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Asmic: An exceptional building block for isocyanide alkylations

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Abstract

Asmic addresses the long-standing challenge of alkylating isocyanides, providing access to isocyanides with diverse substitution patterns. The *o*-anisylsulfanyl group serves a critical dual role by facilitating deprotonation-alkylation and in providing a latent nucleophilic site through an unusual arylsulfanyl-lithium exchange.

TOC Graphic

Isocyanides are prized reactants in an array of multicomponent¹ and transition metal insertion processes.² The versatility of isocyanides, particularly in generating pharmaceutical leads,³ obscures two major deficiencies, namely their limited commercial availability⁴ and the difficulty in synthesizing substituted congeners.⁵ Typically, isocyanides are accessed through late stage formylation-dehydration of amines or activated alcohols which build on a pre-existing carbon scaffold.⁶ The challenge lies in developing a method for rapidly assembling diverse isocyanides.

Unlike virtually any other electron withdrawing group, alkylation adjacent to the isocyanide functionality is extremely difficult; metalation is only efficient for alkylisocyanides with proximal chelating or electron withdrawing groups⁷ and methyl isocyanide, a toxic, noxious isocyanide.⁸ The challenge in alkylating isocyanides is captured in the LiTMP deprotonation of cyclohexylisocyanide (**1**) where trapping with benzaldehyde proceeds in only 6% yield (**1** → **2** → **3a**, Scheme 1).⁹ The difficulty stems from the low acidity of alkylisocyanides,¹⁰ the temperature sensitivity of the resulting metalated isocyanides,¹¹ and their propensity

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toward self-condensation.¹² The deprotonation constraint is problematic because the most bioactive isocyanide-containing natural products feature fully substituted cyclohexanes.⁶ Illustrative of the bioactivity of cyclohexylisocyanides are Kahlalinol F (**5**), a potential lead for treating copper accumulation, and the amphilectadiene **6** which is a potent anti-malarial agent (Figure 1).⁶

Exploratory attempts to alkylate cyclohexylisocyanide (**1**) revealed the inherent problem; the slow deprotonation generates a reactive, unstable organometallic (**2**) that is prone to attack the isocyanide functionality in the reactant and product. Optimal conditions to alkylate cyclohexyl isocyanide **1** employed (TMP)₂Mg.LiCl with excess propyl iodide in situ to rapidly intercept the lithiated isocyanide (**1** → **4a**). Although successful, the in situ protocol places significant constraints on the electrophile. The inherent difficulty of the deprotonation-alkylation requires a conceptually orthogonal strategy, one in which the nucleophilic isocyanide is rapidly generated and then selectively intercepted by external electrophiles.

Sulfoxide-metal exchange appeared attractive for generating metalated isocyanides **8** because the rapid exchange rate offered the potential to circumvent competitive self-condensation (Scheme 2). An extensive investigation with several sulfoxide-substituted isocyanides **7** validated the concept¹³ (**7** → **8** → **9**) but identified several intractable problems: a high propensity of **7** to eliminate sulfenic acid, irreversible adsorption on silica gel, and extensive decomposition. The instability of sulfoxide-substituted isocyanides **7** stimulated a different strategy predicated on a rare *arylsulfanyl* exchange-alkylation (Scheme 2, **11** → **8** → **9**).¹⁵

The requisite arylsulfanylmethylisocyanide precursors **10** were rapidly assembled through a two-step Mannich condensation (arylthiol, paraformaldehyde and formamide) followed by dehydration.¹⁶ Exploratory alkylations employed the naphthylmethylisocyanide **10a** (**10**, Ar = C₁₀H₇) because the relatively stable solid avoids the odiferous and noxious nature of the closely related phenyl and pyridyl analogs (**10**, Ar = phenyl, 2-pyridyl).¹⁷ Alkylation of **10a** with 1,5-dibromopentane was guided by developing chemistry on a prototype that would address the challenge of accessing substituted cyclohexylisocyanides.⁶ The double alkylation of **10a** proved straightforward with NaH in DMF though subsequent alkylations with Asmic (**10d**, Ar = *o*-methoxyphenyl) identified BuLi in THF as superior; sequential deprotonation-alkylation cycles of **10d** with BuLi allowed two different electrophiles to be introduced in one synthetic operation.

Initial attempts to perform an arylsulfanyl exchange-alkylation were not promising (Figure 2). The addition of various organometallics to naphthylisocyanide **12a** followed by benzyl bromide as a test electrophile afforded a complex reaction mixture.¹⁸ Close inspection of the crude reaction mixtures revealed varying amounts of naphthylbutylsulfide that was optimistically interpreted as evidence for the critical arylsulfanyl-lithium exchange. Building on this lead, a series of arylsulfanylmethylisocyanides **12** were synthesized in which the aromatic substituent was varied to optimize the exchange-alkylation.

Initial screening focused on heteroatom-substituted arylsulfanylcyclohexyl isocyanides **12** (Figure 2) because heteroatom coordination was speculated to both facilitate delivery of BuLi to the sulfide and to stabilize the resulting lithiated isocyanide.¹⁹ Although neither *o*-methylthiophenyl (**12b**) nor *o*-phenoxyphenyl (**12c**) substituents were effective, the *o*-methoxyphenyl substituent in **12d** was particularly efficacious. Para and para-meta methoxy substrates **12e** and **12f** did not engage in an arylsulfanyl-lithium exchange implying that the *o*-methoxyphenyl group (**12d**) facilitates the exchange through chelation rather than through an electronic activation. Consistent with the chelating role of the *o*-MeO group, the presence of additional methoxy substitution on the meta and para position was tolerated in **12g**, but provided no advantage over a single *o*-methoxy substituent. The *o*-methoxy, *o*-trifluoromethylphenyl-substituted isocyanide **12h** proved to be particularly delicate, decomposing upon storage and chromatography; an attempted exchange-alkylation afforded a complex mixture.

The efficacy of the Asmic-derived isocyanide **12d** led to exploring the generality of the exchange-alkylation (Table 1). Optimization experiments revealed the sulfanyl-lithium exchange to be complete in less than 5 minutes at -78°C . Electrophilic trapping was performed at -78°C because warming the solution of the putative lithiated isocyanide to 25°C followed by the addition of an electrophile led only to trace amounts of the alkylated isocyanide.¹¹ Alkyl iodides and bromides (entries 1–5) efficiently afforded alkyl isocyanides; tributylstannyl chloride afforded the stannyl isocyanide **4f** in an exceptionally high yield (entry 6). Carbonyl electrophile methyl benzoate gave ketone **4g**, whereas methyl cyanofomate gave ester **4h** (entries 7 and 8, respectively). Cyclohexenone cleanly afforded the keto isocyanide resulting from a conjugate addition, but the isolated yield was compromised by the limited stability of **4i** (entry 9). Trapping with cyclohexanone afforded oxazoline **3b** through attack of the initial alkoxide onto the isocyanide (entry 10). Access to the stannyl isocyanide **4f** provided an independent lithiation route to the oxazoline **3b** with virtually identical efficiency, suggesting that the same lithiated isocyanide is generated in each process.²⁰ Successful alkylation of **12d** with α -bromoacetophenone to afford **3c** required prior transmetalation with Et_2Zn to prevent competitive deprotonation of the acidic methylene (entry 11).²¹ Collectively, these alkylations demonstrate the efficacy of the Asmic sulfanyl-lithium exchange-alkylation over prior deprotonation strategies (cf. **1** $\rightarrow$ **3a**, Scheme 1) by providing an efficient method to access a range of substituted cyclohexylisocyanides.

The bioactivity driven decision to explore the exchange-alkylation with the 6-membered isocyanide **12d** as a prototype proved to be fortuitous. Performing the same BuLi-induced exchange with the 5-membered isocyanide **13** and trapping with benzyl bromide efficiently afforded, not the expected isocyanide, but the corresponding *nitrile* **14a** (eq. 1). The facile rearrangement-alkylation is extremely unusual as isocyanide-nitrile isomerizations typically require temperatures in an excess of 200°C .²² Surmising that the lithiated isocyanide might exhibit carbene character, several metal chelators (HMPA, 18-crown-6, LiCl, DMPU, DME, KOt-Bu and TMEDA) were added in an attempt to suppress the rearrangement.²³ Among these, the introduction of TMEDA to a -78°C , THF solution of **13** before addition of BuLi

was found to afford only isocyanide **15a**, completely suppressing formation of the nitrile **14a**.²⁴

(1)

Including TMEDA in the Asmic exchange suppressed the isocyanide-nitrile rearrangement, allowing smooth exchange-alkylations with a range of cyclic and acyclic isocyanides (Table 2). The BuLi-induced exchange-alkylation with five- and seven-membered isocyanides **13** and **16** efficiently afforded the corresponding trisubstituted isocyanides **15** and **17**, respectively (Table 2, entries 1–3). Similarly, the acyclic isocyanides **18** and **20** afforded isocyanides **19** and **21** (Table 2, entries 4–6). The use of NH_4Cl as an electrophile (Table 2, entry 4) illustrates how Asmic can provide a route to disubstituted isocyanides which, like their trisubstituted counterparts, are challenging to access.²⁵ The exchange-alkylation of **20** proceeds from a diastereomeric mixture to a single diastereomer,²⁶ which is consistent with the rapid configurational equilibration of lithiated isocyanides.²⁷

Asmic is a powerful new building block that provides the rapid, modular assembly of di- and tri-substituted isocyanides. The efficient alkylation, the first generalized isocyanide alkylation method, is predicated on an anisylsulfanyl substituent which both facilitates deprotonation and engages in a highly unusual sulfanyl-lithium exchange. The Asmic exchange-alkylation strategy overcomes the long-standing challenge of alkylating isocyanides, provides diverse isocyanides that were previously difficult to access, and gives insight into the reactivity of lithiated isocyanides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
A prototypical cyclohexylisocyanide alkylation.

Scheme 2.
Sulfur-based isocyanide alkylations.

Figure 1.
Two representative bioactive cyclohexylisocyanides.

Figure 2:
Exchange-benzylations with arylthioisocyanides.

^a Alkylation performed with methyl cyanoformate in place of BnBr

Table 1.

Exchange-alkylation of Asmic-derived isocyanide 12d.

entry	electrophile	exchange-alkylation	yield (%)
1			56
2			72
3			70
4			73
5			66
6	Bu_3SnCl		92
7			75

entry	electrophile	exchange-alkylation	yield (%)
8			47
9			30
10			52
11			52

Table 2.

Diverse isocyanide exchange-alkylations.

entry		electrophile	isocyanide	yield (%)
1	13		15b	52
2	13		15c	50
3	16		17	60
4	18	NH_4Cl	19a	68
5	18	PrI	19b	74
6	20	NH_4Cl	21	52