitriles. As a mechanism, they proposed the dissociation of the radical anion formed by a first electron transfer, the radical formed being reduced by a second electron and then protonated (see Scheme 2, M = zinc electrode) Nevertheless a two-electron reduction yielding the corresponding dianion was proposed in the electrochemical reduction of benzenedicarbonitriles.¹³¹

5.6 Transition metals promoted decyanation reactions

In representative cases, the reductive decyanation of alkyl nitriles was carried out in 58-100% yields by the action of $\text{Fe}(\text{acac})_3\text{-Na}$ in benzene at room temperature ($\text{acac} = \text{C}_5\text{H}_7\text{O}_2$, acetylacetonato).¹³² More recently, the carbocyclization reaction of *o*-iodophenyl ketones **96** with acrylonitrile in the presence of cobalt catalyst and Zn power in acetonitrile at 80 °C afforded indene derivatives **97** in good yields. Interestingly, no cyano group was present in the formed products (Scheme 38). The reason for this reductive decyanation remains unclear.¹³³ The reductive decyanation of a pyrazinecarbonitrile or pyridinecarbonitriles by titanium (III) chloride was also reported.^{125,134}

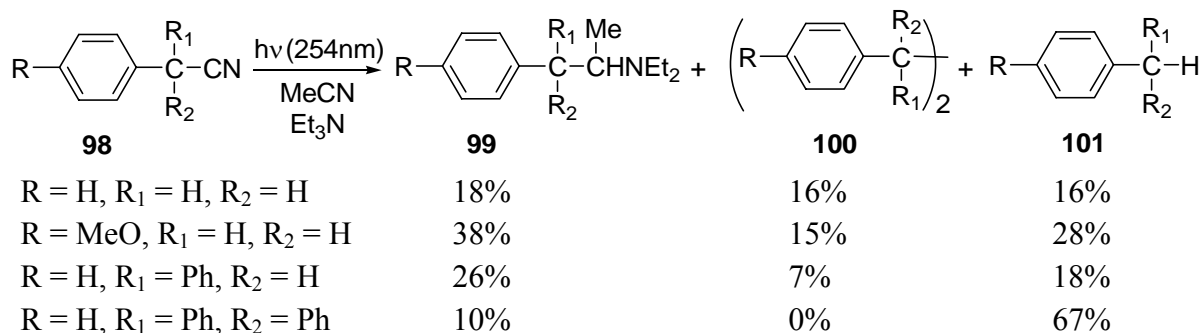


dppe : bis(diphenylphosphino)-ethane

Scheme 38

5.7 Photoinduced decyanations

Photoinduced decyanations lead generally to low yields but show a mechanistic interest.¹³⁵⁻¹³⁸ Homma and Yamada reported that irradiation of phenylacetonitrile and its derivatives **98** in the presence of triethylamine give α -benzylated triethylamine **99**, bibenzyl **100** and toluene **101** (decyanation product, 16-67% yields based on the substrate consumed) derivatives (Scheme 39); the formation of these products is explained in terms of a benzylic intermediate radical formed by electron transfer between the triethylamine and the substrate, followed by elimination of a cyanide anion from the radical anion of the starting compound.¹³⁹



Scheme 39

Conclusions

This review describes a number of methods to perform reductive decyanation. A large variety of procedures are available and much of them proceeds with good yields and stereoselectivities allowing their exploitation in organic synthesis. The most popular one is probably the reductive decyanation using metal dissolving conditions. This methodology was first restricted to tertiary nitriles, poor yields were obtained with primary and secondary nitriles. Improvements using HMPA with a protic cosolvent or the K/dicyclohexano-18-crown-6/toluene system allow decyanation of all classes of nitriles with good yields. The hydride reduction of α -aminonitriles is also a well-explored reaction. The success of the decyanation process depends on the substitution pattern of the α -aminonitrile, the stereoelectronic effects and the strain of the molecule. Factors promoting the formation of the iminium ion also favored the decyanation over the reduction to diamine. Acid or basic promoted decyanation usually requires harsh conditions, nevertheless, several applications are now described. The reduction under radical conditions was first restricted to geminal dinitriles. Extension to α -cyanoesters using SmI_2 could open new perspectives.

Different mechanisms were proposed depending on the reducing agent used : electron transfer (alkali metals), radical chain (Bu_3SnH) reaction or $\text{S}_{\text{N}}1$ reaction (metal hydrides with α -aminonitriles). Sometimes the mechanism involved remains a puzzle. Thus, the mechanism of decyanation of substrates other than α -aminonitriles induced by LiAlH_4 is not yet totally clarified.^{94,97} Several pathways were proposed with organometallic reagents, a 4-centered transition state, an addition-elimination process or an electron transfer mechanism. Similarly, the decyanation induced in basic medium could proceed through an addition-elimination process or a sequence involving hydrolysis and decarboxylation.

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