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# Oxazole Synthesis by Sequential Asmic-Ester Condensations and Sulfanyl−Lithium Exchange−Trapping

Louis G. Mueller, Jr., Allen Chao, Embarek Alwedi, Maanasa Natrajan, and Fraser F. Fleming*

Cite This: *Org. Lett.* 2021, 23, 1500−1503 Read Online

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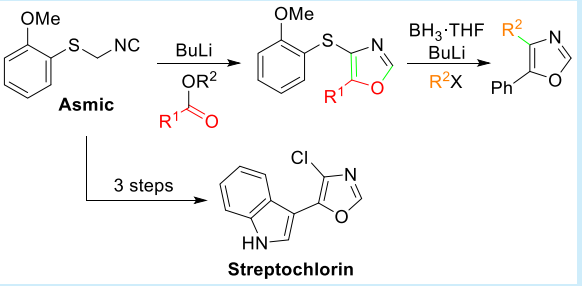
**ABSTRACT:** Oxazoles are rapidly assembled through a sequential deprotonation−condensation of Asmic, anisylsulfanylmethylisocyanide, with esters followed by sulfanyl−lithium exchange−trapping. Deprotonating Asmic affords a metalated isocyanide that efficiently traps esters to afford oxazoles bearing a versatile C-4 anisylsulfanyl substituent. Interchange of the anisylsulfanyl substituent is readily achieved through a first-in-class sulfur−lithium exchange−electrophilic trapping sequence whose versatility is illustrated in the three-step synthesis of the bioactive natural product streptochlorin.

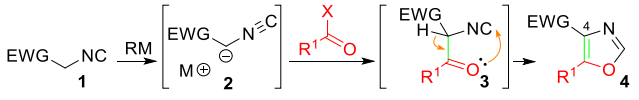





Isocyanides have a rich history as versatile precursors to peptidomimetic pharmacophores[1] and bioactive heterocycles.[2] The privileged status of isocyanides stems from the carbene-like reactivity of the terminal isocyanide carbon;[3] the isocyanide carbon provides a 1,1-connection point in bond constructions that span multicomponent reactions[4] to transition metal catalyzed insertions[5] to cycloadditions.[6]

Isocyanide-based cycloadditions provide a concise route to oxazoles via a highly efficient deprotonation−condensation−cyclization sequence (Scheme 1).[7] Most formal [3 + 2]

**Scheme 1. [3 + 2]-Isocyanide Cycloaddition Route to Oxazoles**

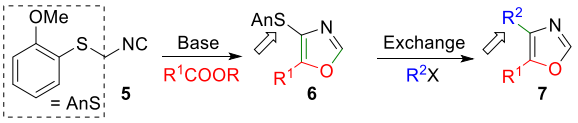



cycloadditions of alkylisocyanides involve deprotonation adjacent to the isocyanide to create a formal 1,3-dipole (**1** → **2**, Scheme 1).[8] Nucleophilic addition of anion **2** to carbonyl electrophiles installs an electron pair in a 1,5-relationship to the carbenoid isocyanide carbon **3** triggering cyclization and a series of proton transfers to generate an oxazole (**3** → **4**).

The isocyanide [3 + 2] cycloaddition route to oxazoles[9] requires an electron-withdrawing group adjacent to the isocyanide to enable an otherwise difficult $\alpha$-deprotonation (Scheme 1).[10] The electron-withdrawing group is beneficial if required in the target, or readily removed, but otherwise adds steps for conversion into the types of substituents found in bioactive oxazoles.[11] A significant advance would be realized with an exchangeable C-4 substituent (**4**) to overcome processing of the vestigial electron-withdrawing group.

The versatile isocyanide building block Asmic (anisylsulfanylmethylisocyanide, **5**)[12] provides an attractive solution for assembling and selectively accessing substituted oxazoles (Scheme 2). Deprotonating Asmic (**5**) followed by trapping

**Scheme 2. Asmic-Based Synthesis of Oxazoles**




with esters is shown to generate anisylsulfanyl-substituted (AnS) oxazoles **6** that engage in a first-in-class sulfur−lithium exchange−trapping to afford C-4 substituted oxazoles **7**.

Optimizing the deprotonation and condensation of Asmic with esters proved remarkably straightforward (Scheme 3). Lithiation[13] of Asmic with BuLi followed by addition of an ester efficiently generated a suite of aliphatic or aromatic anisylsulfanyl-substituted oxazoles (Scheme 3, **9a**−**9d** and **9f**−**9h**, respectively). Intercepting lithiated Asmic with $\alpha$-methyl-$\gamma$-butyrolactone gave the hydroxy-oxazole **9e**. Trapping lithiated Asmic with a benzyl-protected indole-3-carboxylate gave the 5-indoyl-oxazole **9h** that contains the core scaffold found in the fungicidal pimprinine natural products.[14]

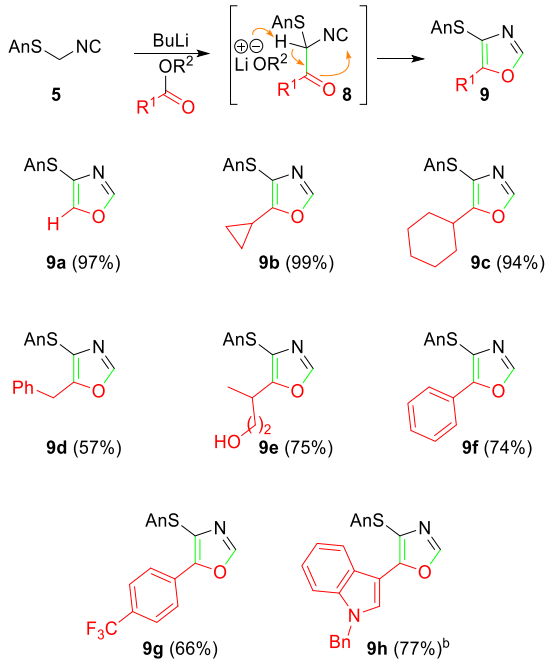
Exploratory forays to substitute the anisylsulfanyl group focused on selective cleavage of the sulfur-oxazole bond in

**Received:** January 25, 2021
**Published:** February 3, 2021



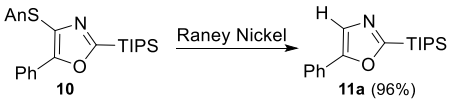

https://dx.doi.org/10.1021/acs.orglett.1c00288
*Org. Lett.* 2021, 23, 1500−1503

**Scheme 3. Oxazole Synthesis by Asmic-ester Condensation**[a]



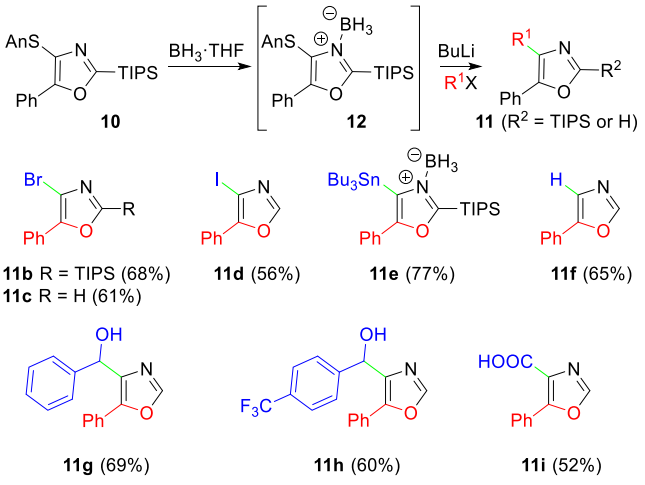

[a]General procedure: Addition of BuLi (1.05−1.1 equiv) to a −78 °C, THF solution of Asmic was followed, after 5−10 min, by the neat ester (1.1 equiv). After 1−2 h, the reaction was allowed to warm to rt, and after 1−2 h, saturated, aqueous $NH_4Cl$ was added, to give, after workup and chromatography, the pure oxazole. [b]2.0 equiv of LDA were used to deprotonate Asmic.

preference to the sulfur-anisyl bond. Raney-nickel hydrogenolysis[15] (**10** → **11a**) provided a route to reductively exchange the C-4 anisylsulfanyl group (eq 1) whereas exchange




processes via catalytic coupling[16] or sulfur−lithium exchange processes identified the latter as more promising.[17] After some optimization, a selective exchange was achieved with the TIPS-protected oxazole **10**[18] as a prototype (Scheme 4); critical for the success was complexation of the oxazole with $BH_3$.[19] Borane complexation likely reduces the electron density in the oxazole **12** to favor a selective BuLi-initiated sulfanyl-lithium exchange. Operationally, the sequential addition of $BH_3$·THF, BuLi,[20] and an electrophile afforded a range of substituted oxazoles (Scheme 4). Electrophilic bromination with $BrCl_2CCCl_2Br$ followed by addition of saturated, aqueous $NH_4Cl$ afforded bromooxazole **11b**,[21] whereas a more acidic workup with ethanolic-HCl afforded the desilylated, deborylated bromooxazole **11c**. The iodination of **10** to afford **11d** was achieved through a highly unusual reverse lithium−iodine exchange with iodoacetonitrile serving as the electrophilic iodine source.[22] Trapping with $Bu_3SnCl$ afforded the stannyloxazole **11e** that was isolated as the stable $BH_3$ complex;[23] an analogous reaction with $Me_3SnCl$ afforded a stannyloxazole that was particularly susceptible to protodestannylation, providing oxazole **11f** (95% yield) after exposure to acetic acid. Halooxazoles and stannyl oxazoles similar to **11b−e** are used as coupling partners for the synthesis of complex oxazoles.[24] The direct exchange−

**Scheme 4. $BH_3$-Promoted Sulfanyl−Lithium Exchange−Trapping**[a]

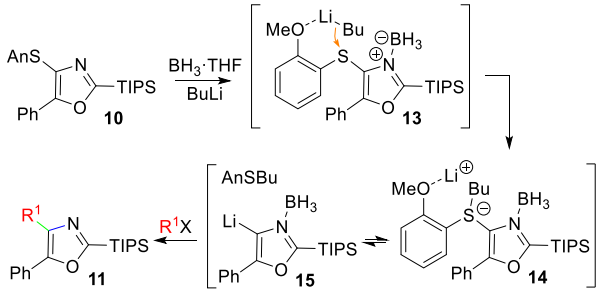



[a]General Procedure: A THF solution of $BH_3$·THF (1.1−1.2 equiv) was added to a rt, THF solution of **14** (1.0 equiv) that was, after 30−40 min, cooled to −78 °C. BuLi (1.75−2.2 equiv) was added followed, after 30−40 min, by the electrophile (1−2 equiv). After warming to rt, a 1:1 mixture of EtOH and 1 M HCl was added, and after 16 h, the crude mixture was concentrated and then extracted with EtOAc to afford a crude material that was chromatographed to afford the pure oxazole. [a]An exchange stannylation−protodestannylation sequence afforded **11a** in 95% yield.

protonation of **10** afforded **11f** whereas exchange−trapping with aldehydes or carbon dioxide afforded the corresponding oxazoles **11g−i**.

The anisylsulfanyl−lithium exchange is envisaged to occur through a chelation-assisted attack of BuLi on the $BH_3$-complexed oxazole (**13**, Scheme 5). Complexation of BuLi to

**Scheme 5. Sulfanyl−Lithium Exchange Mechanism**




the methoxy group[25] facilitates the nucleophilic attack on sulfur to generate the sulfuranylide[26] **14** either as a transition structure en route to the lithiated oxazole **15** or as the nucleophile; no exchange occurs on similar substrates in the absence of an *o*-methoxy group.[27,12b] Electrophilic trapping at C-4 followed by acid-promoted deborylation affords the oxazole **11**.[28]

The versatility of the Asmic-addition−exchange strategy was illustrated via a three-step synthesis of the bioactive agent streptochlorin (Scheme 6, **18**).[29] Deprotonation of Asmic (**5**) followed by trapping with the indole carboxylate **16** gave oxazole **9i**. TIPS protection of **9i** with KHMDS and TIPSOTf followed by sulfanyl−lithium exchange, trapping with hexachlorethane, and global deprotection efficiently gave streptochlorin (**18**).



https://dx.doi.org/10.1021/acs.orglett.1c00288
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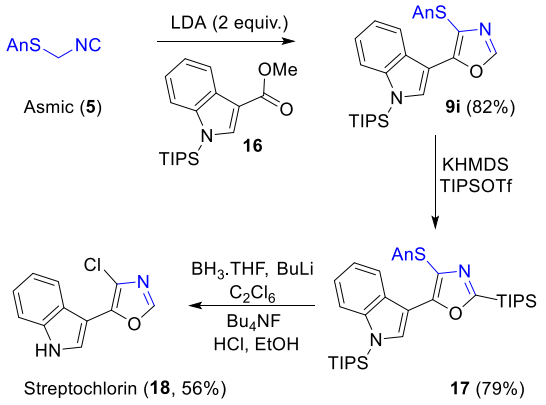
**Scheme 6. Asmic-Exchange Synthesis of Streptochlorin**




The sequential deprotonation of Asmic and trapping with esters provides an efficient synthesis of substituted oxazoles. The resident anisylsulfanyl group serves as a valuable handle to diversify the C-4 substituent by a first-in-class sulfanyl−lithium exchange−trapping sequence as illustrated in the short synthesis of streptochlorin. The Asmic condensation−exchange−alkylation provides a short, efficient method for preparing a suite of oxazoles with excellent control over the nature and position of the substituents.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00288.

Experimental procedures, compound characterization, copies of NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **9a−i**, **10**, **11a−i**, **17**, and **18** (ZIP)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Fraser F. Fleming** − *Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104, United States;* orcid.org/0000-0002-9637-0246; Email: fleming@drexel.edu

### Authors

**Louis G. Mueller, Jr.** − *Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104, United States*

**Allen Chao** − *Wistar Institute, Philadelphia, Pennsylvania 19104, United States*

**Embarek Alwedi** − *Merck Inc., Rahway, New Jersey 07065, United States;* orcid.org/0000-0002-7031-2427

**Maanasa Natrajan** − *Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00288


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support from Drexel University is gratefully acknowledged as are discussions with Dr. Caleb Holyoke, Jr. (Drexel University).

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https://dx.doi.org/10.1021/acs.orglett.1c00288
*Org. Lett.* 2021, 23, 1500−1503