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C-Metalated Nitriles: Electrophile-Dependent Alkylations and Acylations

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Abstract

Sequential carbonyl addition-conjugate addition of Grignard reagents to 3-oxocyclohex-1-ene-1-carbonitrile generates *C*-magnesiates nitriles whose alkylation stereoselectivities intimately depend on the nature of the electrophile. Alkylating these *C*-magnesiates nitriles with alkyl halides, sulfonates, and unstrained ketones occur with retention of the C-Mg configuration, whereas aldehyde and acyl cyanide acylations proceed with inversion of stereochemistry. Mechanistic probes indicate that the stereoselectivity is controlled by stereoelectronic effects for most electrophiles except allylic, benzylic, and cyclopropyl halides where single electron transfer processes intervene. Screening numerous alkylations of *C*-magnesiates nitriles with a diverse range of electrophiles reveals the reaction scope and delineates the fundamental stereoelectronic effects responsible for the highly unusual electrophile-dependent alkylations.

Introduction

Metalated nitriles are powerful nucleophiles that are broadly effective in a diverse range of alkylations.¹ The exceptional nucleophilicity stems from the inductively stabilized² negative charge density localized on the formally anionic carbon. Inductive stabilization² of metalated nitriles, rather than resonance delocalization, is conspicuous from nucleophilicity trends,³ acidity measurements,⁴ and NMR analyses,⁵ and is clearly manifest in the bond distances of metalated nitriles in the solid state.⁶ Particularly significant is the C≡N bond length (1.14–1.20 Å, Figure 1) of metalated nitriles, which is virtually identical to the C≡N bond length of neutral nitriles (1.14 Å).⁷ Correspondingly, the C-CN bond length (1.36–1.45 Å) is appreciably contracted relative to a C-C single bond, reflecting the electrostatic attraction between the negatively charged ‘carbanion’ and the strongly² electron withdrawing nitrile group.

Inductive stabilization of metalated nitriles creates two potential metal coordination sites: at the nitrile nitrogen, and at the adjacent anionic carbon (Figure 1, compare **3** and **4**). Extensive solid state⁶ and solution⁸ analyses reveal that lithiated nitriles exhibit a distinct preference for *N*-coordination with a planar geometry at the formally anionic carbon (**1**, Figure 1).⁹ In contrast, the sodiated nitrile **2** is *N*-metalated and partially pyramidal, typifying the range of solid state structures observed for metalated nitriles.¹⁰ Metalated nitriles with transition metal counter ions show an almost equal propensity for *C*- and *N*-coordination¹¹ with several *N*-metalated nitriles having ruthenium¹² or palladium¹³ counter ions, such as **3**, being converted to their thermodynamically more stable *C*-metalated counterparts **4**, upon heating. The geometry and coordination of synthetically valuable magnesiates¹⁴ and zincated nitriles¹⁵

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Supporting Information Available. Experimental procedures, ¹H NMR, and ¹³C NMR spectra for all new compounds and CIF and ORTEP's for all structures assigned by x-ray crystallography. This material is available free of charge via the Internet at <http://pubs.acs.org>.

remains to be determined by crystallography, although NMR and IR analyses indicate C-metalation in both cases.¹⁴⁻¹⁶

Distinctly different regio- and stereoselectivity preferences emanate from *N*- and *C*-metalated nitriles. For example, intercepting the putative⁸ *N*-lithiated nitrile **6a** with propargyl bromide affords alkynenitrile **7a** through an S_N2 displacement (Scheme 1), whereas alkylation of the analogous *C*-cuprated nitrile **8a** with propargyl bromide gives the S_N2' allenynitrile **7b**.^{14a} Similarly, alkylations of the *N*-lithiated, conformationally locked nitrile **6b** are only modestly diastereoselective, with preferential equatorial methylation affording **7c** in a 2.8:1 ratio (86%).¹⁷ In contrast, alkylation of the putative *C*-magnesiased nitrile **8b** affords **7c** exclusively, under otherwise identical conditions (Scheme 1).^{14b}

The excellent alkylation stereoselectivities of *C*-metalated nitriles highlights the potential of configurationally stable, chiral, *C*-metalated nitriles. Experimentally, overcoming the difficulty of synthesizing *C*-magnesiased nitriles is possible by employing internal coordination to favor formation of pyramidal, *C*-magnesiased nitriles.¹⁸ Remarkably, the resulting *C*-magnesiased nitriles exhibit electrophile-dependent alkylation stereoselectivities previously unprecedented in alkylations of metalated nitriles.¹⁹ Comprehensively surveying the alkylations of cyclic *C*-magnesiased nitriles establishes key electrophile-dependent alkylation trends, reveals the scope of the reaction, and delineates the fundamental stereoelectronic effects responsible for the unusual stereoselectivity preferences.

Results and Discussion

Synthesis of an asymmetric, *C*-magnesiased nitrile was probed by deprotonating a cyclohexanecarbonitrile capable of strong internal coordination. Direct formation of magnesiased nitriles is challenging since magnesium amides do not effectively deprotonate aliphatic nitriles,²⁰ whereas Grignard reagents typically²¹ add to, as well as deprotonate, unactivated nitriles.²² Conceptually, selective deprotonation of nitriles with Grignard reagents is possible by rapidly forming an alkylmagnesium alkoxide²³ in which coordination directs internal proton abstraction *and* geometrically prevents internal alkyl delivery to the electrophilic nitrile group (**9a** → **10a**; Scheme 2). In practice, sequential addition of *i*-PrMgBr and methyl iodide to hydroxy nitrile **9a**²⁴ affords exclusively the *axially* methylated nitrile **9b**—in direct contrast to the usual²⁵ equatorial alkylation of *N*-lithiated cyclohexanecarbonitriles (compare with Scheme 1).

The remarkable installation of a 1,3-diaxial interaction, overriding typical steric preferences,²⁵ implies that stereoelectronic effects direct the retentive alkylation via the *C*-magnesiased nitrile **11a**. Support for the intermediacy of *C*-magnesiased nitrile **11a** stems from the stereodivergent methylation of the corresponding *N*-lithiated nitrile **12a** where steric effects are the sole determinant of the alkylation stereochemistry. Deprotonating **9a** with LDA, followed by addition of BuLi to prevent internal proton return,²⁶ generates the *N*-lithiated nitrile **12a** that alkylates methyl iodide exclusively²⁷ from the sterically more accessible equatorial direction to afford **13b** (Scheme 2). The stereodivergent alkylations of the *C*- and *N*-metalated nitriles **11a** and **12a** stimulated a comprehensive series of alkylations of *C*-magnesiased nitriles with an array of electrophiles.

***C*-Magnesiased nitrile alkylations with alkyl halides.** Rapid access to different *C*-magnesiased nitriles was conveniently achieved through sequential 1,2-1,4-Grignard additions²⁸ to 3-oxocyclohex-1-ene-1-carbonitrile (**14**,²⁹ Scheme 3). Addition of methylmagnesium chloride to **14** generates the halomagnesium alkoxide **15** which exchanges^{23a} with a second Grignard reagent to afford **16** that, in turn, triggers conjugate addition³⁰ to the alkenenitrile functionality. The resulting bis-magnesiased nitrile **17** is

conformationally destabilized by the two axial alkyl substituents, favoring equilibration to the C-magnesiased nitrile **11** (cf. **11a**, Scheme 2).

Alkylating the C-magnesiased nitrile **11** with an array of electrophiles reveals a remarkable electrophile-dependent stereoselectivity (Table 1).^{19,31} Prior coordination between the electrophile and the magnesium atom of **11** does not appear to control the stereoselectivity³² since alkylation with Me₂SO₄, an electrophile capable of metal-directed alkylation,³³ affords exactly the same axially methylated nitrile **9b** as that obtained by alkyating with MeI (Table 1, entries 1-2). Intercepting **11** with the more sterically demanding propyl iodide maintains the preference for axial alkylation despite the increased steric compression relative to alkylation with MeI (Table 1, entry 3). Alternatively, increasing the steric demand in the methylation by incorporating a phenyl group adjacent to the magnesiased nitrile-bearing carbon, still furnishes the axially methylated nitrile (Table 1, entry 4).

Despite significant steric compression, the C-magnesiased nitrile **11** consistently intercepts alkyl halides and sulfonates with an exclusive preference for axial alkylation. Axial alkylation of the C-magnesiased nitrile **11** requires side-on overlap of the electrophilic σ^* orbital with the large lobe of metal carbon σ bond³⁶ in a retentive, electrophilic substitution- S_E2_{Ret} ³⁷ (Scheme 4, **11a''**). Although the side-on orbital overlap is far from optimal, the alternative co-linear approach of an sp³ hybridized electrophile to the small σ lobe of the C-Mg bond is sterically prohibitive (Scheme 4, **11a'**).³⁷ Reducing the side-on orbital overlap by alkylating **11a** with PrBr, having a smaller σ^* orbital, is considerably more difficult³⁸ than with PrI, leading to incomplete alkylation (13% of **9c** for PrBr compared to 70% for PrI). The reactivity difference is not due to a competitive E₂ elimination with PrBr since the addition of D₂O results in high deuterium incorporation from the axial direction, analogous to preferential axial protonation upon addition of aqueous NH₄Cl (Table 1, entry 5).³⁹ Collectively, these comparative alkylations indicate that C-magnesiased nitriles require the more reactive alkyl iodides as electrophiles since incomplete alkylation occurs with the less reactive alkyl bromides.

The retentive alkylations of C-magnesiased nitriles with alkyl halide and sulfonate electrophiles contrast with the non-selective alkylations of **11** with allyl and benzyl bromide (Table 1, entries 6-8). Conceptually, the more reactive benzylic and allylic electrophiles, having larger σ^* orbitals, might be able to access the small lobe of the Mg-C σ -bond for alkylation through an $S_E2_{(Inv)}$ mechanism in addition to a side-on $S_E2_{(ret)}$ alkylation (cf. **11a'** and **11a''**, Scheme 4). Alternatively, single electron transfer (SET) from the electron rich C-magnesiased nitrile **11**, formally a dianion, could generate a radical cation and an alkyl bromide radical anion.⁴⁰ Subsequent bromide ejection from the radical anion and non-selective radical-radical recombination would account for the mixture of diastereomers.

Differentiating between these mechanistic scenarios was achieved through alkylations with cyclopropylmethyl iodide (Scheme 5).⁴¹ Cyclopropylmethyl iodide is a useful mechanistic probe:⁴² cyclopropylmethyl substitution provides evidence for an ionic S_N2 displacement whereas butenyl alkylation, through single electron transfer, ring opening, and radical-radical recombination (**18**), indicates radical formation (Scheme 5).⁴³ Experimentally, alkylating **11a** with cyclopropylmethyl iodide affords approximately equal ratios of cyclopropylmethyl carbonitriles (**9q** and **13q**) and but-3-enyl carbonitriles (**9r** and **13r**), implying that a combination of electrophilic $S_E2_{(Inv)}$ and $S_E2_{(Ret)}$ alkylations compete with single electron transfer processes.⁴⁴ A similar mechanistic scenario accounts for the diastereomers generated during alkylations with allyl and benzyl bromide (Table 1, entries 6-8).

C-Magnesiased nitrile alkylations with carbonyl electrophiles. Carbonyl electrophiles exhibit an extremely delicate stereoselectivity dependence in alkylations with the C-magnesiased nitrile **11** (Table 1, entries 9-15).⁴⁵ Alkylations with phenyl isocyanate,

cyclohexanone, and acetone proceed with exclusive retention of configuration (Table 1, entries 9-11) whereas cyclopropanecarboxaldehyde and cyclobutanone afford primarily the nitriles resulting from equatorial alkylation (Table 1, entries 12-13).⁴⁶ In contrast, magnesiated nitrile **11a** reacts with excess methyl cyanoformate and benzoyl cyanide to afford bis-acylated nitriles in which C-acylation occurs only from the equatorial direction (Table 1, entries 14 and 15).

A tentative explanation for the stereoselectivity differences exhibited in alkylations of **11** with carbonyl electrophiles emerges by comparing the reactivity of the π^* orbitals. Particularly reactive carbonyl electrophiles, with large, diffuse π^* orbitals, such as methyl cyanoformate and benzoyl cyanide, exert a sufficiently small steric demand to permit a co-linear approach to the small σ lobe of the C-Mg bond (**11a'''**, Figure 2). The co-linear trajectory, while more hindered than the side-on axial approach, benefits from a more favorable orbital overlap. Carbonyl electrophiles with a large steric demand, such as cyclohexanone, are unable to achieve sufficient proximity for overlap in a co-linear equatorial approach and preferentially alkylate by side-on overlap (**11a''''**, Figure 2).

The difference in the sizes of the π^* orbitals effectively explains the rather perplexing 7:1 preference for the equatorial alkylation with cyclobutanone and the axial alkylation with acetone (Table 1, entries 13 and 11, respectively). The larger π^* orbital of cyclobutanone,⁴⁷ permits a more facile $S_E2(\text{Inv})$ by more effectively interacting with the small σ lobe in **11a'''** than acetone which has a similar steric demand, but a smaller π^* orbital and therefore preferentially alkylates only from the axial orientation. Acylations with methyl cyanoformate and benzoyl cyanide, particularly electron deficient electrophiles with large π^* orbitals, similarly react through $S_E2(\text{Inv})$ processes.⁴⁵

Conclusion

Alkylations of C-magnesiated nitriles exhibit an unprecedented stereoselectivity dependence on the nature of the electrophile. C-Magnesiated nitriles efficiently alkylate alkyl iodides and sulfonates with retention of stereochemistry whereas acylations with aldehyde and acyl cyanide electrophiles occur with inversion of stereochemistry. Mechanistic probes indicate that the alkylations of C-magnesiated nitriles are primarily controlled by stereoelectronic effects, depending intimately on the size of the antibonding σ^* or π^* orbital. Allyl- and benzyl bromide and cyclopropylmethyl iodide are exceptions in which single electron transfer processes compete with substitution reactions.

The stereoelectronically controlled alkylations of C-magnesiated nitriles are stereochemically complementary to the sterically controlled alkylations of N-metalated nitriles. Synthetically, these two divergent strategies permit selective installation of diastereomeric, quaternary centers from a single metalated nitrile.

Experimental⁴⁸

General Grignard addition-alkylation procedure: A THF solution of the Grignard reagent (2 equiv) was added to a -78 °C, THF solution (0.1M) of 3-oxocyclohex-1-ene-1-carbonitrile (**14**).²⁹ After 1 h at -78 °C, a THF solution of the second Grignard reagent (1.5 equiv) was added, or for reactions with only one Grignard reagent, 3.5 eq was added initially. The mixture was stirred at -78 °C for 10 min, and then warmed to room temperature. After 1.5 h, the electrophile (3 equiv) was added neat, either at room temperature or with prior cooling to -78 °C. Subsequent addition of saturated NH_4Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried (MgSO_4), concentrated, and purified by radial chromatography to afford the pure nitrile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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45. No alkylation was observed between **11a** and DMF, methyl benzoate, or dimethyl carbonate
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hydrolyzes to **iii**

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Figure 1.
X-Ray Structures of *N*- and *C*-Metalated Nitriles.

Scheme 1.
Divergent Regio- and Stereoselectivities of *N*- and *C*-Metalated Nitriles

Scheme 2.
Stereodivergent Alkylations of *N*- and *C*-Magnesiased Nitriles.

Scheme 3.
Sequential 1,2-1,4-Grignard Additions to Oxonitrile **14**.

Scheme 4.
Stereoelectronic $S_{E2}(\text{Ret})$ Alkylations of Metalated Nitriles

Scheme 5.
Mechanistic Probe for C-Metalated Nitrile Alkylations

Figure 2.
Stereoelectronic control with carbonyl electrophiles.

Table 1.
Electrophile-Dependent Alkylations of C-Magnesiated Nitriles

Entry	Grignard Reagent R^1MgX ; R^2MgX	Electrophile	Nitrile ^a	Yield ^b
1	MeMgCl (excess)	Mel		86%
2	MeMgCl (excess)	Me ₂ SO ₄		57%
3	MeMgCl (excess)			70%
4	MeMgCl; PhMgCl	Mel		71%
5	MeMgCl (excess)	NH ₄ Cl		90%
6	MeMgCl (excess)			71%
7	MeMgCl (excess)	BnBr		71%
8	MeMgCl; PhMgCl	BnBr		61%

Entry	Grignard Reagent R^1MgX ; R^2MgX	Electrophile	Nitrile ^a	Yield ^b
9	MeMgCl (excess)	$\text{O}=\text{C}=\text{N}_2\text{PI}$		58%
10	MeMgCl (excess)			68%
11	MeMgCl (excess)			64%
12	MeMgCl (excess)			55% ^c
13	MeMgCl (excess)			59% ^d
14	MeMgCl (excess)			55%
15	MeMgCl (excess)			61%

^aUnless stated otherwise the stereochemical assignments are based on x-ray crystallographic analysis.

^bRepresents the overall 3-step yield for 1,2-addition, 1,4-addition, and alkylation.

^cThe cyclopropylmethyl stereochemistry was assigned by intramolecular etherification to **9o**.³⁴

^d Stereochemical assignments are based on the downfield shift of an equatorial nitrile carbon in ¹³C NMR spectra.³⁵