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Synthesis of Cyclic Azomethine Imines by Cycloaddition Reactions of *N*-Isocyanates and *N*-Isothiocyanates

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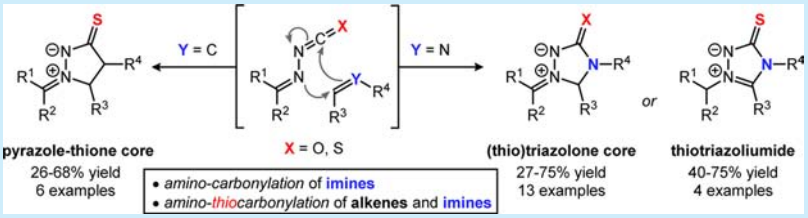
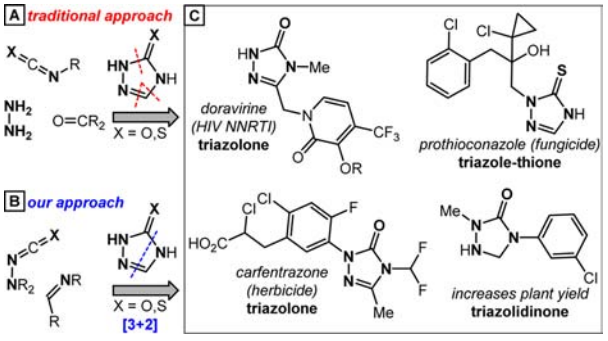
Supporting Information



ABSTRACT: Various nitrogen-substituted iso(thio)cyanates engage in [3 + 2]-cycloaddition reactions to form azomethine imines containing triazolone, triazole−thione, and pyrazole−thione cores. First, iminoisothiocyanates are shown to undergo aminothiocarbonylation reactions with strained alkenes, and a comparison with recently reported reactions of iminoisocyanates highlights their reduced reactivity. In contrast, amino(thio)carbonylation reactions of imines with iminoisocyanates and iminoisothiocyanates proved more efficient, providing access to triazolone and triazole−thione cores. The dipole products can be converted to valuable heterocyclic cores through simple derivatization reactions.

Isocyanates and isothiocyanates are important building blocks in heterocyclic synthesis.[1] Their use in intermolecular cycloadditions is also established, the most well-known being the [2 + 2] reaction of chlorosulfonyl isocyanate with alkenes to synthesize β-lactams.[1b,c] Isocyanates are also key starting materials in modular syntheses of heterocycles, including systems containing the N−N−CO subunit, which exists in many pharmaceuticals and agrochemicals (Scheme 1C).[2−4] However, there

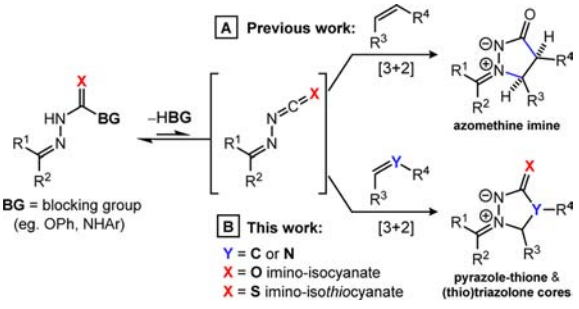
Scheme 1. Structures and Synthesis of Useful Heterocycles with N−N−CO and N−N−CS Motifs



can be practical difficulties with current modular syntheses involving hydrazine derivatives (Scheme 1A), including sensitivity or chemoselectivity issues. Toxicity and poor functional group diversity associated with the isocyanate component can also be problematic. From this perspective, nitrogen-substituted isocyanates (*N*-isocyanates) offer alternative disconnections for the synthesis of heterocycles possessing the N−N−CO motif (Scheme 1B),[5−7] though their use is rare.[6d] As part of our program on the use of *N*-isocyanates, we were drawn to their potential to provide new routes to useful heterocycles.

More precisely, we recently reported the intermolecular aminocarbonylation reaction of iminoisocyanates with alkenes, which involves a stereospecific [3 + 2] cycloaddition (Scheme 2A).[8,9]

Scheme 2. Intermolecular [3 + 2] Cycloaddition of Alkenes and Imines with Iso(thio)cyanate Precursors



In this work, hydrazones and semicarbazones provide the reactive *N*-isocyanate intermediate through loss of the blocking group, in analogy to blocked (masked) isocyanates used in industry.[10] This approach provides access to N−N−CO-containing heterocycles

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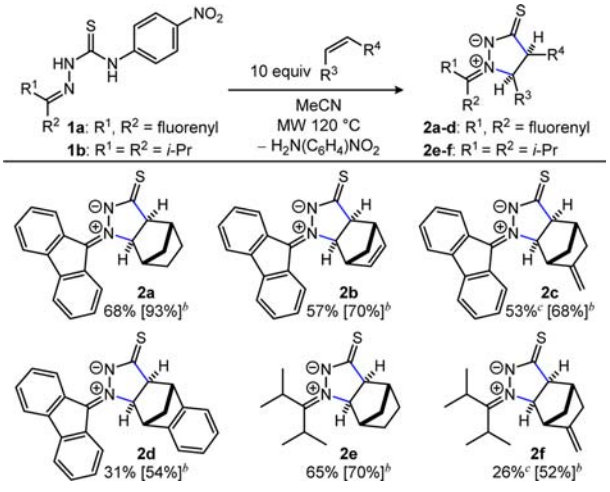
by derivatization of the azomethine imine product,[11] including pyrazolones and enantioenriched pyrazolidinones.[9d,12]

We became interested in using related [3 + 2] cycloadditions to access more diverse azomethine imines and their derivatization products. This led us to explore the reactivity of other intermediates, iminoisothiocyanates,[7] and different electron-rich double bonds, such as imines (Scheme 2B). Herein, we report the synthesis of sulfur- and nitrogen-containing azomethine imines and related heterocyclic cores using rare iminoisothiocyanates and the unprecedented cycloaddition of iminoisocyanates with imines.

Alkenes are abundant and readily available but rarely used as substrates in the synthesis of heterocycles with the pyrazolone core.[13a,b] Furthermore, the addition of nitrogen and C═S across the double bond of an alkene (aminothiocarbonylation) is a rare transformation, with only two reports.[13b,c] With iminoisothiocyanates, this intermolecular reaction would provide thioxoazomethine imines (**2**, 3-thioxopyrazolidin-1-ium-2-ides). Such compounds have been synthesized only by the treatment of the parent carbonyl-containing azomethine imines with Lawesson's reagent.[14] Thus, the development of new aminothiocarbonylation reactivity holds potential as a streamlined approach to pyrazolidine-3-thiones, pyrazole-3-thiones, and other β-amino-thiocarbonyl compounds. To access these products, we required a precursor to the iminoisothiocyanate with a suitable blocking group (Scheme 2). In our previous studies with the parent carbonyl precursors, we found that PhO− served as an excellent blocking group, providing the iminoisocyanate in situ for the cycloaddition reaction.[9b] However, the synthesis of the analogous isothiocyanate precursor was difficult, and yields were not reproducible. Fortunately, we found that thiosemicarbazone precursors **1** (BG = *p*-$(NO_2)C_6H_4NH$−)[15] effectively produced the reactive iminoisothiocyanates for the intermolecular alkene aminothiocarbonylation reaction. These precursors are easy to synthesize from simple hydrazones and 4-nitrophenyl thioisocyanate. Optimization with reagent **1** revealed that the reaction required anhydrous solvent and excess alkene, and these conditions were used to survey the alkene scope (Scheme 3, see the Supporting Information for optimization data).

Scheme 3. Intermolecular Alkene Aminothiocarbonylation Using Iminoisothiocyanate Precursors[a]

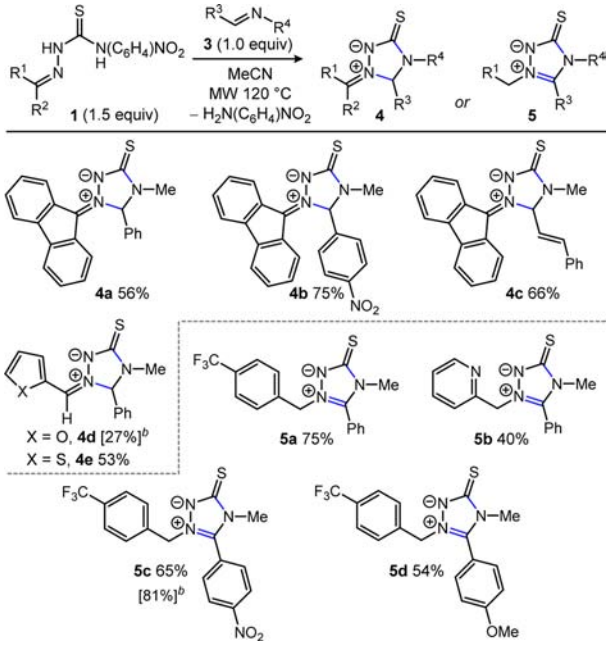


[a]Conditions: **1a** or **1b** (1.0 equiv), alkene (10 equiv), MeCN (0.05 M), heated (microwave) to 120 °C in a sealed vial under argon. Isolated yields are provided. [b]NMR yield (shown in square brackets) with 1,3,5-trimethoxybenzene as internal standard. [c]Mixture of methylene regioisomers for **2c** (1.3:1) and **2f** (1.1:1); major isomer is shown.

In alkene aminothiocarbonylation reactions with **1**, strained norbornene derivatives were the best substrates, providing dipoles **2a**−**f** in 26−68% isolated yields (Scheme 3). It was observed that the NMR yields were considerably higher than the isolated yields (**2a** NMR yield = 93%). These reduced yields upon isolation are attributed to the high polarity of the products and degradation during chromatographic isolation. Overall, iminoisothiocyanates as reactive intermediates proved less versatile compared to iminoisocyanates,[9b,d] showing only modest reactivity with unactivated alkenes (see the Supporting Information). Nevertheless this work presents a proof of concept for the aminothiocarbonylation of alkenes. These results also support that the stabilizing frontier molecular orbital interaction during these [3 + 2] cycloadditions involves the HOMO of the alkene with the LUMO of the iminoiso(thio)cyanate.

We then explored the use of imines (C═N bonds) as alternative substrates to alkenes in such [3 + 2] cycloadditions, with the objective to form azomethine imines containing a triazolethione core (Scheme 4). Optimization of the reaction with iminoisothiocyanate

Scheme 4. Intermolecular C═N Aminocarbonylation of Aldimines Using Iminoisothiocyanate Precursors[a]



[a]Conditions: **1** (1.5 equiv), imine **3** (1.0 equiv), MeCN (0.05 M), heated (microwave) to 120 °C in a sealed vial under argon. Isolated yields are provided (except **4d**). [b]NMR yield with 1,3,5-trimethoxybenzene internal standard.

precursor **1a** and imine **3a** revealed that using the imine as the limiting reagent gave the highest yields (Supporting Information). This shows that imines are significantly more reactive than alkenes in cycloadditions with iminoisothiocyanates. Under these conditions, **1a** also provided products with electron-poor (**4b**) and electron-rich (**4c**) aromatic *N*-methylimines. A variety of aldehyde-derived thiosemicarbazones (**1c**−**h**) were also synthesized and tested. In the reaction with imine **3a**, furyl- and thienyl-containing precursors gave lower yields of azomethine imines (**4d**, 27% NMR yield; **4e**, 53% isolated yield) compared to **1a**. These lower yields are in line with the observation that the products are prone to degradation by hydrolysis. An unexpected transformation occurred with electron-withdrawing R^1

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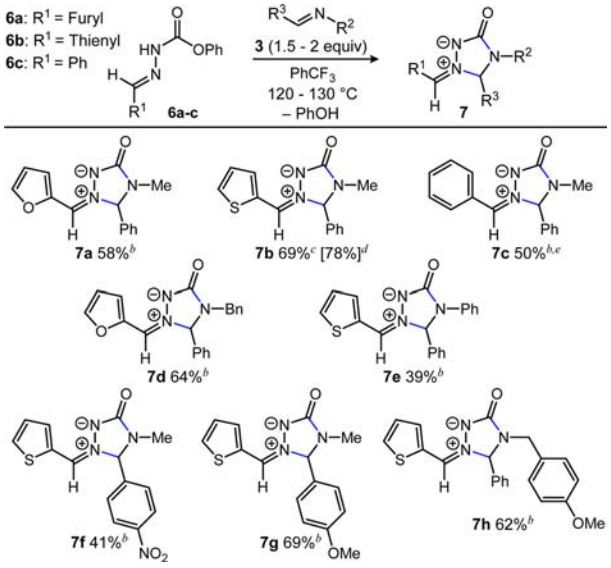
substituents: isomerization to yield aromatic derivatives, the thiotriazoliniumides **5a–d**.[16] In these cases, only the isomerized product could be detected.

Given the high reactivity observed, we were optimistic that imines would also engage in cycloaddition reactions with iminoisocyanates. After exploring various carbazones with **3a**, we found that iminoisocyanate precursors derived from aldehydes provided the best reactivity (Scheme 5), with furyl (**6a**) and

Scheme 5. Intermolecular C═N Aminocarbonylation of Imines Using Iminoisocyanate Precursors[a]



[a]Conditions: **6** (1.0 equiv), imine **3** (1.5–2.0 equiv), $PhCF_3$ (0.05–0.10 M), heated (microwave or conventional) to [b]Heated (microwave or conventional) to 120 °C for 1–3 h in a sealed vial under argon. Isolated yields are provided. [c]Heated (microwave or conventional) to 130 °C for 1–3 h in a sealed vial under argon. Isolated yields are provided. [d]NMR yield (shown in square brackets) with 1,3,5-trimethoxybenzene as internal standard. [e]NMR yield of **7c** = 50%. Isolation by reduction of **7c** with $NaBH_4$; isolated yield = 39% over two steps.

thienyl (**6b**) carbazones leading to the highest yields and facilitating product isolation. Again in contrast to the modest reactivity observed with alkenes,[9c] using only a slight excess of the imines (1.5–2.0 equiv) was sufficient. Imines prepared from aromatic aldehydes bearing electron-withdrawing (**7f**, 41% yield) and electron-donating (**7g**, 69% yield) substituents showed good reactivity. Higher yields were obtained in the presence of *N*-alkyl substituents (**7a–d,f–h**), while an *N*-Ph imine provided **7e** in only 39% yield. Unfortunately, no products were observed with ketimines (e.g., benzophenone imine, *N*-methylacetonimine). Due to their sensitivity, the products were isolated by trituration of the crude mixture in Et_2O, and thus, yields were often higher at larger scale.

An X-ray crystal structure was obtained for **7b** (Figure 1), providing unambiguous proof of structure. This also gave insight into the cyclization efficiency and improved product stability observed with the thienyl group (see the Supporting Information for competition experiments), resulting from potential S···N chalcogen bonding.[17] The S···N distance is 2.84 Å, which is less than the sum of the van der Waals radii (S + N = 3.35 Å) and within the range of known thienyl S···N noncovalent interactions (2.7–3.0 Å).[17] The thienyl group and triazolone core are near coplanar, with dihedral angles (S–C–C–N–N) of $\varphi_1 = 0.59°$

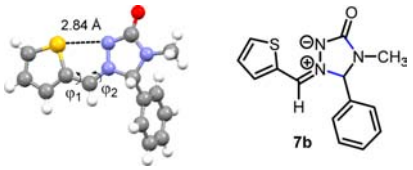
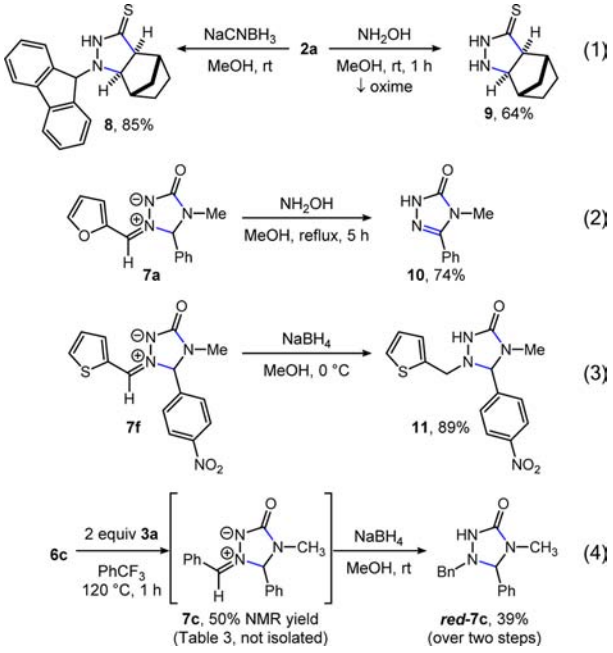


Figure 1. Single-crystal X-ray structure of **7b**. Proximity of the thienyl sulfur and N^- is shown (S···N distance = 2.84 Å). Dihedral angles $\varphi_1 = 0.59°$, $\varphi_2 = -1.20°$.

and $\varphi_2 = -1.20°$. This conformation is attributed to maximized charge delocalization into the aromatic ring.

The azomethine imines in Schemes 3–5 are precursors to a variety of useful heterocycles with the pyrazolone or triazolone core, as illustrated by simple derivatization reactions (eqs 1–3).[18] In addition, products unstable toward hydrolysis (e.g., **7c**, Scheme 5) can be isolated in the stable, reduced form (***red*-7c**) by simple reduction of the crude mixture with $NaBH_4$ (eq 4).

In summary, we expanded the applicability of underexplored [3 + 2] cycloaddition reactions of iminoisocyanates and iminoisothiocyanates. First, it was shown that iminoisothiocyanates also



engage in reactions with alkenes but showed reduced reactivity compared to iminoisocyanates. Conditions to engage both types of reagents in aminocarbonylation reactions of imines were also developed and showed increased reactivity. Overall, this modular approach provides a new strategy for the synthesis of heterocycles with high-heteroatom content and includes proof-of-concept results for aminothiocarbonylation reactions of electron-rich double bonds. Other new reactivity of amphoteric reagents is currently being pursued and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01788.

Complete experimental procedures, characterization and optimization data, and X-ray crystallographic information (PDF)

X-ray crystallographic data for **7b** (CIF)

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Notes

The authors declare no competing financial interest.

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