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Non-reductive decyanation reactions of disubstituted malononitrile derivatives promoted by NaHMDS

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ABSTRACT

A new method for achieving the decyanation of disubstituted malononitrile derivatives without using reducing agents has been developed. Treatment of a six-membered malononitrile derivative with NaHMDS followed by methanol afforded the corresponding acetonitrile derivative in high yield. The present method was applicable to the decyanation reactions of a variety of malononitriles including four- and five-membered compounds as well as acyclic ones.

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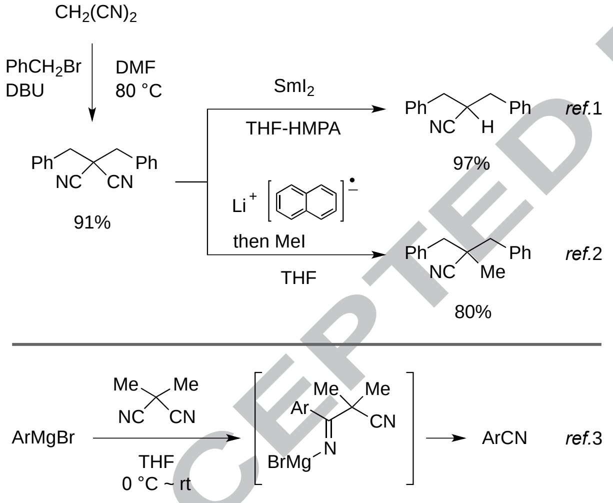
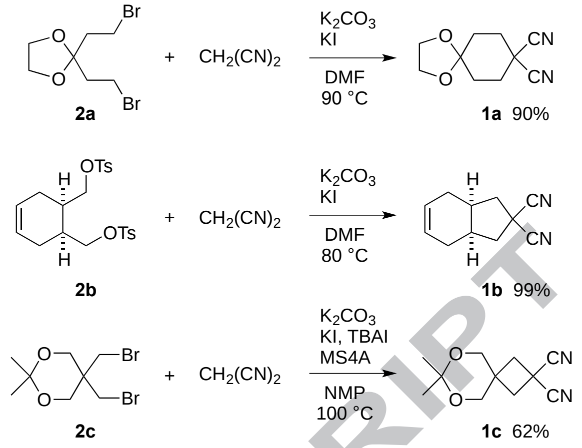
Alkylation reactions of active methylene compounds have found widespread use in organic synthesis, mainly because these reactions proceed under mild conditions using a weak base. For example, the reaction of an alkyl bromide and diethyl malonate under the influence of sodium ethoxide affords an α-substituted malonate which can be converted to the corresponding α-substituted acetic acid through hydrolysis of the ester moiety followed by decarboxylation. For obtaining an α-substituted acetonitrile, a similar procedure starting from ethyl cyanoacetate is available. On the other hand, an alkylation reaction of malononitrile followed by a decyanation reaction provides an alternative way to achieve the same purpose. While SmI$_2$[1] and lithium naphthalenide[2] are reported to induce the reductive cleavage of a cyano group from substituted malononitrile derivatives, there are few example of non-reductive decyanation reactions of them (Scheme 1).

Thus, Reeves[3] reported a cyanation of aryl Grignard reagent or lithium reagents by the addition reaction with dimethylmalononitrile. In this reaction, the anionic intermediate undergoes decomposition into the desired arenecarbonitrile and an α-carbanion of isobutyronitrile, which shows promise for achieving a non-reductive decyanation of α,α-disubstituted malononitrile derivatives. We herein report that the reactions of α,α-disubstituted malononitrile derivatives with a suitable nucleophile provided the corresponding α,α-disubstituted acetonitriles in high yield.



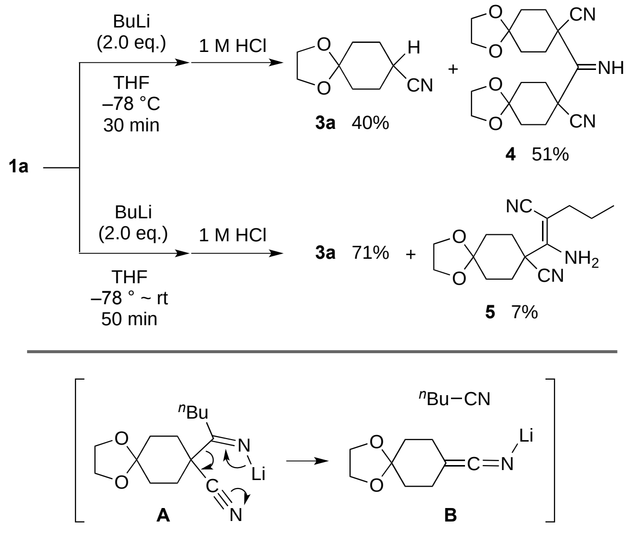
Scheme 1. Conventional decyanation reactions of malononitriles

Initially, six-, five-, and four-membered malononitrile derivatives **1a**-**1c** were synthesized from the corresponding dibromide or ditosylate **2a**-**2c** and malononitrile (Scheme 2). The combined use of K$_2$CO$_3$ and KI[4] in DMF was effective for the synthesis of **1a** and **1b**, while modified reaction conditions[5] were required for constructing the four-membered ring of **1c**.



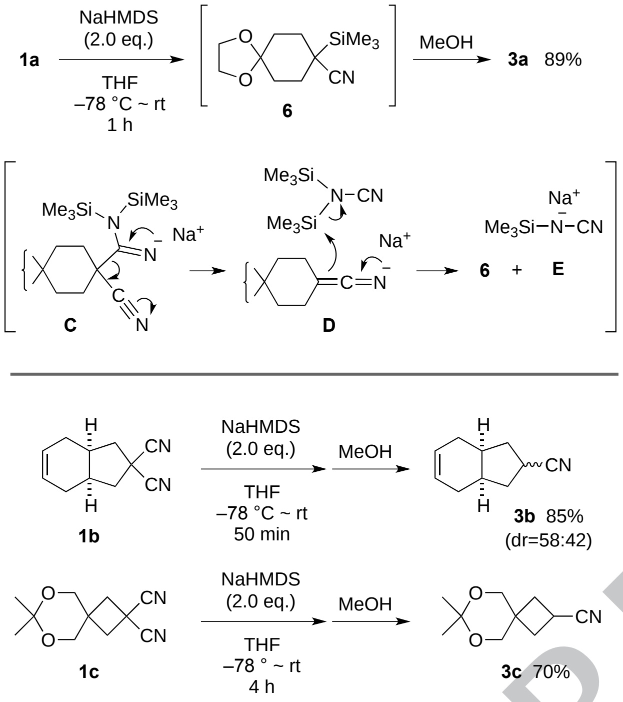
Scheme 2. Synthesis of cyclic malononitriles **1**

With a view to inducing decyanation via a nucleophilic addition reaction, malononitrile **1a** was treated with 2 equiv. of *n*-BuLi in THF at –78 °C (Scheme 3). After 30 min, the reaction was quenched with diluted hydrochloric acid to give the desired nitrile **3a** in 40% isolated yield along with 51% of byproduct **4**. The result suggested that the reaction proceeded through decomposition of the anionic intermediate **A** into the α-cyano anion **B** even at –78 °C which attacked the remaining substrate **1a** to form **4**. On the other hand, the yield of nitrile **3a** was increased to 71% upon warming the reaction to room temperature before quenching. In this case, a small amount (7%) of byproduct **5**, which would come from pentanenitrile and malononitrile **1a**.



Scheme 3. Decyanation reactions of cyclic malononitrile **1a**

After several efforts to solve the problem, it was unexpectedly found that NaHMDS is a choice of nucleophiles, leading to nitrile **3a** in high yield (Scheme 4). Thus, malononitrile **1a** was reacted with 2 equiv. of NaHMDS[6] in THF at room temperature, and the mixture was treated with methanol before quenching with water. During the experiment, α-trimethylsilyl nitrile **6** was found to be the initial product of the reaction,[7] which enabled us to understand the reason for the successful decyanation process using NaHMDS. Thus, anionic intermediate **C** decomposes into α-cyano anion **D** and bis(trimethylsilyl)cyanamide[8] which readily undergo an inter-molecular transfer of a silyl group. Therefore, the reactive anion **D** is immediately captured by a silyl group to give **6**, and the resulting anion **E** is sufficiently stable to avoid side reactions. The silyl group of **6** is then removed in one-pot simply by adding methanol to the reaction mixture. The protocol was also effective for the decyanation reactions of malononitriles **1b** and **1c**, giving rise to the corresponding nitriles **3b** and **3c** in 85% and 70% yields, respectively.

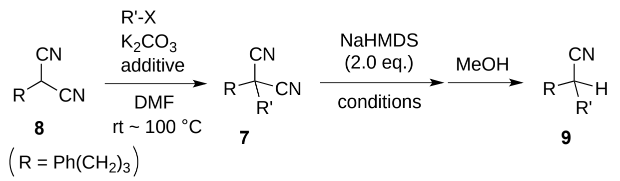


Scheme 4. Decyanation reaction of malononitriles mediated by NaHMDS

We then turned our attention to the decyanation of acyclic substrates. Various α,α-disubstituted malononitriles **7** were easily synthesized from (3-phenylpropyl)malononitrile (**8**) and the corresponding alkylating agents in a similar fashion with the preparation of **1a** (Table 1). Upon treatment with NaHMDS in THF followed by methanol, malononitriles **7** possessing a methyl group or a (2-benzyloxy)ethyl group at the α-position underwent smooth decyanation reactions to afford nitriles **9** in good yields (entries 1 and 2). Surprisingly, the substrate having an allyl group failed to give the desired product, resulting in formation of a complex mixture (entry 3). We found that the use of less polar solvents dramatically changes the result. Thus, the desired nitrile **9** was obtained in 85% yield by the reaction in a mixture of ether and toluene (entry 4), and an analogue having a prenyl group was also synthesized in a similar manner (entry 5).

Since nitriles **9** would also be obtainable directly from 5-phenylpentanenitrile through the alkylation reactions with R'-X,[9] the present two-step synthesis of **9** via decyanation of malononitriles **7** may show little advancement. On the other hand, it has been recognized that malononitrile can serve as an effective nucleophile in Michael addition to α,β-unsaturated ketones,[10] which contrasts with that a simple alkanenitrile generally prefers 1,2-addition rather than 1,4-addition.

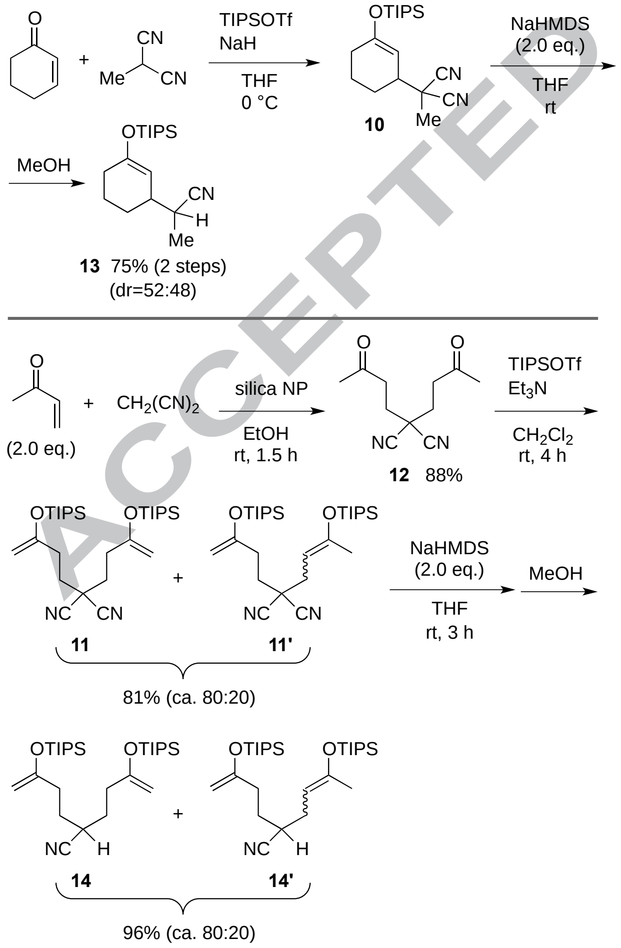
Table 1. Two-step synthesis of acyclic nitriles [a]



Entry	R'-X	Additive	Yield of 7	Conditions	Yield of 9
1	MeI	-	90%	(i)	96%
2	$BnOCH_2CH_2OMs$	NaI	83%	(i)	95%
3	CH_2=$CHCH_2I$	-	98%	(i)	-
4	CH_2=$CHCH_2I$	-	98%	(ii)	85%
5	Me_2C=$CHCH_2Br$	NaI	96%	(ii)	96%

[a] Reaction condition (i): To a THF solution of **7** was added a 1.1 M THF solution of NaHMDS at –78 °C, and the solution was warmed up to room temperature. After 2.5 h, the reaction was quenched with methanol at room temperature. Reaction condition (ii): To an ethereal solution of **7** was added a 0.6 M toluene solution of NaHMDS at –78 °C, and the solution was warmed up to room temperature. After 3 h, the reaction was quenched with methanol at room temperature.

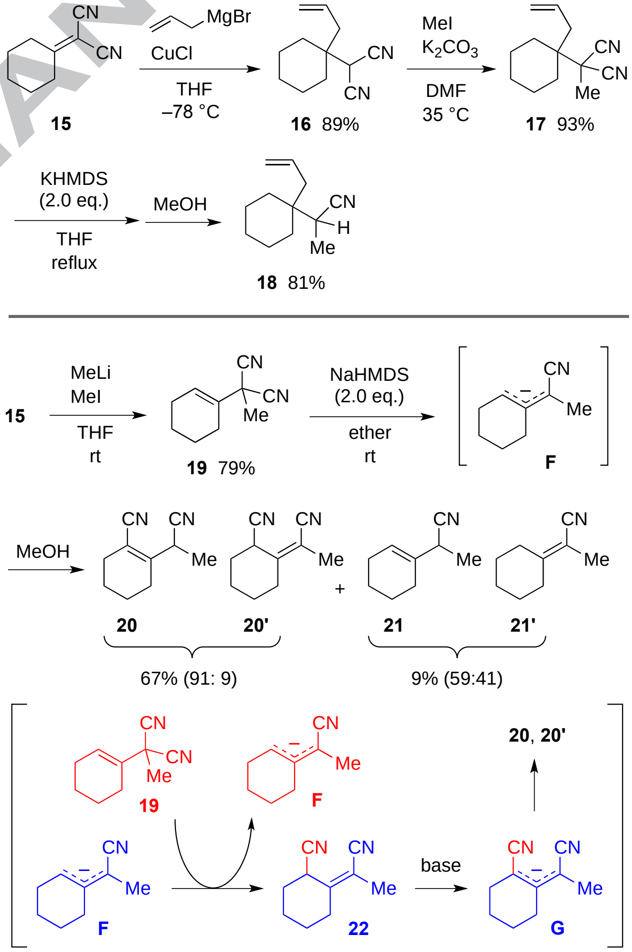
Indeed, the advancement of the indirect method for obtaining nitriles was shown in Scheme 5. Thus, under the influence of sodium hydride and TIPSOTf, methylmalononitrile reacted with 2-cyclohexen-1-one to afford enol silyl ether **10** in excellent yield.[11]



Scheme 5. Synthesis of nitriles through conjugate addition reactions

A regioisomeric mixture of malononitriles **11** and **11'** was also synthesized from the corresponding diketone **12** which was prepared from malononitrile and methyl vinyl ketone by the double Michael reaction mediated by a silica nano-particle.[12] Upon treatment with NaHMDS in THF followed by methanol, malononitriles **10** and **11** (containing **11'**) were cleanly transformed into the desired nitriles **13** and **14** (containing **14'**), respectively.

We next turned our attention to the Michael addition reactions of 1,1-dicyanoalkene with nucleophiles, which showed promise for preparing malononitriles with a bulky substituent (Scheme 6). The condensation reaction of cyclohexanone with malononitrile afforded dicyano compound **15** in high yield.[13, 14] The reaction of **15** with a Grignard reagent in the presence of copper(I) chloride[15] proceeded in good yield to afford malononitrile **16** which was subjected to the alkylation reaction with MeI. Although NaHMDS failed to induce the decyanation reaction of the sterically demanding malononitrile **17** even under refluxing condition, the use of KHMDS led to formation of the desired nitrile **18** in 81% yield.



Scheme 6. Conversion of 1,1-dicyanoalkene **15** to nitriles through decyanation reactions

Interestingly, the reaction of β, γ-unsaturated malononitrile **19**, which was prepared by the methylation of **15**[16], mainly afforded dinitrile **20** along with the desired nitrile **21** in 9% yield. The unusual result can be explained by the transcyanation of the anionic intermediate **F** with the remaining substrate **19** at the γposition of the cyano group to afford intermediate **22**. which is converted to **20** via anionic intermediate **G**.

In conclusion, a new method for achieving the decyanation of disubstituted malononitrile derivatives without using reducing agents has been developed. Treatment of a six-membered malononitrile derivative with NaHMDS followed by methanol afforded the corresponding acetonitrile derivative in high yield. The present method was applicable to the decyanation reactions of a variety of malononitriles including four- and five-membered compounds as well as acyclic ones. The mild non-reductive reaction condition tolerates functional groups such as benzyl ether (Table 1, entry 2), which shows promise for use in natural product synthesis.

Acknowledgments

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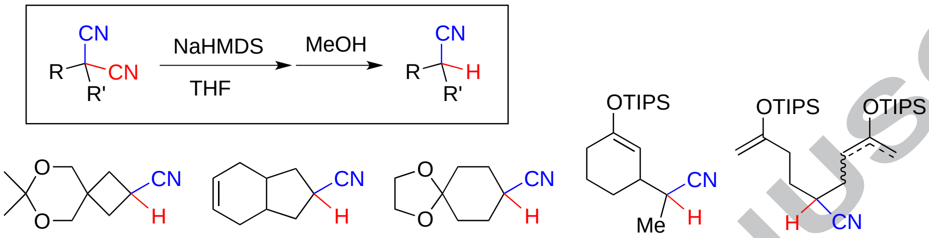

A new synthetic method of aliphatic and alicyclic mononitriles is described.

Treatment of substituted malononitriles with NaHMDS followed by MeOH gave nitriles.

The clean transformation is attributable to formation of α-silylated intermediates.