Synthetic Methods

International Edition: DOI: 10.1002/anie.201607806
German Edition: DOI: 10.1002/ange.201607806

Direct Conversion of Nitriles to Alkene "Isonitriles"

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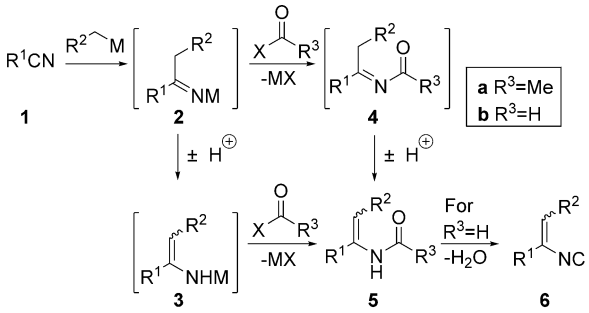
Abstract: *The sequenced addition of RLi to nitriles, trapping with isopropylformate, and dehydration with phosphoryl chloride provides an efficient, direct synthesis of alkene isocyanides. The one-pot sequence involves a series of carefully orchestrated steps: addition, formylation, tautomerization, and dehydration, with CuCN catalyzing a key equilibration of a formyl imine to an N-formyl enamine. The resulting aromatic alkeneisocyanides, that are otherwise challenging to synthesize, engage in an unusual [4+2]-type cycloaddition/1,3-H shift/ decyanation sequence to afford substituted naphthalenes.*

Isocyanides are exceptionally versatile synthetic precursors that react with nucleophiles, electrophiles, radicals, and transition metals to rapidly generate complex molecules.[1] The ambident reactivity of isocyanides stems from the unique electronic configuration of the formal carbene carbon that often serves as a central connection point in heterocycle synthesis.[2]

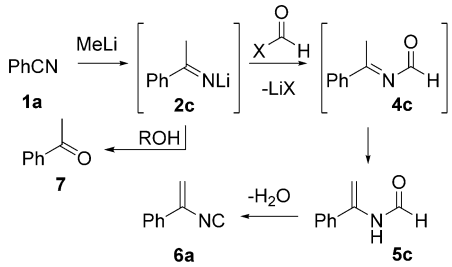
Despite the demonstrable value of isocyanides, few are commercially available in gram quantities.[3] Access to alkeneisocyanides is particularly acute because few methods exist for their synthesis[4] though an exception is the recent use of isocyanomethylenetriphenylphosphorane.[5] Classic carbonyl condensations of activated alkylisocyanides are complicated by concomitant hydrolysis to the corresponding formamide.[6] The paucity of methods to synthesize alkeneisocyanides currently limits their use in synthesis and is stifling the discovery of new reactions. Described below is a direct, one-pot method that addresses the challenge of synthesizing alkeneisocyanides and the disclosure of a new [4+2]-type cycloaddition with alkeneisocyanides.

The alkeneisocyanide synthesis is predicated on a method for synthesizing *N*-acyl enamines **5a** (Scheme 1).[7] The *N*-acyl enamines **5a** were generated by nucleophilic addition of organolithiums to a nitrile (**1**) followed by acylation of metalloimine **2** and isomerization to the *N*-acyl enamine **5a**. Conceptually, an analogous formylation of metalloimine **2**, isomerization of **4b** to the *N*-formyl enamine **5b**, and dehydration should generate the alkeneisocyanide **6**. Coaxing **2** to the reversed sequence: equilibration (**2**→**3**), formylation (**3**→**5**), and dehydration, would also provide alkeneisocyanide **6**.

Initial forays to convert benzonitrile (**1a**) to the alkeneisocyanide **6a** explored sequential addition of methyllithium



Scheme 1. Nitrile to alkeneisocyanide conversion.



Scheme 2. Direct conversion of benzonitrile to 1-phenyl alkeneisocyanide.

and formylation of lithio imine **2c** (Scheme 2).[8] ^{1}H NMR analysis of the crude reaction mixture indicated the formation of the *N*-formyl enamine **5c**, acetophenone (**7**), and a species tentatively assigned as the formyl imine **4c**; identification of **4c** implies that formylation (**2c**→**4c**, Scheme 2) precedes equilibration (cf. **2b**→**3b**, Scheme 1). Presumably acetophenone (**7**) arose from adventitious protonation of the metalloimine **2c** followed by hydrolysis. Raising the molar ratio of methyl formate from 2 to 5 equivalents, to out-compete protonation of the imine **2c**, increased conversion to the *N*-formyl enamine **5c**.

The equilibration of **4c** to **5c** is likely triggered by the lithium methoxide released upon formylation, with the methanol, formed upon deprotonation, facilitating the proton transfers. Reasoning that methanol might prematurely protonate the metalloimine **2c**, the formylation was performed with isopropyl formate with the expectation that the less basic isopropanol would minimize protonation of **2c**. An increase in the ratio of **5c**:**7** to 7:1 is consistent with this mechanistic understanding. Conversion to the *N*-formyl enamine **5c** was further improved by performing the reaction at 50 °C (> 99:1 ratio of **5c**:**7**).

Further optimization was performed after dehydration of the formyl enamine **5c** to the alkeneisocyanide **6a** because **5c** was strongly adsorbed on silica gel during purification.

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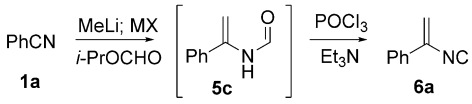
Several dehydrating reagents (phosphoryl chloride, trifluoromethanesulfonic anhydride, and triphosgene) were evaluated in the quest to directly convert the *N*-formyl enamine **5c** to the alkeneisocyanide **6a**. Phosphoryl chloride, with added Et_3N, although typically used in dichloromethane,[9] performed admirably in THF.[10] A curious cation effect was observed during optimization; while organolithiums worked well the analogous reaction with Grignard reagents gave complex mixtures.

During optimization, CuCN was added to promote the addition of MeLi to the nitrile.[11] ^{1}H NMR monitoring indicated an improved yield with CuCN, not from an improved addition, but by promoting the isomerization of **4c** to **5c** (Table 1).[12] Although CuI, CuBr·SMe_2, and 4-MePhSCu exerted only a modest influence on the reaction

Table 1: Effect of metal salts on alkeneisocyanide yield.[a]



Entry	Metal salt (mol%)	Yield [%]
1	–	39
2	LiBr (120)	30
3	CuCN (10)	43
4	CuI (10)	40
5	CuBr·SMe_2 (10)	38
6	4-MePhSCu (10)	34
7	CuCN (5)	58
8	CuCN (2)	73

[a] Reaction conditions: MeLi (1.2 equiv) was added to a 0 °C, THF solution (0.1 M) of the nitrile (1.0 equiv) and the metal salt. After 15–30 min, neat isopropyl formate (5.0 equiv) was added. After 16 h, the reaction was cooled to −30 °C and then neat phosphoryl chloride (3.0 equiv) and triethylamine (9.0 equiv) were added.

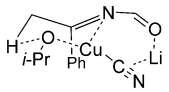
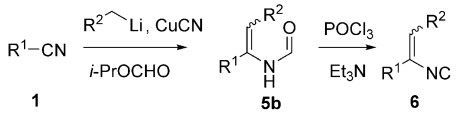


Figure 1. Cu-assisted deprotonation of *N*-formyl imine **4c**.

(Table 1, entries 3–6), an increased efficacy occurred with CuCN at decreased loading (Table 1, compare entry 3 with entries 7 and 8). The addition of LiBr was deleterious, suggesting that CuCN does not only function as a Lewis acid[7] (Table 1, entry 2). Although speculative, the CuCN may facilitate the equilibration of the *N*-formyl imine **4c** to *N*-formyl enamine **5c** though a 6-membered copper complex (Figure 1).

The reaction scope was explored with a series of alkyllithiums and nitriles (Table 2). Methyl, ethyl, or butyl lithium added equally well to benzonitrile to afford alkeneisocyanides **6a** and *Z*-**6b**–**6c**[13] (Table 2, entries 1–3). Aromatic nitriles with alkyl or aryl substituents (Table 2, entries 4–6), electron-rich substituents (Table 2, entries 7–9), and an electron-deficient chloride[14] (Table 2, entry 10) efficiently formed the corresponding alkeneisocyanides **6d**–**6j**. The TBS and benzyl protecting groups are unaffected during the process (Table 2, entries 7 and 9). Double addition of MeLi to the two cyano groups of terephthalonitrile

Table 2: Synthesis of alkeneisocyanides from nitriles.[a]



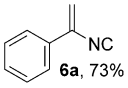
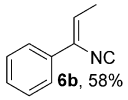
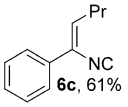
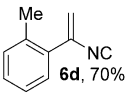
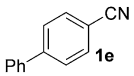
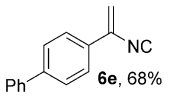
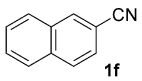
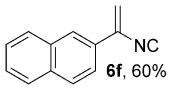
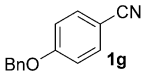
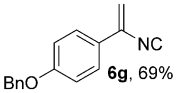
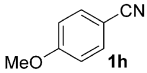
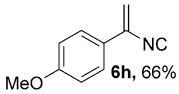
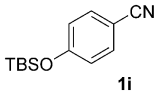
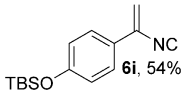
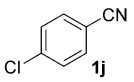
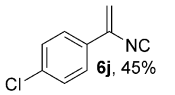
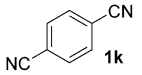
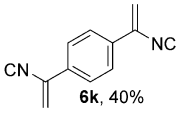
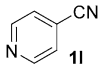
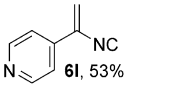
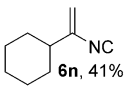
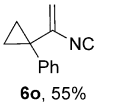
Entry	Nitrile	RLi	Alkeneisocyanide
1	 **1a**	MeLi	 **6a**, 73%
2	 **1a**	EtLi	 **6b**, 58%
3	 **1a**	BuLi	 **6c**, 61%
4	 **1d**	MeLi	 **6d**, 70%
5[b]	 **1e**	MeLi	 **6e**, 68%
6	 **1f**	MeLi	 **6f**, 60%
7	 **1g**	MeLi	 **6g**, 69%
8	 **1h**	MeLi	 **6h**, 66%
9	 **1i**	MeLi	 **6i**, 54%
10[c]	 **1j**	MeLi	 **6j**, 45%
11[d]	 **1k**	MeLi	 **6k**, 40%
12[e]	 **1l**	MeLi	 **6l**, 53%
13	 **1n**	MeLi	 **6n**, 41%
14	 **1o**	MeLi	 **6o**, 55%

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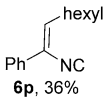
Table 2: (Continued)

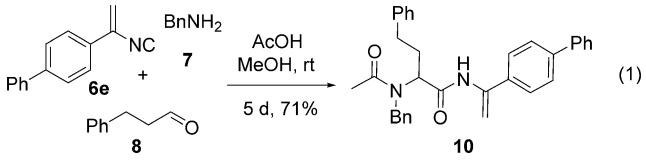
Entry	Nitrile	RLi	Alkene-isocyanide
15	 **1p**	PhLi	 **6p**, 36%

[a] Reaction conditions: RLi (1.2 equiv) was added to a 0 °C, THF solution (0.1 M) of the nitrile (1.0 equiv) and CuCN (2 mol %). After 15–30 min, neat isopropyl formate (5.0 equiv) was added and then the reaction was heated to 50 °C. After 12–20 h, the reaction was cooled to −30 °C and then neat phosphoryl chloride (3.0 equiv) and triethylamine (9.0 equiv) were added. [b] The yield of a 2.8 mmol reaction afforded 65 % (372 mg) of **6e**. [c] Employed an inverse addition of the nitrile to MeLi and CuCN. [d] MeLi (2.4 equiv), isopropyl formate (10.0 equiv), phosphoryl chloride (6.0 equiv) and triethylamine (18.0 equiv). [e] The intermediate formamide **5l** was isolated, dissolved in dichloromethane, and dehydrated with $POCl_3/Et_3N$.

effectively delivered the symmetric alkeneisocyanide **6k** (Table 2, entry 11). Although heterocycles containing an adjacent nitrile reacted inefficiently,[15] the conversion of 4-cyanopyridine (**1l**) to the corresponding alkeneisocyanide **6l** demonstrated the viability of performing the reaction on heterocycles in which the heteroatom is remote from the isocyanide.

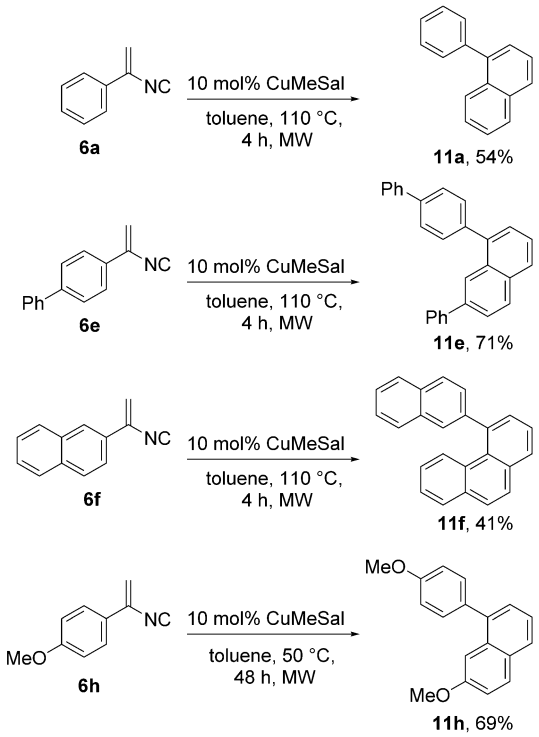
The direct conversion of *alkyl* nitriles to alkeneisocyanides can be performed using the same protocol (Table 2, entries 13–15). Addition of MeLi to cyclohexanecarbonitrile and 1-phenyl-1-cyclopropanecarbonitrile (Table 2, entries 13 and 14) afforded the alkeneisocyanides **6n** and **6o**. Reversing the isomerization point through the addition of phenyllithium to octanenitrile afforded a modest yield of alkeneisocyanide **6p** (Table 2, entry 15), presumably because of competitive deprotonation.

Alkeneisocyanides are valuable substrates for a variety of reactions. As an illustration, alkeneisocyanide **6e** was subjected to a four-component Ugi reaction with benzylamine (**7**), 3-phenylpropanal (**8**), and acetic acid (**9**) to afford amide **10** [71 % yield, Eq. (1)].



(1)

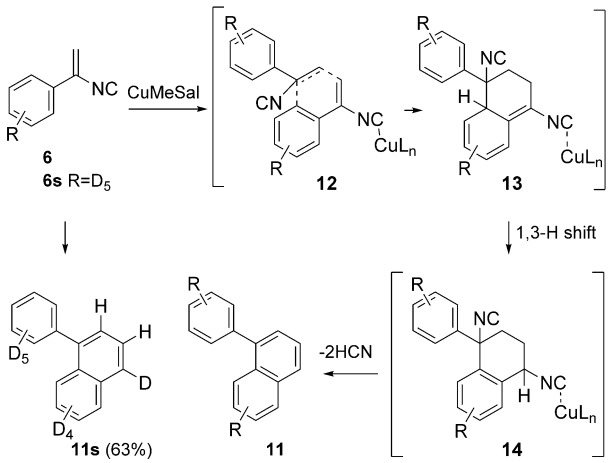
Access to diverse alkeneisocyanides provides precursors for exploring new chemistry. The venerable [4+2] cycloaddition is illustrative as this fundamental reaction is virtually unexplored with alkeneisocyanides.[16] Difficulties in coaxing the cycloaddition of alkeneisocyanides **6e** and **6h** to traditional dienes[17] led to an examination of copper(I) salts as catalysts because these are one of the few transition metal salts capable of reversible complexation with isocyanides.[18] From this lead, 10 mol % of copper methylsalicylate[19] was found to trigger a highly unusual [4+2] dimerization of **6a**, **6e**, **6f**, and **6h** to the corresponding naphthalenes **11a**, **11e**, **11f**, and **11h**, respectively (Scheme 3).[20]



Scheme 3. Alkeneisocyanide [4+2] cycloadditions.

The cyclization is presumed to occur via a [4+2] cycloaddition–decyanation sequence (Scheme 4).[21] Complexation of copper[22] likely activates the alkeneisocyanide for cycloaddition (**6**→**12**) to afford **13**. A 1,3-H shift in **13** restores the aromaticity which primes **14** for two sequential copper-assisted decyanations. Consistent with the mechanistic proposal, cycloaddition of the D_5-alkeneisocyanide **6s**[23] afforded the naphthalene **11s** in which the newly formed ring contains a transposed deuterium.

The one-pot RLi addition, formylation, equilibration, and dehydration provides a direct conversion of nitriles to



Scheme 4. Tentative cycloaddition mechanism.

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alkeneisocyanides that are otherwise challenging to synthesize. Aromatic and aliphatic nitriles react equally well in an efficient and general route to structurally diverse alkeneisocyanides. The alkeneisocyanides are valuable precursors, as illustrated by a multi-component reaction and a highly unusual [4+2] cycloaddition–decyanation sequence.

Acknowledgements

Financial support from the National Institutes of Health (2R15AI051352-04) and Drexel University is gratefully acknowledged. Allen Chao is thanked for experimental details pertaining to a 2.8 mmol scale reaction.

Keywords: alkeneisocyanide · copper catalysis · isocyanide · naphthalene · nitrile

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[3] Although numerous isocyanides are commercially available in milligram quantities, less than a dozen are readily available at commodity prices with 1-isocyanocyclohex-1-ene as the only readily available example of an alkeneisocyanide.

[4] a) M. C. Pirrung, S. Ghorai, T. R. Ibarra-Revera, *J. Org. Chem.* **2009**, *74*, 4110 – 4117; b) J. E. Baldwin, I. A. O'Neil, *Synlett* **1990**, 603 – 604; c) J. E. Baldwin, Y. Yamaguchi, *Tetrahedron Lett.* **1989**, *30*, 3335 – 3338; d) D. H. R. Barton, T. Bowles, S. Husinec, J. E. Forbes, A. Llobera, A. E. A. Porter, S. Z. Zard, *Tetrahedron Lett.* **1988**, *29*, 3343 – 3346; e) T. Saegusa, I. Murase, Y. Ito, *Tetrahedron* **1971**, *27*, 3795 – 3801.

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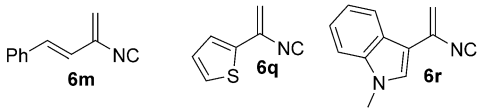
[14] Addition of MeLi to 4-iodobenzonitrile and 4-bromobenzonitrile failed to afford the corresponding metalloimines. Inverse addition of 4-chlorobenzonitrile to the methyllithium-CuCN solution was crucial to provide **6j** in reasonable yield.

[15] 2-Cyanopyridine afforded the *N*-formyl enamine but the dehydration is problematic, possibly because of complexation to the pyridine nitrogen and the formamide. Thiophene-2-carbonitrile and 1-methyl-1*H*-indole-3-carbonitrile afforded alkeneisocyanide **6q** (27%) and alkeneisocyanide **6r** (31%), respectively. Cinnamonitrile afforded alkeneisocyanide **6m** in 31% yield.



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[17] No reaction of **6a** or **6h** was observed with 3,4-dihydro-2*H*-pyran, ethyl acrylate, or benzylidenemalononitrile at temperatures up to 110 °C.

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[19] Reducing the amount of CuMeSal to 5 mol% led to 90% conversion and doubled the reaction time whereas with 1 mol% CuMeSal the reaction stalled at 30% conversion after 10 h at 110 °C.

[20] No [4+2] dimerization was observed with electron-deficient alkeneisocyanide **6j** or the methyl-substituted alkeneisocyanide **6b**.

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[23] Prepared in 53% yield following the standard procedure. See the Supporting Information for details.

Received: August 10, 2016
Revised: October 8, 2016
Published online: ■■ ■■, ■■■■

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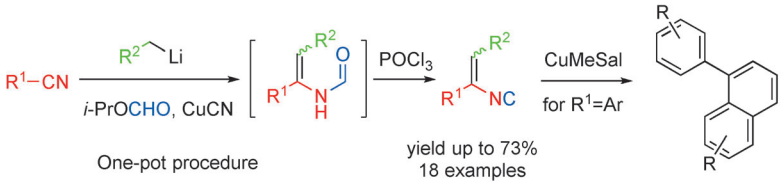
Communications

Synthetic Methods

Y. Li, F. F. Fleming* _____ ■■■■–■■■■

Direct Conversion of Nitriles to Alkene "Isonitriles"



An orchestrated sequence: An efficient synthesis of alkeneisocyanides is achieved through the sequenced addition of RLi to nitriles, formylation, and dehydration. A key step in this one-pot sequence is a CuCN-catalyzed equilibration of a formyl imine to an *N*-formyl enamine. The utility of the reaction is illustrated in a new [4+2]-type cycloaddition/1,3-H shift/decyanation.

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