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ARTICLE TYPE

Chemoselective Efficient Synthesis of Functionalized β-oxonitriles through Cyanomethylation of Weinreb Amides

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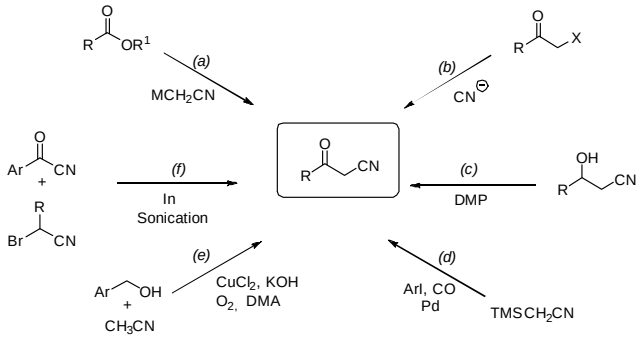
A synthesis of β-oxonitriles is reported via the generation of R^1R^2CLiCN species followed by the trapping with variously decorated Weinreb amides. The optimization study revealed that lithiation of acetonitriles is best accomplished by deprotonation with MeLi-LiBr at low temperature. The protocol can be conveniently adapted to the synthesis of α-mono or α,α-disubstituted cyanoketones. ^{15}N- and ^{17}O-NMR data are reported for selected compounds.

β-Oxonitriles, also referred as α-cyanoketones, are valuable synthons in organic synthesis because of the multiple manipulations that both the carbonyl and the nitrile functionalities can undergo.[1] In this sense, they represent useful building blocks for the construction of biologically active heterocycles such as HIV inhibitors[2] or anti-inflammators.[3] Moreover, stereoselective reductions of the ketone moiety would afford enantiopure β-hydroxynitriles[4] that are versatile scaffolds in the synthesis of important drugs such as the antidepressants (*S*)-fluoxetine[5] (Prozac®) and (*S*)-duloxetine[6] (Cymbalta®). Thus, the synthesis of this motif has been object of several studies during the years and a closer examination allows to include them in the following main categories (Scheme 1): a) homologation of a given carbonyl precursor (*i.e.* ester) with a metalated cyanomethyl carbanion (MCH_2CN, M = Li, MgHal, K, Na, Sm);[7] b) nucleophilic substitution with the highly toxic cyanide anion on an α-haloketone;[8] c) oxidation of a cyanohydrin;[9] d) Pd-catalysed carbonylation of aryl iodides and $TMSCH_2CN$[10] or unactivated nitriles;[11] e) Cu-catalysed oxidative coupling of aromatic alcohols and CH_3CN;[12] f) In-mediated coupling of bromoacetonitriles with acyl cyanides;[13] g) *C*-arylation of resin-bound cyanoacetates.[14] Historically, the homologation strategies have constituted the method of choice because of the conceptually simplicity of the process and the easy availability of the required reagents (a carboxylic acid derivative and CH_3CN). However, this significant advantage compared to other procedures, has been limited severely by the lack of general applicability to sensitive carboxylic esters and by non-uniform efficiency in terms of reaction yields. Recently, Trenkle and co-workers reported that by deprotonating acetonitrile with KO*t*-amyl, reaction yields can be improved, though the scope is rather limited in terms of both esters and substituted acetonitriles:[7c] in particular, disubstituted ones (*i.e* R^1R^2CHCN) have not been employed. Moreover, the higher reactivity displayed in Pd-catalysed carbonylations by aryl iodides compared to aliphatic counterparts renders it applicable only to the synthesis of aromatic α-cyanoketones.[10] An analogous limitation affects the oxidative coupling strategy recently described by Liu and co-workers.[12]

Scheme 1. Summary of available methods to access β-oxonitriles.

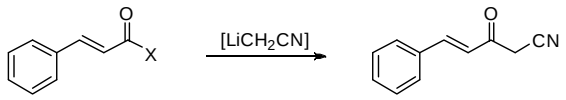


Considering the exceptional nucleophilic properties of metalated nitriles,[15] as highlighted in a series of illuminating works by Fleming and collaborators,[1c,7j,15b,16] we decided to investigate the reaction by considering simultaneously the effects of *i*) the electrophilic carboxylic derivative used for the homologation and *ii*) the nature of the metalated nitrile. Recently our group demonstrated that Weinreb amides,[17] due to the stability of the tetrahedral intermediate generated upon reaction with an organometallic reagent, are well-suited placeholders[18] for reactions involving α-halosubstituted organolithiums reagents (*e.g.* $LiCH_2X$, X = Cl, Br, I).[19] In fact, the simple switching to these easily-prepared substrates allows to maximize reactions' efficiency compared to the corresponding esters or acid halides. In this Communication we present a versatile, chemoselective, high-yielding access to (α-substituted) α-cyanoketones through the generation of lithiated acetonitriles followed by the trapping with variously functionalized Weinreb amides. We also report previously undisclosed ^{15}N- and ^{17}O-NMR data for selected examples of this class of structures.

Commercially available methyl cinnamate (**1a**) was reacted with 4 equiv of $LiCH_2CN$ (generated from CH_3CN (4.5 equiv) and *n*-BuLi (4.0 equiv) giving the desired α'-cyano-α,β-unsaturated ketone **2** in 66% yield (Table 1, entry 1). Surprisingly, in contrast with our previous findings dealing with halomethylation of Weinreb amides,[18] we found that lowering the loading of $LiCH_2CN$ to 1.5 equiv, an increase of **2** was noticed (entries 2-3). Moreover, the addition of this lithiated species did not give any corresponding carbinol product (as we observed in the case of

$LiCH_2Cl$)[18a] resulting from the double addition to the ester. Further optimization revealed that MeLi-LiBr was the best base to accomplish CH_3CN deprotonation compared to other ones such as simple MeLi, *s*-BuLi, LDA, LTMP, LHDMS or $LiNH_2$ (entries 4-9). Considering MeLi-LiBr the optimal base for generating the reacting lithiated acetonitrile, we tested the corresponding Weinreb amide **1b**: pleasingly, **2** could be obtained in an excellent 86% isolated yield after simple washing (brine) work-up thus, without needing to perform chromatographic purification (entry 10). Increasing the temperature up to 0 °C causes a dramatic decrease of yields and the formation of significant amounts of impurities difficult to remove by chromatography (entries 11-12). The use of diethyl ether does not affect the reaction at much extent (entry 13), while performing the process in *tert*-butyl methyl ether (MTBE) or 2-methyltetrahydrofuran (MTHF)[20] significantly drops the yields (entries 14-15). Generating $LiCH_2CN$ from ICH_2CN and *n*-BuLi[7j,16b] followed by the addition of the electrophile (entries 16-17) or generating it under Barbier-type conditions (entry 18) did not give satisfactory results with this particular substrate.

Table 1. Reaction optimization.



X = OMe (**1a**)
X = N(OMe)Me (**1b**)

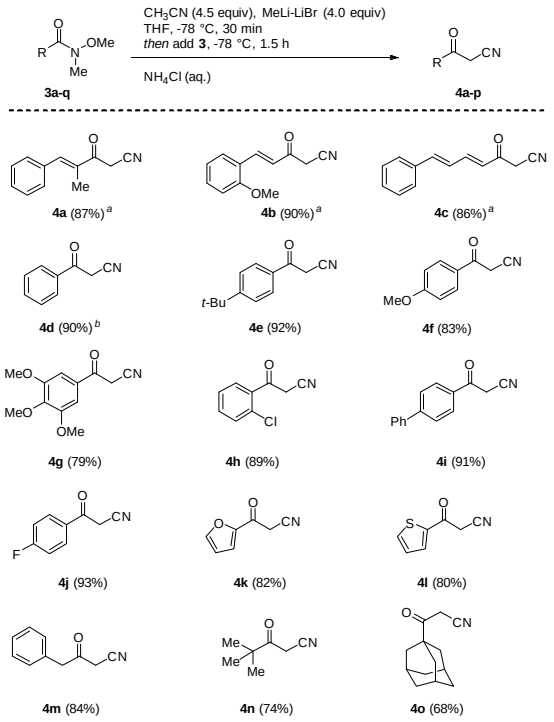
2

Entry	Substrate	Metal reagent	[$LiCH_2CN$] equiv	Solvent / Temp. (° C)	Yield of **2** (%) [a]
1	**1a**	*n*-BuLi	4.0	THF / -78	66
2	**1a**	*n*-BuLi	2.0	THF / -78	68
3	**1a**	*n*-BuLi	1.5	THF / -78	69
4	**1a**	MeLi-LiBr	1.5	THF / -78	71
5	**1a**	*s*-BuLi	1.5	THF / -78	62
6	**1a**	LDA	1.5	THF / -78	66
7	**1a**	LTMP	1.5	THF / -78	61
8	**1a**	LHDMS	1.5	THF / -78	66
9	**1a**	$LiNH_2$	1.5	THF / -78	47
10	**1b**	MeLi-LiBr	1.5	THF / -78	86
11	**1b**	MeLi-LiBr	1.5	THF / -40	65
12	**1b**	MeLi-LiBr	1.5	THF / 0	44
13	**1b**	MeLi-LiBr	1.5	Et_2O / -78	83
14	**1b**	MeLi-LiBr	1.5	MTBE / -78	71
15	**1b**	MeLi-LiBr	1.5	MTHF / -78	68
16	**1b**	*n*-BuLi [b]	1.5	THF / - 78	11 [c]
17	**1b**	*n*-BuLi [d]	1.5	THF / - 78	12 [c]
18	**1b**	*n*-BuLi [e]	1.5	THF / - 78	7 [c]

[a] Isolated yields. [b] **1b** was added after 1 min from the end of the addition of *n*-BuLi to ICH_2CN. [c] NMR yields (1,3,5-trimethoxybenzene as internal standard). [d] **1b** was added after 5 min from the end of the addition of *n*-BuLi to ICH_2CN. [e] **1b** was present at the beginning of the addition of *n*-BuLi to ICH_2CN (*i.e.* "Barbier-type" condition).

Subsequently, different α,β-unsaturated Weinreb amides were subjected to the optimal reaction conditions for cyanomethylation (Scheme 2). Substitution across the olefinic double bond is tolerated, as ketone **4a** was obtained in high yield. Interestingly, the protocol works well also in the case of vinyl-homologue **4c**. However, the employment of such conditions (1.5 equiv of $LiCH_2CN$) to non-α,β-unsaturated Weinreb amides resulted in lower conversion: pleasingly, we found beneficial to use an excess of $LiCH_2CN$ (4.0 equiv) to obtain **4d** in 90% yield (*vs.* 75% yield with 1.5 equiv of $LiCH_2CN$). These results point out to a comparatively high electrophilicity of the α,β-unsaturated systems although, in the mean time, strongly suggest that a higher loading of the cyanomethylating reagent may interfere with the olefinic double bond, thus resulting in decreased yields. Aromatic substrates are well-suitable for the transformation (**4d-4j**): however, slightly decrements were observed for strong electron-donating substituted ones (**4f-g**), compared to analogues with a weak electron-donor (**4e**), or with electron-withdrawing functionalities (**4h-j**). No deleterious effects were noticed in the presence of an halogen substituent (**4h**, **4j**) or, when heteroaromatic nuclei (**4k-l**) were installed into the core of the reagent. Aliphatic substrates react efficiently even in the presence of pronounced steric congestion as in the case of a *tert*-butyl group (**4n**) and an adamantyl moiety (**4o**). Pleasingly, the use of a Weinreb amide bearing acidic hydrogens performs equally very well: no side reactions derived from acidic-base equilibria promoted by the basic homologating reagent could be observed in the case of **4m**.

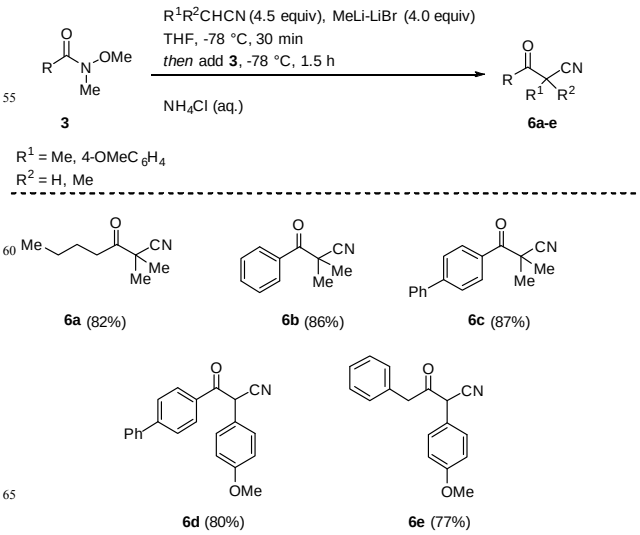
Scheme 2. Scope of the reaction.



[a] $LiCH_2CN$ (1.5 equiv); [b] 75% yield when 1.5 equiv of $LiCH_2CN$ were employed

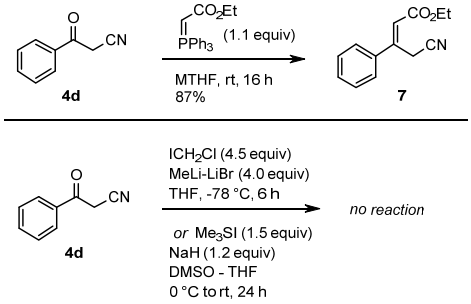
With the aim to expand the synthetic portfolio of the transformation, we focused on the employment of substituted acetonitriles. Upon forming the lithiated species under the usual conditions, a series of α,α-dimethyl-α-cyanoketones could be obtained in very good yields with aliphatic or aromatic Weinreb amides (**6a-c**, Scheme 3). This approach shows how the easy generation of the functionalised lithiated acetonitrile may be considered the method of choice for accessing such particular cyanoketones. In fact, previously reported syntheses through the direct α-methylation of the parent benzoylacetonitrile[21] or, the electrophilic addition of chlorosulfonyl isocyanate to ketones in the presence of DMF,[22] or the NaCN treatment of aroylhydrazones under PTC conditions[23] lack of general applicability and their potential is somewhat limited by almost uniformly modest yields. Analogously, the protocol allows the addition of a lithiated α-arylacetonitrile in high yields (**6d** and **6e**, Scheme 2).

Scheme 3. Synthesis of α-mono and α,α-disubstituted cyanoketones from functionalized acetonitrile derivatives.



Inspired by our interest towards homologation chemistry,[18-19,19d] we evaluated the reactivity of cyanoketone **4d** with a stabilized phosphorous ylide. Thus, β-cyanomethyl-β-phenyl ethyl acrylate **7** was easily obtained in high yield (Scheme 4, *up*). Surprisingly, neither a lithium carbenoid nor a sulphur ylide (Corey-Chaykovsky),[24] that are well-known reagents for carbonyl epoxidations, did react with substrate **4d**.

Scheme 4. Attempted homologations with an α-cyanoketone.



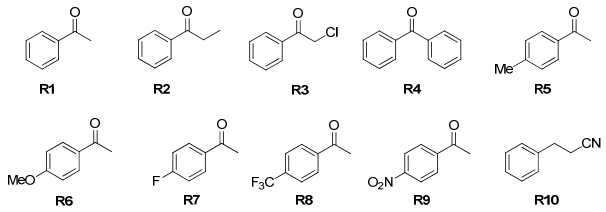
Finally, due to the very limited availability of ^{15}N- and ^{17}O-NMR data for ß-oxonitriles,[25] we herein provide the ^{15}N NMR chemical shifts (of C≡N) and ^{17}O NMR chemical shifts (of C=O) of selected representatives (Table 2). Moreover, in Table 2 are also reported the corresponding data we measured for some related structures to gain information on how minimal changes on the structure are reflected on spectroscopic data (**R1**-**R10**).

Table 2. ^{17}O and ^{15}N shifts for selected cyanoketones and correlation with various α-substituted ketones.

Entry	Compound	^{17}O (δ, ppm)	^{15}N (δ, ppm)
1	**4d**	542	-126.0
2	**4f**	521[a]	-126.7
3	**4j**	536	-125.6
4	**4k**	510[b]	-126.9
5	**4n**	560	-127.8
6	**4o**	561	-127.5
7	**R1**	541	-
8	**R2**	532	-
9	**R3**	538	-
10	**R4**	546	-
11	**R5**	525	-
12	**R6**	527	-
13	**R7**	540	-
14	**R8**	556	-
15	**R9**	574	-
16	**R10**	-	-135.3

[a] OMe: 65 ppm. [b] Furan-O: 239 ppm.

Reference compounds:



The ^{15}N NMR chemical shifts of the nitrile-N of compounds **4** are very consistent and located in the range between -126.0 and -127.8 ppm. Removal of the carbonyl oxygen atom of **4d** (**4d** → **R10**) results in an upfield shift of 9.3 ppm in compound **R10** (entry 16).

The ^{17}O NMR chemical shifts of the carbonyl-O in β-cyanoketones **4** are markedly influenced by the second substituent attached to the carbonyl moiety. Compounds carrying a (cyclo)aliphatic rest (**4n**: 560, **4o**: 561 ppm) show somewhat larger shifts, whereas congeners with aromatic (**4d**: 542, **4f**: 521, **4j**: 536 ppm) or heteroaromatic substituents (**4k**: 510 ppm) exhibit smaller ones, obviously depending in addition on the electron donating properties of the (hetero)aromatic moiety. A similar trend regarding the influence of substituents attached to the phenyl ring of related acetophenones can be read off from the data of **R1**-**R9**, which are incorporated in Table 2 for comparison purposes. Expectedly, substitution of the nitrile moiety in **4d** by hydrogen (**R1**), methyl (**R2**) or chlorine (**R3**) has a comparably smaller effect on the ^{17}O chemical shift of C=O.

In conclusion, given the excellent nucleophilicities of nitrile-type carbanions and the unique acylating properties of Weinreb amides, we have developed a simple, efficient, protocol for the synthesis of variously functionalised α-cyanoketones. Key features of the method are: a) uniformly high yields, without necessity to purify by chromatography, depending neither on the substituted acetonitrile structure nor on the Weinreb amide used; b) possibility to access polysubstituted cyanomethylketones by simply selecting the proper R^1R^2CLiCN carbanion; c) excellent chemoselectivity found in particular systems such as α,β-unsaturated Weinreb amides.

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Notes and references

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