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Terminal Alkyne Addition to Diazodicarboxylates: Synthesis of Hydrazide Linked Alkynes (Ynehydrazides)

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ABSTRACT

A new route to form C_{sp}–N bonds has been developed via addition of *in situ* generated lithium acetylides to sterically hindered diazodicarboxylates. The reaction provides straightforward access to a previously unexplored ynehydrazide class of stable N-linked alkynes directly from commercially available precursors. Preliminary results show that alkynyl hydrazides are useful reagents for the selective installation of nitrogen functional groups and as precursors to pharmaceutically relevant heterocycles using metal catalyzed cycloadditions and condensations.

Over the past decade, N-functionalized ynamide alkyne derivatives (Figure 1) have received considerable attention as useful building blocks in organic chemistry, enabling selective introduction of nitrogen functional groups in complex systems.[1] Important features of these reagents include stability, ease of preparation,[2–4] and predictable reaction regioselectivity due to the polarization of the alkyne bond. As a result,

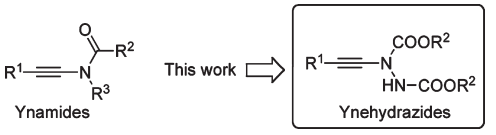

Figure 1. Amide and hydrazide N-linked alkynes.

these amide-linked alkynes have been widely investigated in a variety of reactions demonstrating value as privileged precursors for the synthesis of highly functionalized molecules and biologically interesting heterocycle scaffolds,[1,5] including the total syntheses of natural products.[6]

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Our interest in this area was driven by previous studies on enamide[7] and heterocycle synthesis in our laboratory,[8] and a desire to develop approaches using both C−N bond couplings and metal catalyzed heterocycle synthesis for the construction of novel polyheterocyclic core structures. The ynehydrazide functional group attracted our interest since, despite the utility and popularity of ynamides, the related dinitrogen ynehydrazine or ynehydrazide alkynes are virtually unknown. The overall significance of hydrazine and hydrazide functional groups in drug discovery research,[9] the frequent use of hydrazine derivatives[10] and alkynes[11] as precursors to heterocycles, and the application of N−N bond cleavage to access amines/amides[12] suggested that ynehydrazides could serve as intriguing reagents for organic synthesis.

Despite their potential value as functionalized hydrazine and heterocycle precursors, and as masked ynamides, a general approach to ynehydrazide synthesis is not known. There are a few reports on the synthesis of trimethyl substituted ynehydrazines,[13] but these examples are not amenable to providing differentially substituted hydrazine derived functional groups (e.g., dinitrogen containing heterocycles), and there exists only one example of an ynehydrazide.[14] We now report the development of a general route to ynehydrazides and provide an exploration of their chemistry, including their utility for the selective synthesis of heterocyclic structures by exploiting both alkyne and hydrazide functional groups in ring-forming reactions. These studies demonstrate that ynehydrazides are complementary reagents to ynamides.

Based on the success of copper-promoted C_{sp}−N cross-coupling approaches to generate ynamides,[2] a similar strategy was initially envisaged for ynehydrazide synthesis via coupling of a suitably triprotected hydrazide with alkynyl bromides (Scheme 1). Hydrazide **1** was chosen as a model substrate since it could be readily generated from phthalic anhydride in gram-scale quantities;[15] however, under typical copper-catalyzed or mediated ynamide synthesis conditions, low yields of the desired ynehydrazides **2** were observed (Scheme 1).

Scheme 1. A Copper-Promoted Hydrazide C_{sp}−N Cross-Coupling Approach to Ynehydrazides

Conditions A: $CuSO_4$ (20 mol %), 1,10-phenanthroline (40 mol %), K_3PO_4 (2.0 equiv), toluene, 120 °C, 24 h
R^1= *n*-Hexyl, 12%; R^1= Ph, 28%
Conditions B: CuI (1.1 equiv), KHMDS (1.1 equiv), pyridine, rt, 24 h
R^1= *n*-Hexyl, 0%

An alternative approach was therefore considered through which formation of the C_{sp}−N bond could be achieved via addition of terminal acetylide nucleophiles to readily available diazodicarboxylates (Scheme 2). Despite the known examples of organometallic addition to these electrophilic nitrogen sources,[16] reaction of alkynyl nucleophiles across the N=N bond of these species has not been reported as a strategy to generate C_{sp}−N bonds. Such an approach is a potentially attractive one given its generality, the availability of the reagents, and the stabilizing

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(13) (a) De Croutte, H.; Janousek, Z.; Pongo, L.; Mere, R.; Viehe, H. G. *Bull. Soc. Chim. Fr.* **1990**, *127*, 745. (b) Loffler, A.; Himbert, G. *Synthesis* **1994**, 383–386. (c) Himbert, G.; NaBhan, H.; Gerulat, O. *Synthesis* **1997**, 293–294.

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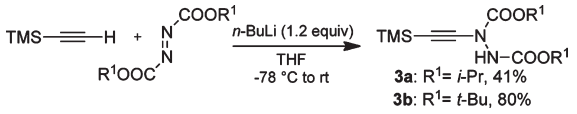
Scheme 2. A Direct Formation of Ynehydrazide C_{sp}–N Bonds via Lithium Acetylide Addition to Diazodicarboxylates



effects of the electron-withdrawing carbamate group on the product ynehydrazides.

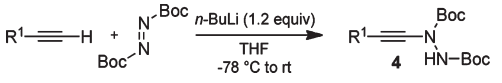
Initial results toward generating ynehydrazides using *in situ* generated lithium acetylides with the commercially available diethyl azodicarboxylate (DEAD) and dibenzyl azodicarboxylate (DBnAD) resulted in complex reaction mixtures and generated only trace amounts of ynehydrazide products. In these cases, acetylide addition to the carbamate functional group instead of across the desired N=N bond was observed as a major side product.

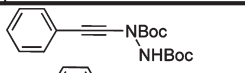
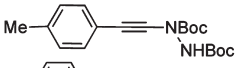
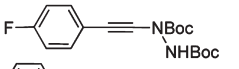
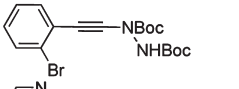
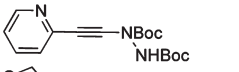
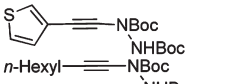
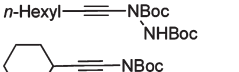
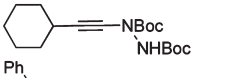
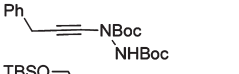
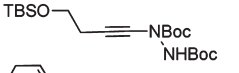
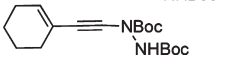
To avoid competitive addition to the carbamate more sterically hindered diazodicarboxylate esters were employed. Reaction of diisopropyl azodicarboxylate (DIAD) with TMS-acetylide led to the isolation of ynehydrazide **3a** in moderate yield (Scheme 2); however, use of the more sterically hindered precursor di-*tert*-butylazodicarboxylate (DBAD) led to the formation of ynehydrazide **3b** in high yield (Scheme 2).[17]

This protocol was found to be quite general, and a wide range of alkynes were found to undergo addition to DBAD via the corresponding lithiated intermediates. The reaction scope includes formation of aryl, heteroaryl, alkyl, benzyl, and alkenyl substituted DBAD derived ynehydrazides **4** (Table 1). Isolated yields of these compounds are generally good except for those containing electron-withdrawing groups such as compounds **4c**–**e**. In these cases, the use of other metal acetylides did not improve reaction yields,[18] potentially due to their inherently decreased nucleophilicity.

Also, commercially available terminal organometallic acetylides did not yield the desired terminal ynehydrazides using the above protocol. Similarly, ethyl propiolate was not compatible with the metalation conditions. To overcome these drawbacks, rapid TBAF mediated silyl group deprotection of the TMS-protected ynehydrazides **3** provided a convenient route to terminal ynehydrazides **5** in good yields (Scheme 3).[17] Thus these products could then be used as precursors to prepare other functionalized ynehydrazides such as the ester **6**, which was not directly accessible through the lithium acetylide addition to diazodicarboxylates.

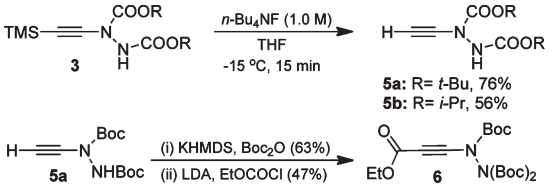
Table 1. Lithium Acetylide Addition to DBAD[a]



entry	product		isolated yield
1		**4a**	65%
2		**4b**	64%
3		**4c**	42%
4		**4d**[b]	29%
5		**4e**	30%
6		**4f**	55%
7		**4g**	75%
8		**4h**	75%
9		**4i**	53%
10		**4j**	65%
11		**4k**	87%

[a] *n*-BuLi (1.2 mmol) was added to alkyne (1.0 mmol) in THF (5 mL) at −78 °C under N_2, followed by addition of DBAD (1.5 mmol) dissolved in THF (3 mL) and allowed to warm to rt over 30 min. [b] 1.2 equiv. LDA used instead of *n*-BuLi.

Scheme 3. Synthesis of Terminal and Carbonyl Substituted Ynehydrazides



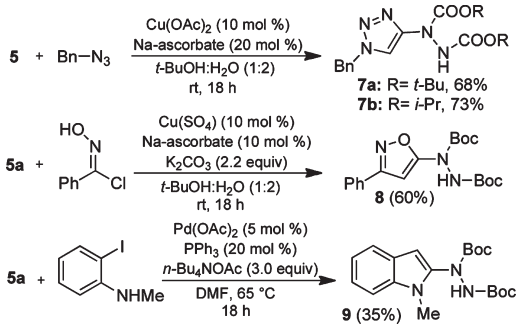
Ynehydrazides **3**–**6** were observed to be generally quite stable to silica gel chromatography and storage.[19] Since ynehydrazides are an almost unexplored compound class, a study of their properties and synthetic utility was next undertaken, with a focus on using the alkyne and hydrazide functional groups for the formation of heterocycles of potential medicinal relevance using metal catalyzed transformations. The terminal ynehydrazides **5** underwent rt regioselective Cu-catalyzed "click-type" [3 + 2] cycloadditions

(17) **3b** could be obtained in similar yield on a 3 mmol scale; however, an initial attempt to conduct the reaction on a larger scale led to a lower yield of **3b**. Batch preparation of **3b** (2 × 3 mmol scale) was used for the synthesis of terminal ynehydrazide **5a** (see Supporting Information).

(18) Transmetalation of the lithium acetylide to copper (CuI) or zinc ($ZnCl_2$) before DBAD addition did not lead to a productive reaction. Transmetalation to cerium ($CeCl_3$) generated product but in 10% lower yield than the Li-acetylide. Use of KHMDS in place of *n*-BuLi did not lead to a productive reaction.

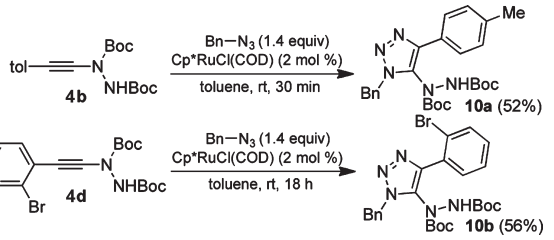
(19) The products could be stored on the bench for multiple weeks to months without significant decomposition as monitored by TLC and ^{1}H NMR analysis, with the only exceptions being **4e** and **4i** which decomposed on the bench after 2 days. In these cases, however, freezer storage (−10 °C) enhanced their life span to multiple weeks.

Scheme 4. Synthesis of Hydrazide Functionalized Heterocycles from Terminal Ynehydrazides



with 1,3-dipoles such as azides or nitrile oxides, enabling selective hydrazide incorporation into 1,2,3-triazole (**7**) and isoxazole (**8**) cores, respectively (Scheme 4). The 2-hydrazide functionalized indole **9** was generated in moderate yield through Pd-catalyzed Larock-type heterocyclization conditions from 2-iodoaniline. These N-linked heterocycles are interesting since they would be difficult to prepare under alternative conditions (e.g., cross-coupling of hydrazides or a nitration/reduction/diazotization sequence) and represent previously unexplored heterocyclic cores. In addition, internal ynehydrazides were found to undergo regioselective rt Ru-catalyzed azide/alkyne cycloaddition[20] to yield highly substituted hydrazide functionalized 1,2,3-triazoles **10** (Scheme 5).

Scheme 5. Formation of Hydrazide Functionalized 1,2,3-Triazoles from Internal Ynehydrazides

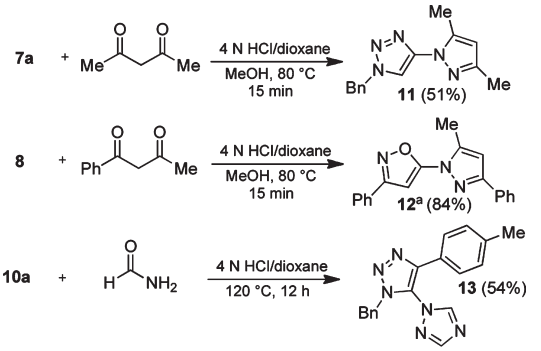


In agreement with Fokin's observations of Ru-catalyzed 1,3-dipolar cycloadditions of this type, a complete regioselectivity switch is observed, providing exclusively the isomers shown.

Significantly, these DBAD derived hydrazide functionalized heterocycles can be readily deprotected and applied

(20) Boren, B. C.; Naravan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

Scheme 6. One-Pot N-Heterocycle Functionalized Pyrazole and Triazole Synthesis from Ynehydrazide Derived Heterocycles



[a] Combined yield of both pyrazole regioisomers; 3:1 in favor of the one shown.

toward our original goal of exploiting both alkyne and hydrazine functional groups in orthogonal ring-forming reactions. For example, *N*,*N*′-di-Boc hydrazide functionalized heterocycles such as **7a** and **8** were rapidly transformed into *N*-triazole and *N*-isoxazole functionalized pyrazoles **11** and **12** via simple addition of 1,3-dicarbonyls and anhydrous HCl (Scheme 6).[16c,e] In a related fashion, 1,2,3-triazole **10a** was directly converted in one pot to an unusual *N*-1,2,3-triazole functionalized 1,2,4-triazole **13** via treatment with formamide and anhydrous HCl. Overall, these heterocycle targets would be difficult to disconnect via alternative chemistry and demonstrate the significant promise of ynehydrazides for use in heterocycle synthesis.

In summary, a previously unexplored class of ynehydrazide heteroatom-linked alkyne reagents are demonstrated to be stable, storable compounds which can be prepared conveniently from commercially available alkynes and diazodicarboxylates. Preliminary results demonstrate that these compounds are useful reagents to selectively install hydrazine units and convert them into medicinally important heterocycles such as pyrazoles and 1,2,4-triazoles. Further work on the reactivity of these interesting fragments, including their use as masked ynamides, is ongoing and will be reported in due course.

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Supporting Information Available. Full experimental details and characterization data for all compounds including ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.