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Asmic: An Exceptional Building Block for Isocyanide Alkylations

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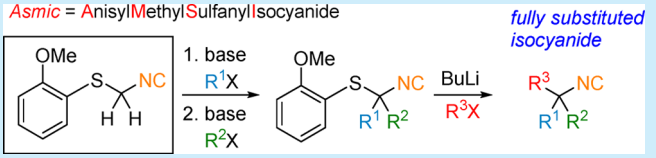
Supporting Information

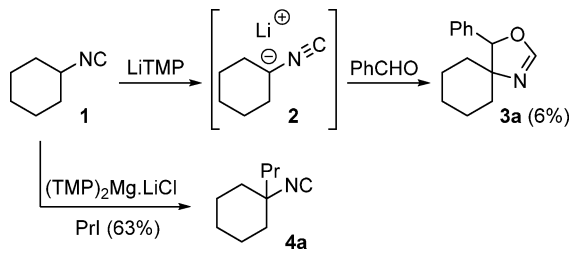
ABSTRACT: Asmic addresses the long-standing challenge of alkylating isocyanides, providing access to isocyanides with diverse substitution patterns. The *o*-anisylsulfanyl group serves a critical dual role by facilitating deprotonation−alkylation and providing a latent nucleophilic site through an unusual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



Isocyanides are prized reactants in an array of multicomponent[1] and transition metal insertion processes.[2] The versatility of isocyanides, particularly in generating pharmaceutical leads,[3] obscures two major deficiencies, namely, their limited commercial availability[4] and the difficulty in synthesizing substituted congeners.[5] Typically, isocyanides are accessed through late-stage formylation−dehydration of amines or activated alcohols that 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 efficient only for alkyl isocyanides with proximal chelating or electron-withdrawing groups[7] and methyl isocyanide, a toxic, noxious isocyanide.[8] The challenge in alkylating isocyanides is captured in the LiTMP deprotonation of cyclohexyl isocyanide (**1**), where trapping with benzaldehyde proceeds in only 6% yield (**1** → **2** → **3a**; Scheme 1).[9] The difficulty stems from the low acidity of alkyl isocyanides,[10] the temperature sensitivity of the resulting metalated isocyanides,[11] and their propensity 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 cyclohexyl isocyanides are kahlahinol F (**5**), a potential lead for treating copper accumulation, and amphilectadiene **6**, which is a potent antimalarial agent (Figure 1).[6]

Scheme 1. A Prototypical Cylohexyl Isocyanide Alkylation



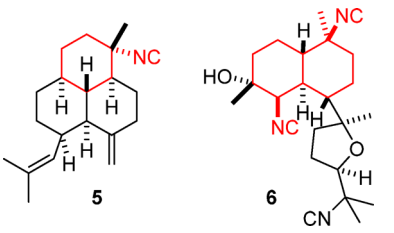


Figure 1. Two representative bioactive cyclohexyl isocyanides.

Exploratory attempts to alkylate **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 **1** employed $(TMP)_2Mg{\cdot}LiCl$ 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 to be attractive for generating metalated isocyanides **8** because the rapid exchange offered the potential to circumvent competitive self-condensation (Scheme 2). An extensive investigation with several sulfoxide-substituted isocyanides **7** validated the concept[13] (**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**[14] stimulated a different strategy predicated on a rare *arylsulfanyl* exchange−alkylation (**11** → **8** → **9**; Scheme 2).[15]

The requisite arylsulfanylmethyl isocyanide precursors **10** were rapidly assembled through a two-step Mannich condensation (arylthiol, paraformaldehyde, and formamide)

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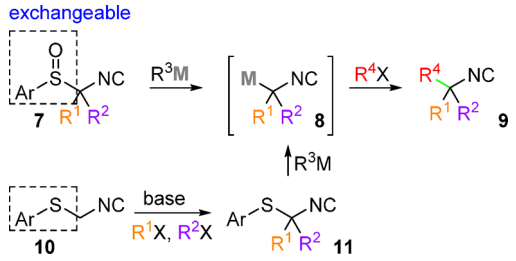
Scheme 2. Sulfur-Based Isocyanide Alkylations



followed by dehydration.[16] Exploratory alkylations employed naphthylsulfanylmethyl isocyanide (**10a**) (**10**, Ar = $C_{10}H_7$) because the relatively stable solid avoids the odiferous and noxious nature of the closely related phenyl and pyridyl analogues (**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 cyclohexyl isocyanides.[6] The double alkylation of **10a** proved straightforward with NaH in DMF, though subsequent alkylations with Asmic (**10d**) (**10**, 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

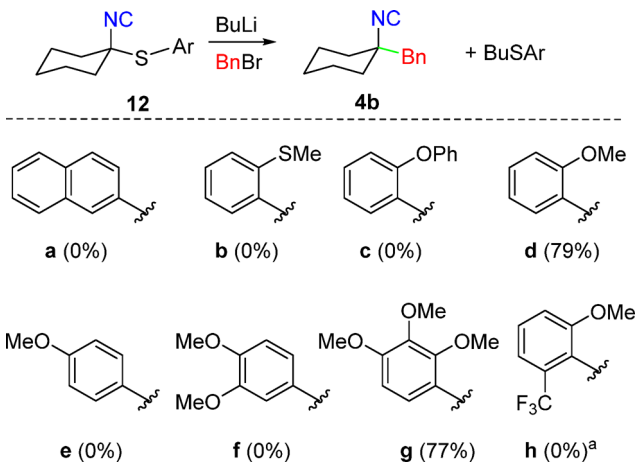


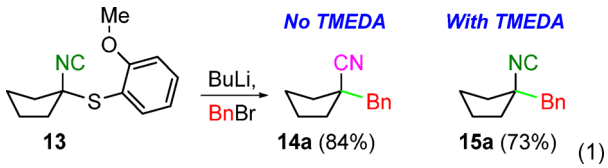
Figure 2. Exchange–benzylations with arylthio isocyanides. [a]Alkylation was performed with methyl cyanoformate in place of BnBr.

various organometallics to naphthyl isocyanide **12a** followed by benzyl bromide as a test electrophile afforded a complex reaction mixture.[18] Close inspection of the crude reaction mixtures revealed the presence of varying amounts of naphthyl butyl sulfide, which was optimistically interpreted as evidence for the critical arylsulfanyl–lithium exchange. Building on this lead, a series of arylsulfanylmethyl isocyanides **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 both to 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 electronic activation. Consistent with the chelating role of the *o*-MeO group, the presence of additional methoxy substitution at the meta and para positions 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 Asmic-derived isocyanide **12d** led to an exploration of the generality of the exchange–alkylation (Table 1). Optimization experiments revealed the sulfanyl–lithium exchange to be complete in less than 5 min at −78 °C. Electrophilic trapping was performed at −78 °C because warming of the solution of the putative lithiated isocyanide to 25 °C followed by addition of an electrophile led to only trace amounts of the alkylated isocyanide.[11] Alkyl iodides and bromides (entries 1–5) efficiently afforded alkyl isocyanides; tributylstannyl chloride afforded stannyl isocyanide **4f** in an exceptionally high yield (entry 6). The carbonyl electrophile methyl benzoate gave ketone **4g** (entry 7), whereas methyl cyanoformate gave ester **4h** (entry 8). 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 on the isocyanide (entry 10). Access to stannyl isocyanide **4f** provided an independent lithiation route to oxazoline **3b** with virtually identical efficiency, suggesting that the same lithiated isocyanide is generated in both processes.[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** → **3a**; Scheme 1) by providing an efficient method to access a range of substituted cyclohexyl isocyanides.

The bioactivity-driven decision to explore the exchange–alkylation with isocyanide **12d** containing a six-membered ring as a prototype proved to be fortuitous. Performing the same BuLi-induced exchange with isocyanide **13** containing a five-membered ring 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 excess of 200 °C.[22] Surmising that the lithiated isocyanide might exhibit carbene character, several metal chelators were added (HMPA, 18-crown-6, LiCl, DMPU, DME, KOt-Bu, and TMEDA) in an attempt to suppress the rearrangement.[23] Among these, the introduction of TMEDA to a −78 °C THF solution of **13** before the

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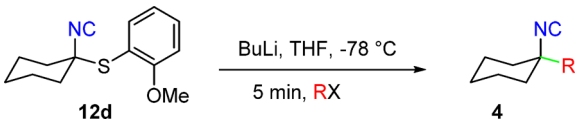
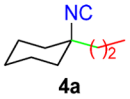
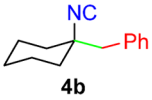
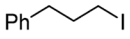
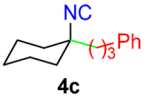
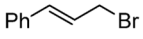
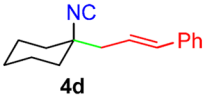
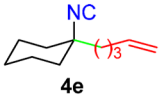
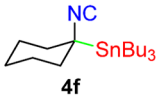
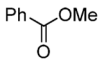
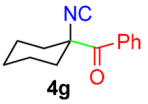
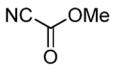
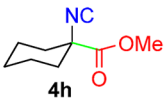
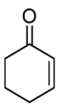
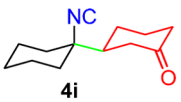
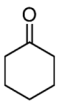
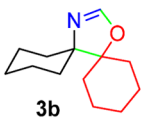
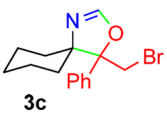
Table 1. Exchange–Alkylation of Asmic-Derived Isocyanide 12d

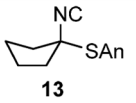
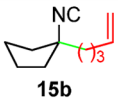
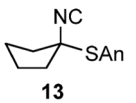
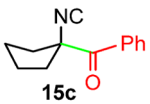
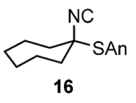
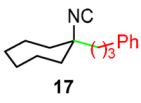
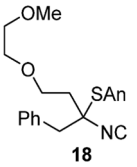
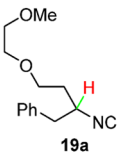
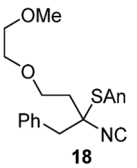
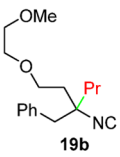
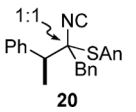


entry	electrophile	exchange-alkylation	yield (%)
1		 **4a**	56
2		 **4b**	72
3		 **4c**	70
4		 **4d**	73
5		 **4e**	66
6	Bu_3SnCl	 **4f**	92
7		 **4g**	75
8		 **4h**	47
9		 **4i**	30
10		 **3b**	52
11		 **3c**	52

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

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 isocyanides

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

13 and **16** containing five- and seven-membered rings membered efficiently afforded the corresponding trisubstituted isocyanides **15** and **17**, respectively (Table 2, entries 1–3). Similarly, acyclic isocyanides **18** and **20** afforded isocyanides **19** and **21**, respectively (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 rapid modular assembly of di- and trisubstituted isocyanides. The efficient alkylation, the first generalized isocyanide alkylation method, is predicated on an anisylsulfanyl substituent that 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.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02574.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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