Conjugate Addition

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Alkenyl Isocyanide Conjugate Additions: A Rapid Route to γ-Carbolines

*Sergiy V. Chepyshev, J. Armando Lujan-Montelongo, Allen Chao, and Fraser F. Fleming**

Abstract: *Isocyanides are exceptional building blocks, the wide deployment of which in multicomponent and metal-insertion reactions belies their limited availability. The first conjugate addition/alkylation to alkenyl isocyanides is described, which addresses this deficiency. An array of organolithiums, magnesiates, enolates, and metalated nitriles add conjugately to β- and β,β-disubstituted arylsulfonyl alkenyl isocyanides to rapidly assemble diverse isocyanide scaffolds. The intermediate metalated isocyanides are efficiently trapped with electrophiles to generate substituted isocyanides incorporating contiguous tri- and tetra-substituted centers. The substituted isocyanides are ideally functionalized for elaboration into synthetic targets as illustrated by the three-step synthesis of γ-carboline N-methyl ingenine B.*

Isocyanides are unusual carbon-based functional groups in that they formally contain a carbon atom with a free electron pair.[1] The carbene-like structure (Figure 1)[2] confers ambiphilic reactivity on the isocyanide carbon atom that results in an exceptionally diverse reactivity for one functional group: metal insertion,[3] radical additions,[4] nucleophilic additions,[1] and electrophilic alkylations.[5] The high reactivity toward disparate reagents is particularly valuable for multicomponent reactions,[5] heterocycle synthesis,[6] and accessing acyclic nitrogenous scaffolds.[6]

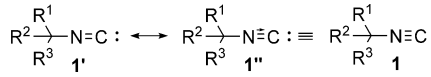
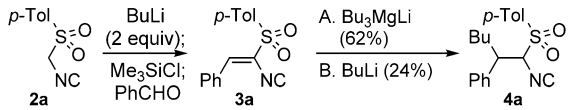


Figure 1. Isocyanide representations.

Isocyanide-containing metabolites, mostly from marine sources,[7] epitomize the challenge of working with isocyanides. The reactive carbene-like carbon center confers biological activity through the same type of bonding that creates a susceptibility of the R-NC unit toward irreversible complexation with transition metals, hydrolysis, and oxidation.[1] The tendency of isocyanides to ligate to transition metals results from strong σ-donation of the electron pair on the carbon atom coupled with removal of electron density from the metal into the RN≡C π* orbitals.[8]

The high reactivity and delicate nature of isocyanides, combined with their propensity to coordinate to transition metals, means that there are few methods available for manipulating the carbon scaffold while retaining the isocyanide functionality.[1] Most isocyanides are installed through a late-stage, three-step sequence: amine deprotection, formylation, and dehydration.[9] Described below is the first conjugate addition/alkylation of alkenyl isocyanides by employing main-group organometallics, which effectively expands the limited repertoire of isocyanide-based bond constructions.

The viability of using main-group organometallics to develop a general conjugate addition to unsaturated isocyanides was predicated on sporadic additions of Grignards[10] and sulfur ylides[11] to isocyanoacrylates. Initial attempts to develop the conjugate addition employed the alkenyl isocyanide **3a**, derived from TosMIC (**2a**, Scheme 1).[12] Exploratory additions of BuMgCl, Me_2CuLi, and $Et_2BuZnLi$[13] to **3a** afforded complex mixtures of products, thus suggesting that the process involves more than a simple addition to a vinyl sulfone.[14] Further screening led to promising additions with BuLi (24%) and the magnesiate Bu_3MgLi[15] (62%, Scheme 1).



Scheme 1. Synthesis of and addition to sulfonylisocyanide **3a**.

Attempts to expand the conjugate additions to **3a** with additional organometallic reagents led to an effective reaction with lithiated dithiane (Table 1, entry 1) but identified two limitations: poor tolerance of structural diversity in the organometallic reagent and a pronounced instability of the resulting isocyanides toward storage and purification.[16] These limitations stimulated efforts to tune the electronic and steric nature of the arylsulfone substituent to maximize reactivity and stability (Table 1).[17] Electron-deficient arylsulfonyl substituents were anticipated to facilitate the conjugate addition, and while the trifluoromethyl-substituted isocyanide **3b** reacted well with Bu_3MgLi, the adduct was particularly unstable (Table 1, entry 2). Incorporating *o*-CF_3 and *o*-OMe substituents (**3c**) improved the conjugate addi-

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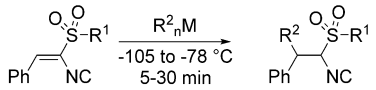
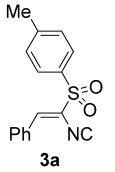
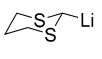
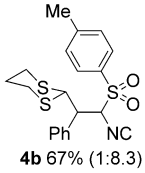
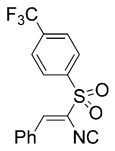
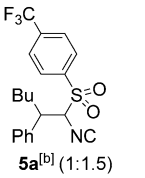
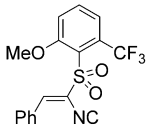
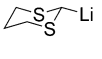
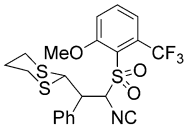
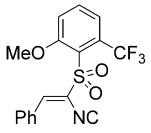
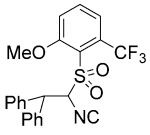
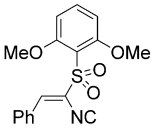
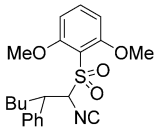
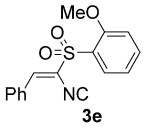
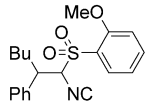
Table 1: Dependence of conjugate addition efficiency on sulfone structure.



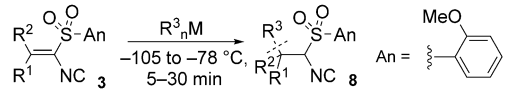
Entry	Sulfonyl isocyanide	Nucleophile	Yield [%] (d.r.)[a]
1	 **3a**		 **4b** 67% (1:8.3)
2	 **3b**	Bu_3MgLi	 **5a**[b] (1:1.5)
3	 **3c**		 **6a** 53% (1:4.9)
4	 **3c**	PhLi	 **6b** 87%
5	 **3d**	Bu_3MgLi	 **7a** 24% (1:1.4)
6	 **3e**	A. Bu_3MgLi B. BuLi	 **8a** (A 54%, B 53%) (1:1.8)

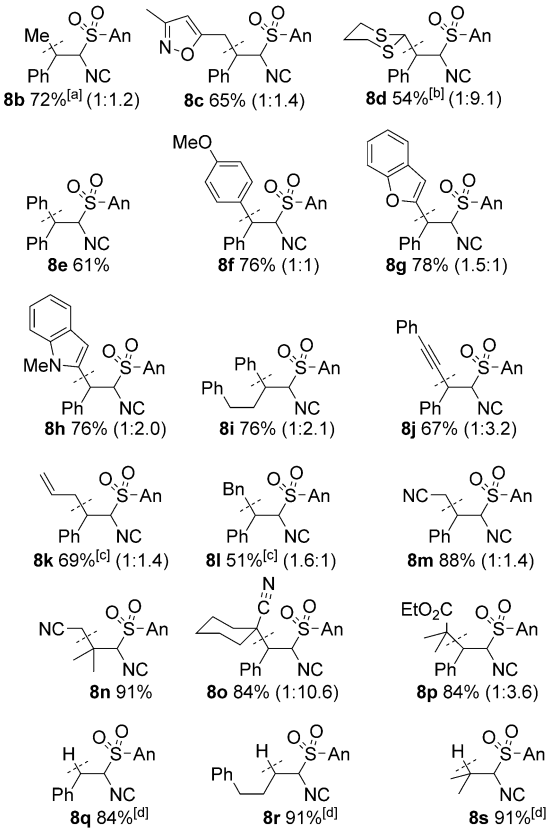
[a] The diastereomeric ratios were determined by ^{1}H NMR integration of diagnostic methine signals. [b] The isocyanide could not be purified for characterization.

tion with PhLi and lithiated dithiane but the resulting isocyanides **6a** and **6b** were prone to decompose during purification (Table 1, entries 3 and 4).[16] Speculating that the efficacy of **3c** was due to precomplexation between the organometallic and the *o*-OMe[18] led to the evaluation of di-*o*-methoxyphenylisocyanide **3d** and *o*-anisyl (An) isocyanide **3e**. While the addition of Bu_3MgLi to **3d** afforded a modest yield of **7a**, the *o*-anisyl isocyanide **3e** efficiently reacted with Bu_3MgLi and BuLi to afford stable **8a** in 54% and 53% yield, respectively (Table 1, entry 6).

The generality of the conjugate addition to (*o*-anisyl)sulfonyl alkenyl isocyanides was probed with a variety of organometallic reagents (Table 2). Diverse organolithiums with sp^3, sp^2, and sp hybridization readily added to (*o*-anisyl)sulfonyl alkenyl isocyanides **3** (Table 2, **8b**–**8d**, **8e**–**8i**,

Table 2: Conjugate additions to *o*-anisylsulfonyl alkenisocyanides **3**.





[a] Use of MeLi afforded a 62% yield (d.r. 1:3.0[22]). [b] The configuration was unambiguously secured by crystallography.[23] [c] Prepared using $RMgBu_2Li$. [d] Prepared using $NaBH_4$.

and **8j**).[19] The conjugate addition of MeLi to afford **8b**, initially performed between −100 to −95 °C (62% yield), was found to be cleaner and give higher yield with MeLi·LiBr at −78 °C (72% yield). Selective allyl and benzyl additions[20] were performed from the mixed organomagnesiates $allylMgBu_2Li$ and $BnMgBu_2Li$ to afford isocyanides **8k** and **8l**, respectively. Lithiated acetonitrile and lithiated cyclohexanecarbonitrile afforded the nitrile-containing isocyanides **8m**–**8o**, two of which contain quaternary centers. The lithium enolate derived from ethyl 2-methylpropionate afforded ester-isocyanide **8p**, with the installation of a quaternary center. Conjugate reduction with $NaBH_4$ afforded the alkylisocyanides **8q** to **8s**, which provides a valuable route to branched isocyanides.[21]

The conjugate additions generated metalated isocyanides that were effectively intercepted by electrophiles (Table 3). Initial optimization focused on the methylation of the lithiated isocyanide derived from addition of PhLi to **3e**. Methylation afforded **9a** (53%) with incomplete conversion; addition of HMPA or DMPU (4 equiv) improved the reaction efficiency to 74% and 79%, respectively (Table 3, entry 1, HMPA = hexamethylphosphoramide, DMPU = 1,3-dimeth-

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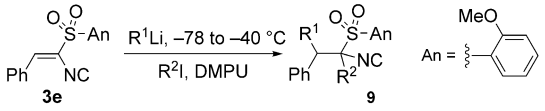
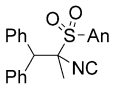
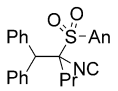
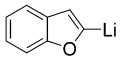
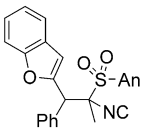
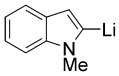
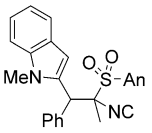
Table 3: Conjugate addition/alkylations with alkenyl isocyanide **3e**.

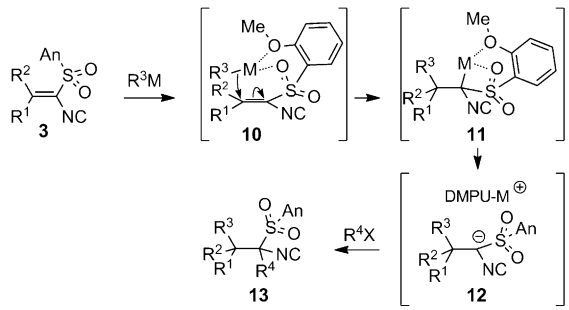


Entry	R^1Li	R^2I	Alkaneisocyanide yield [%] (d.r.)[a]
1	PhLi	MeI	 **9a** 79%
2	PhLi	PrI	 **9b** 82%
3		MeI	 **9c** 82% (3.2:1)
4		MeI	 **9d** 63%[b] (4.0:1)

[a] The diastereomeric ratios were determined by ^1H NMR integration of diagnostic methine signals in the crude reaction mixture. [b] The configuration was unambiguously secured by X-ray diffraction.

yl-3,4,5,6-tetrahydro-2-pyrimidinone). DMPU-promoted electrophilic capture led to efficient addition/alkylations of **3e** with PhLi and PrI (Table 3, entry 2) and addition/methylations with lithiated benzofuran and lithiated *N*-methyl indole (Table 3, entries 3–4). The conjugate addition/alkylation provides valuable access to sterically encumbered alkylisocyanides that are challenging to prepare by direct alkylation of sulfonylmethylisocyanides such as TosMIC (**2a**).[24]

Mechanistically, the conjugate addition likely proceeds through a preassociation of the organometallic species with the sulfone and anisyl oxygens (Scheme 2).[18] Close proximity between the nucleophilic organometallic species and the alkenyl isocyanide would facilitate intramolecular delivery of the alkyl group to the β-carbon (**10**) while preventing attack on the isocyanide. Complexation within the resultant lithiated isocyanide **11** may retard the alkylation, which DMPU assists by solvation to a more nucleophilic, and accessible, solvent-separated ion pair (**12** → **13**).

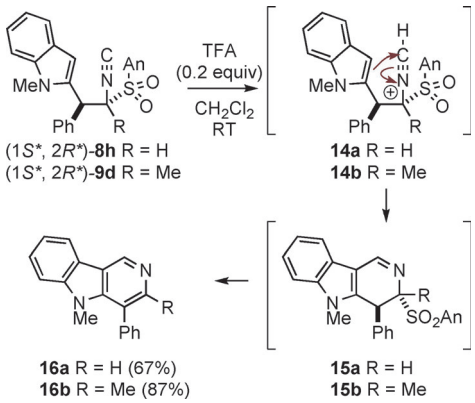


Scheme 2. Conjugate addition/alkylation mechanism.

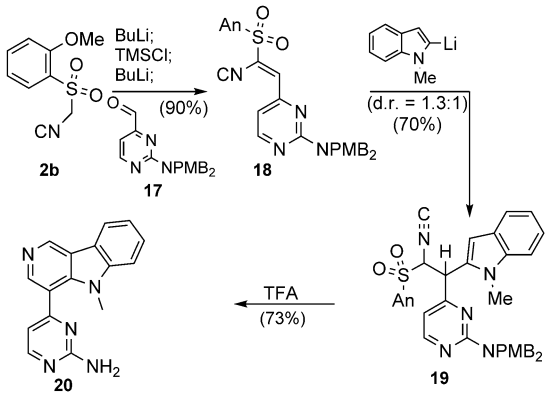
The conjugate addition affords substituted isocyanides that are ideally functionalized for heterocyclic synthesis. Rapid access to the indole-containing isocyanides **8h** and **9d** prompted cyclization to the γ-carboline scaffold,[25] an emerging pharmacophore.[26] Optimization experiments revealed that substoichiometric trifluoroacetic acid (TFA) triggered an efficient cyclization with (1*S**, 2*R**)-**8h** or **9d** (Scheme 3).[27] Generation of the nitrilium ion **14** likely triggers cyclization to imine **15**, which eliminates sulfinic acid to afford γ-carboline **16**.[28] Rapid access to γ-carbolines such as **16a**[29] is significant because of their potential as hepatitis C inhibitors.[30]

The versatility of the isocyanide conjugate addition/cyclization is illustrated in the synthesis of *N*-methyl ingenine B (**20**, Scheme 4).[31] In situ silylation/olefination of **2b**[12] with aldehyde **17**[32] afforded alkenyl isocyanide **18**, which participated in a smooth conjugate addition with lithiated *N*-methylindole to provide **19** (Scheme 4). (1*S**, 2*R**)-**19**[33] was efficiently converted into *N*-methyl ingenine B (**20**)[34] upon exposure to TFA, a process involving cyclization, sulfinic acid elimination, and debenzylation.

Main-group organometallics react with (*o*-anisyl)sulfonyl alkeneisocyanides in the first conjugate addition/alkylation of alkenyl isocyanides. Diverse organolithiums, magnesiates, enolates, and metalated nitriles afford metalated isocyanides



Scheme 3. Isocyanide cyclization to γ-carbolines.



Scheme 4. Synthesis of *N*-methyl ingenine B (**20**).

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that are readily intercepted by electrophiles to efficiently install contiguous tri- and tetra-substituted centers. The highly substituted isocyanides are ideally functionalized for elaboration into synthetic targets as illustrated by the three-step synthesis of the γ-carboline *N*-methyl ingenine B (**20**).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: conjugate addition · isocyanides · organometallics · γ-carbolines · synthetic methods

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[34] An oxidative demethylation was successfully performed on **16a** but application of the same sequence to *N*-methyl ingenine B (**20**) caused significant degradation.

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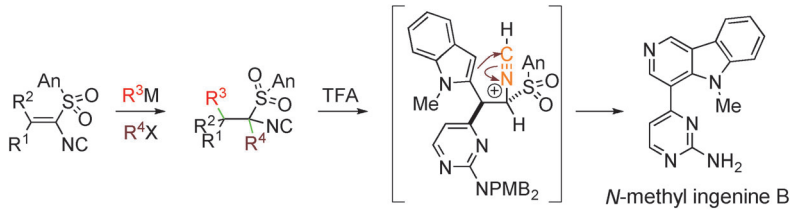
Communications

Conjugate Addition

S. V. Chepyshev, J. A. Lujan-Montelongo, A. Chao, F. F. Fleming* ——

Alkenyl Isocyanide Conjugate Additions: A Rapid Route to γ-Carbolines



Conjugate addition of diverse organometallics to sulfonyl-substituted alkenyl isocyanides overcomes the historical challenge of rapidly assembling complex isocyanides that retain the isocyanide functionality. The strategy affords complex isocyanides that are poised for elaboration into heterocycles, as illustrated by the three-step synthesis of *N*-methyl ingenine B.

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