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Isocyanide Isomerization

Asmic Isocyanide-Nitrile Isomerization-Alkylations

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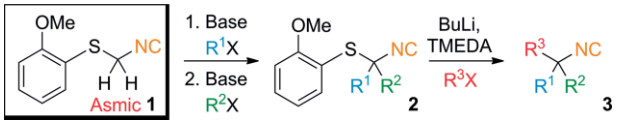
Abstract: Anisylsulfanylmethylisocyanide, Asmic, is a versatile building block whose alkylations provide a range of substituted isocyanides. The anisylsulfanyl group plays a critical role in the sequenced deprotonation-alkylation *and* the subsequent sulfanyl-lithium exchange. Complexation of the anisylsulfanyl group to BuLi in the presence of TMEDA affords a lithiated isocyanide whose alkylations generate trisubstituted isocyanides. In the absence of TMEDA, BuLi triggers cyanide expulsion to afford a transient carbene; reorientation of cyanide with attack at the carbene affords a lithiated nitrile whose alkylations afford quaternary *nitriles*. The complexation-induced isocyanide-nitrile rearrangement is exceptionally facile, occurring within 5 min at –78 °C. Detailed mechanistic and computational analyses identify the importance of chelation in the bifurcating mechanism: internal chelation favors cyanide extrusion to form a carbene whereas chelating agents favor arylsulfanyl-lithium exchange to generate a lithiated isocyanide. The combined experimental and computational analyses reveal a new mechanism for isocyanide-nitrile isomerization which provides valuable insight for rapidly assembling substituted isocyanides.

Introduction

Anisylsulfanylmethylisocyanide (Asmic, **1**) is a versatile isocyanide building block that provides rapid access to a range of isocyanides (Scheme 1).[1] Deprotonating Asmic (**1**) with LDA, NaH, or BuLi rapidly generates a potent nucleophile that intercepts an array of electrophiles through sequential deprotonation-alkylation cycles to install two substituents in one synthetic operation (**1**→**2**). Subsequent addition of BuLi to isocyanide **2** triggers an arylsulfanyl-lithium exchange affording a lithiated isocyanide that efficiently traps electrophiles to provide a range of di- and tri-substituted isocyanides (**3**, R^3 = H or R, respectively).



Scheme 1. Asmic alkylation route to substituted isocyanides **3**.

Results and Discussion

During the development of Asmic,[1] the sulfanyl-lithium exchange-alkylation of several isocyanides **2** afforded not the expected isocyanide **3** but the corresponding *nitrile* **4** (Scheme 2). Addition of BuLi to a –78 °C, THF solution of the acyclic and cyclic isocyanides **2a**–**2c** followed by BnBr triggered a remarkably facile synthesis of the corresponding benzylated nitriles **4a**–**4c** (Scheme 2). The rapid rearrangement at –78 °C in less than 5 minutes is extremely unusual[2] because isomerization of isocyanides to their thermodynamically more stable nitrile counterparts typically requires temperatures in excess of 200 °C.[3]

The limited stability of metalated isocyanides[4] suggested that the rearrangement might involve cyanide expulsion with formation of a carbene. Subsequent reorientation with attack from the carbon of the cyanide ion on the carbene[5] would generate a lithiated nitrile whose alkylation would afford the corresponding quaternary nitrile.[6] The speculation led to screening several additives known to suppress carbene formation:[7] HMPA, 18-crown-6, LiCl, DMPU, DME, KO*t*Bu and TMEDA. TMEDA proved optimal in suppressing the rearrangement, allowing for sulfanyl-lithium exchange-alkylations for a variety of electrophiles;[1] the exchange-stannylation of **2b** to afford isocyanide **2d**[8] is representative (Scheme 2).

Access to the stannyl isocyanide **2d** provided an independent route to access the lithiated isocyanide to probe the rearrangement. Addition of BuLi to the stannyl isocyanide **2d** and trapping with BnBr provided benzyl isocyanide **3a** without any trace of the corresponding nitrile[9] (Scheme 2). Efficient benzylation of the lithiated isocyanide prepared by stannyl-lithium ex-

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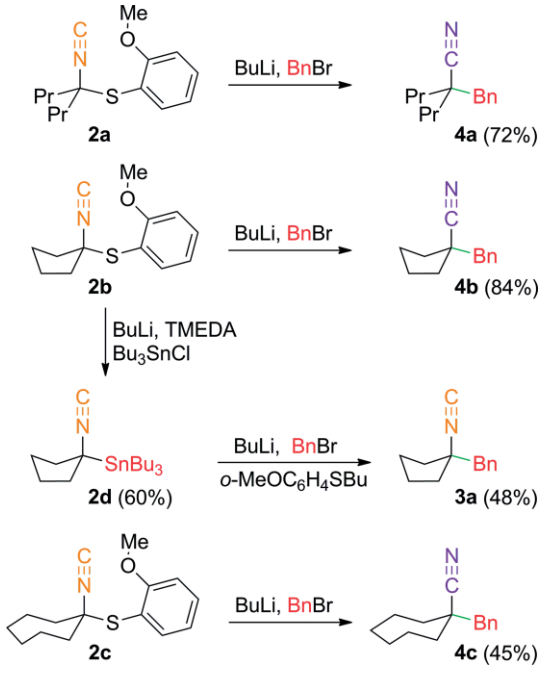
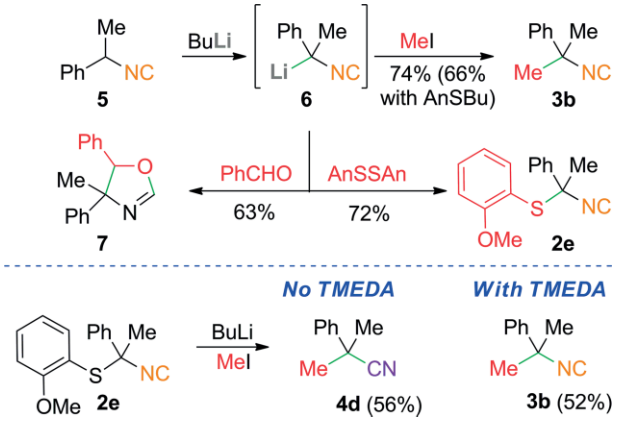


Scheme 2. BuLi-induced isocyanide to nitrile isomerization.

change implies that the isocyanide-nitrile isomerization must occur *prior* to the formation of the lithiated isocyanide. The macroscopic stability of the lithiated isocyanide is consistent with a previous stannyl-lithium exchange of a stannylmethyl isocyanide.[10]

Insight into the low temperature isocyanide-nitrile isomerization was gleaned from comparative lithiations of benzylic isocyanides **5** and **2e** (Scheme 3). Key to these lithiations is the direct deprotonation of benzylic isocyanides with BuLi[11] which provides a point of comparison for the exchange-lithiation of the anisylsulfanylisocyanide **2e**. Direct deprotonation of **5** followed by trapping with MeI, *o*-anisyl disulfide, or benzaldehyde afforded only the corresponding isocyanides **3b** and **2e**, or the oxazoline **7** derived from cyclization of an intermediate alkoxy isocyanide (Scheme 3).[12] Addition of exogenous anisylbutylsulfane (AnSBu), the disulfide produced in Asmic exchange-alkylations, to the lithiated isocyanide **6** prior to the addition of

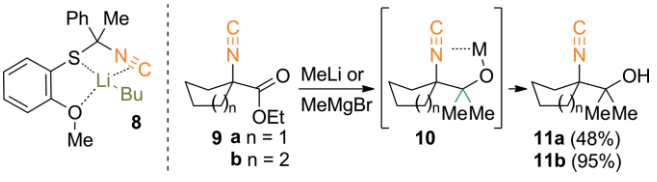


Scheme 3. Probing rearrangement-alkylations with benzylic isocyanides.

MeI afforded isocyanide **3b** (66 % yield). The logical inference is that the anisylbutylsulfane produced during the anisylsulfanyl-lithium exchange is not responsible for the isocyanide-nitrile isomerization.

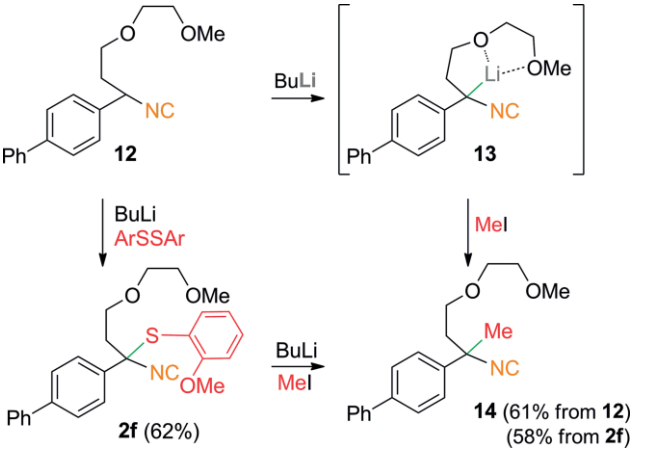
The lithiation-alkylations of the isocyanide **5** are in distinct contrast to the lithiation-alkylations of the Asmic-like isocyanide **2e** (Scheme 3). Sequential addition of BuLi and methyl iodide to isocyanide **2e** afforded the *nitrile* **4d**, pinpointing the crucial role of the anisylsulfanyl substituent in triggering the rearrangement. Repeating the sulfanyl-lithium exchange under identical conditions but with the addition of TMEDA gave only isocyanide **3b** (Scheme 3, bottom). The addition of TMEDA completely suppressed formation of the nitrile **4d**.

The efficacy of TMEDA to inhibit the isocyanide-nitrile isomerization suggested a role in disrupting internal complexation, possibly between lithium and the isocyanide π-electrons (**8**, Scheme 4).[13] Related metal complexation with nitrile π-electrons profoundly influence a range of reactions.[14] Speculating that an analogous lithium-π coordination might promote the isocyanide-nitrile isomerization, MeLi was added to the isocyanides **9a** and **9b** to promote rearrangement through the lithium alkoxide **10** (M = Li); no isocyanide-to-nitrile-rearrangement was observed. An analogous addition of MeMgBr to **9b** afforded the hydroxyisocyanide **11b** in 95 % yield, again without formation of the corresponding nitrile.



Scheme 4. Probing chelation in isocyanide-nitrile rearrangement.

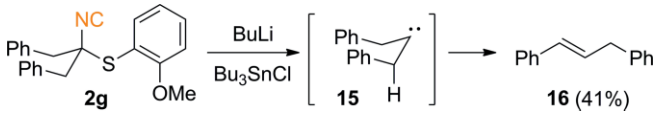
The role of chelation was further probed through comparative alkylations of the glycol-containing isocyanide **12** and the anisylsulfanyl-containing isocyanide **2f** (Scheme 5). Incorporating a glycol provides a complementary chelation motif to prevent lithiated isocyanide **13** from evolving to a carbene.[15] Addition of BuLi to **12**, in the absence of TMEDA, followed by



Scheme 5. Glycol complexation to prevent isocyanide-nitrile rearrangement.

MeI or AnSSAn afforded the isocyanides **14** and **2f**, respectively. Sequential addition of BuLi and MeI to the anisylsulfanyl isocyanide **2f** afforded isocyanide **14** in a similar yield as from **12** with no trace of the corresponding nitrile. Comparing the structurally similar isocyanides **2e** and **2f** (Scheme 3 and Scheme 5, respectively) implies that the glycol out-competes chelation of BuLi to the anisylsulfanyl moiety to suppress the isocyanide-nitrile rearrangement.

Strong support for the involvement of a carbene in the isocyanide-nitrile rearrangement came from a serendipitous attempt to stannylate isocyanide **2g** (Scheme 6). Sequential addition of BuLi and Bu_3SnCl to **2g** afforded 1,3-diphenylpropene (**16**) presumably through insertion of the intermediate carbene of **15** into one of the four benzylic C-H bonds.[16]



Scheme 6. Putative carbene insertion during sulfanyl-lithium exchange.

The bifurcation of the sulfanyl-lithium exchange in the presence or absence of chelators implicates a key role of lithium-isocyanide complexation in the rearrangement. Insight into the precise interplay between the exchange and isomerization was gained from computational modelling (Figure 1).[17] Calculations using a solvent continuum identified formation of the low energy complex **17** from BuLi and isocyanide **2b** in which lithium is coordinated to the oxygen and sulfur atoms of the sulfanyl ether. Fragmentation of **17**[18] leads to the lithiated isocyanide **18** in which lithium has η^3-bonding with the isocyanide π-system and O- and S-coordination with the sulfanyl ether. The η^3 bonding correlates with prior metalated isocyanide structures identified in computational analyses.[19]

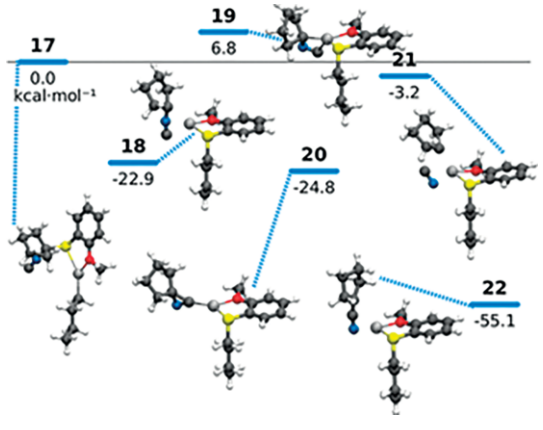


Figure 1. Computational identification of reactive intermediates in the sulfanyl-lithium exchange.

In the absence of TMEDA, the lithiated isocyanide **18** evolves to a lithiated azirine similar to the thermal isocyanide-nitrile mechanism.[3] Distortion of **18** through a bending at the central nitrogen leads to transition structure **19** in which lithium maintains an interaction with the formally anionic carbon (2.10 Å) and the isocyanide carbon (2.76 Å). Scission of the more substituted lithium–carbon bond with concomitant bonding between the two carbons affords the lithiated azirine **20**.[20] Cyanide ejection[21] from **20** via transition structure **21** exposes a formal carbene that suffers a carbon-centered attack by cyanide[5] to afford the π complexed lithiated nitrile **22**.[22]

Experimentally, the presence of TMEDA effectively prevents evolution of the lithiated isocyanide to the corresponding lithiated nitrile. Calculations that incorporate TMEDA were carried out in analogy with the carbene path (Figure 1). Isocyanide **2b**, TMEDA, and BuLi afforded complex **23** in which the lithium atom is bound to the butyl fragment with interactions with the two TMEDA nitrogen atoms, the isocyanide π-electrons, and sulfur (Figure 2). Fragmentation of **23** to lithiated isocyanide **24** directly parallels the computational progression in the absence of TMEDA (cf. Figure 1) except that subsequent evolution of **24** through the distorted transition structure **25** to the lithiated azirine **26** requires a significantly higher energy barrier (38.1 kcal/mol for **24** to **25** vs. 29.7 kcal/mol for **18** to **19**). The higher energy barrier to rearrangement with coordinated TMEDA allows interception of the lithiated isocyanide **24** by electrophiles.

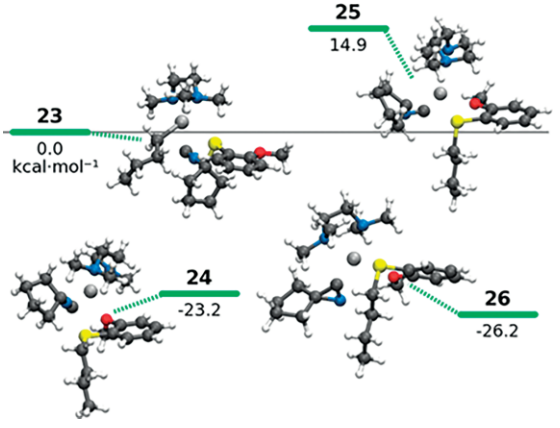


Figure 2. Influence of TMEDA in the sulfanyl-lithium exchange.

Exploring the precise orientation of the five-membered ring revealed an isomerization path that is dependent upon the cyclopentane conformation (Figure 3). The low-energy complex **18** that evolves from complex **17** (both common to Figure 1), can be distorted through bending of the central isocyanide nitrogen to access transition structure **27** (Figure 3)**.** Compared to the analogous structure **19**, the five-membered ring is bent in a different orientation which is considerably higher in energy. Progression through transition structure **27** leads to the lithiated azirine **28** which ruptures the ring carbon–nitrogen bond progressing through transition structure **29** to the lithiated nitrile **30**. Transition structure **29** does not show the carbene-like character present in structure **19**. The key difference between the evolution of **18** through transition structures **27** and **29** (Figure 3) vs. **19** and **21** (Figure 1) is their much higher energies (43.4 kcal/mol for **18** → **27** and 40.3 kcal/mol for **28** → **29**); the former isomerization pathway through **19** benefits from a delocalized interaction of the π-electrons with lithium that is not available in **27** or **29**. The value of these calculations lies in showing that conformation plays a role in the isocyanide-nitrile isomerization, casting light on why the conformationally

less mobile 6-membered isocyanides may not isomerize in the absence of TMEDA.[1]

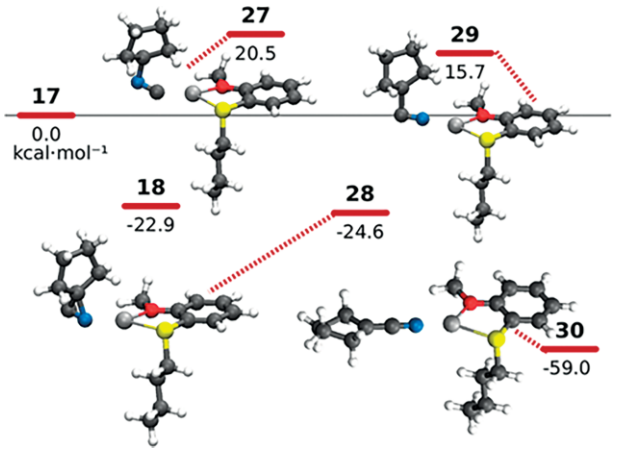
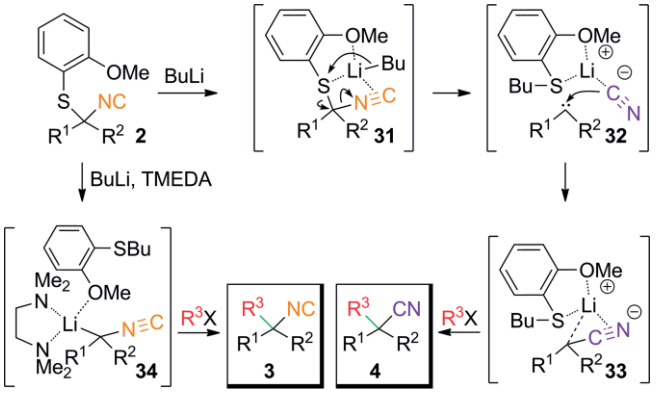


Figure 3. Effect of ring distortion over non-TMEDA path in the sulfanyl-lithium exchange.

The computational and mechanistic analyses are summarized in Scheme 7. Addition of BuLi to the anisylsulfanyl isocyanide **2** leads to chelation between lithium, the isocyanide π-cloud, and the oxygen and sulfur moieties (**31**). The three-point binding of BuLi facilitates nucleophilic attack on sulfur with concomitant ejection of cyanide (**31** → **32**). Reorientation of cyanide with attack on the carbene **32** generates the lithiated nitrile **33** whose alkylation affords the quaternary nitrile **4**. In the presence of TMEDA, addition of BuLi to **2** or substrates with an internal glycol-linker prevents complexation between lithium and the isocyanide allowing sulfur-lithium exchange to afford lithiated isocyanide **34**. Alkylation of **34** affords the substituted isocyanide **3**.



Scheme 7. Bifurcating exchange isocyanide-nitrile rearrangement mechanisms.

Conclusions

Asmic provides a versatile route to substituted isocyanides through a unique series of alkylations. The anisylsulfanyl group is critical for the sulfanyl-lithium exchange, an unusual process that affords a lithiated isocyanide or a lithiated nitrile depending on the presence or absence of TMEDA, respectively. The low temperature isocyanide-nitrile rearrangement-alkylation is highly unusual. Mechanistic experiments, supported by computational analyses, are consistent with formation of a carbene intermediate formed by ejection of isocyanide in the form of lithium cyanide. Reorientation and attack of cyanide on the carbene generates a lithiated nitrile that effectively alkylates electrophiles. Interrupting the cyanide ejection is readily achieved through addition of external TMEDA or with a glycol substituent. Effective lithium chelation allows efficient exchange-alkylations by preventing the isocyanide-to-nitrile isomerization. Collectively, the computational and mechanistic analyses provide insight into the isocyanide-nitrile rearrangement and provide robust conditions to prepare an array of substituted nitriles or isocyanides.

Experimental Section

Full experimental details including the computational analyses are provided in the supporting information.

Acknowledgments

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Keywords: Isocyanide · Rearrangement · Asmic · Carbenes · Alkylation

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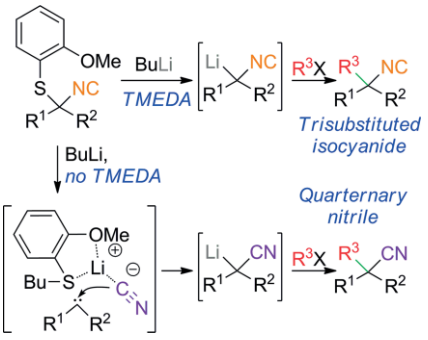
Asmic Isocyanide-Nitrile Isomerization-Alkylations



Carbene intermediates are implicated for the first time in an extremely unusual low temperature, isocyanide-to-nitrile isomerization. Chelators such as TMEDA redirect the exchange to a lithiated isocyanide whose alkylation affords trisubstituted isocyanides.

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