OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 2918–2922

pubs.acs.org/OrgLett

A General Copper-Catalyzed Synthesis of Ynamides from 1,2-Dichloroenamides

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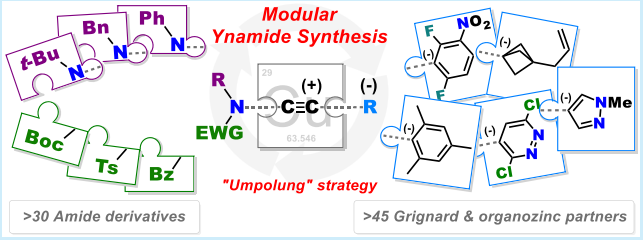
Supporting Information

ABSTRACT: Ynamides are accessed via copper-catalyzed coupling of Grignard or organozinc nucleophiles with chloroynamides, formed in situ from 1,2-dichloroenamides. The reaction exhibits a broad substrate scope, is readily scaled, and overcomes typical limitations in ynamide synthesis such as the use of ureas, carbamates, and bulky or aromatic amide derivatives. This modular approach contrasts with previous routes by installing both the *N*- and *C*-substituents of the ynamide as nucleophilic components.



Ynamides (**1**, Figure 1) are valuable building blocks in organic synthesis.[1,2] As precursors to an array of reactive

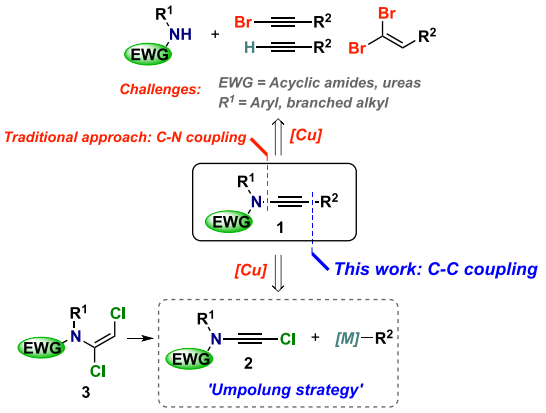


Figure 1. 'Traditional' and 'umpolung' copper-catalyzed ynamide formation.

intermediates,[3] they offer access to a wide variety of azacycles[4] and are also of interest in medicinal chemistry.[5] The prevailing strategy for ynamide synthesis involves copper-catalyzed C−N coupling of an amide nucleophile with an alkyne,[6] haloalkyne,[7] or dibromoalkene[8] electrophile.[9] Despite the utility of these methods for substrates such as unhindered sulfonamides and oxazolidinones, other classes of ynamide are far less accessible. Acyclic amides, carbamates, and ureas are challenging coupling partners[10] as are *N*-aryl and sterically hindered amides, which generally require prolonged heating to achieve even modest conversions.[7c,11] The use of alkynyliodonium triflates as electrophilic coupling partners can overcome some of these restrictions,[10a,12] but a general solution remains elusive for these substrates, preventing their wider exploitation in ynamide chemistry.

We targeted an alternative route to ynamides in which the disconnection point is shifted from C−N to C−C bond formation. All previous examples of this tactic have employed nucleophilic ynamide components (for example, in reactions of metalated ynamides with *C*-centered electrophiles,[13] or cross-coupling of terminal ynamides,[14] which can be complicated by ynamide homodimerization). In contrast, the coupling of *C*-centered *nucleophiles* with ynamide *electrophiles* is without precedent, but is an appealing approach given the ready availability of carbon-based organometallics.

In our previous work, chloroynamides **2** were identified as intermediates en route to lithiated ynamides from 1,2-dichloroenamides **3**.[13f] We questioned whether these substrates could instead serve as the electrophilic component in C−C coupling, albeit only a single report exists on chloroalkyne cross-coupling in general.[15] Here we describe the realization of this *C*-nucleophile coupling route to ynamides, a method that displays broad substrate scope and overcomes previous synthetic limitations such as high steric hindrance on either the *N*- or *C*-component, and enables the synthesis of acyclic urea-, carbamate-, and amide-ynamides.

To initiate studies, dichloroenamide **3a** (Figure 2) was prepared on 0.2 mol scale (66 g, 96%) from *N*-tosylaniline using our reported conditions.[13f] Reaction of **3a** with 1.2 equiv of LiHMDS in THF enabled smooth conversion to chloroynamide **2a**. This could be isolated in good yield;[16] however, for the purposes of ynamide synthesis it proved equally convenient to perform the subsequent coupling in situ. A number of copper salts (e.g., CuCl, CuBr·SMe$_2$, CuI, CuCl$_2$,

Received: March 19, 2019
Published: April 3, 2019

DOI: 10.1021/acs.orglett.9b00971
Org. Lett. 2019, 21, 2918–2922

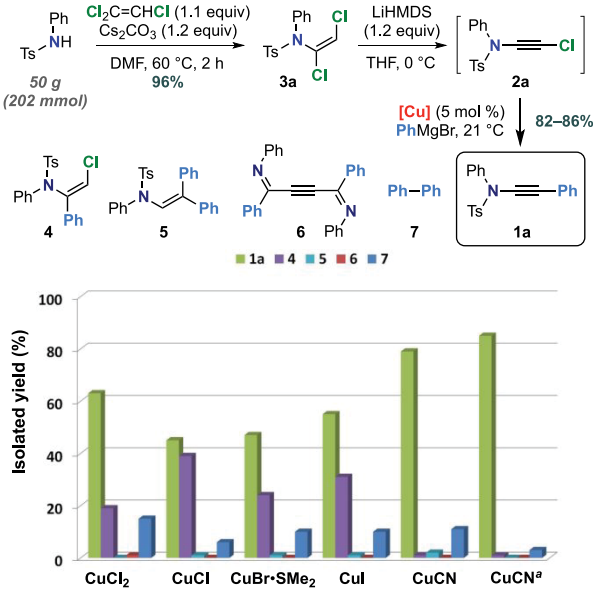
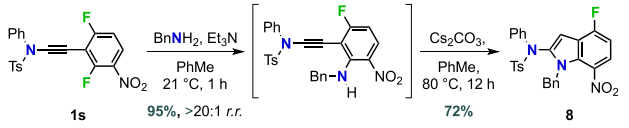


Figure 2. Optimization of the conversion of dichloroenamide **3a** to ynamide **1a**. [a] Optimized conditions: PhMgBr (1.03 equiv), [CuCN·2P(OMe)$_3$] (1.25 mol %), TBME (0.34 M), 21 °C, 10 min, 82–86%.

CuCN) were screened as catalysts in the reaction with PhMgBr (1.2 equiv),[15,16] with all reactions reaching completion in 10–15 min at 21 °C. However, alongside the desired ynamide **1a**, most also afforded (*Z*)-chloroenamide **4** as a significant side product (19–39%), along with small amounts of **5**–**7**.[17] CuCN[18] alone delivered **1a** in high yield and selectivity (79%, **1a**:**4** > 20:1). The inclusion of trimethyl phosphite (10 mol %) minimized the formation of biphenyl **7**,[19] while decreasing the amount of PhMgBr to 1.03 equiv suppressed the formation of **6**. TBME proved a superior reaction solvent, and finally the catalyst loading could be reduced to 1.25 mol % (2.5 mol % P(OMe)$_3$) without detriment. Under these optimized conditions, ynamide **2a** was isolated in 82–86% yield over five runs.[20]

These conditions were broadly applicable to couplings with both Grignard and organozinc reagents (Figure 3a), with 38 organometallic coupling partners spanning a range of electron-rich and electron-poor aromatics, and 1°/2°/3° alkyl groups, being successfully converted to ynamides on reaction with **3a**. Amide, ester, nitrile, and nitro functionalities were tolerated (**1c**, **1p**–**1s**), as were potentially reactive halides (**1h**, **1n**), and hindered nucleophiles (**1f**–**1i**). A range of heterocyclic Grignards also underwent efficient couplings (**1t**, **1w**–**1ab**), while the formation of ynamide **1al** demonstrates an interesting entry to alkynyl bicyclo[1.1.1]pentanes.[21] Organozinc partners proved useful where Grignard reagents were unavailable or unstable, including several heteroaromatics (**1u**, **1v**, and **1ac**), albeit these substrates required extended reaction times (12 h versus 10–30 min for Grignard coupling). For many of these examples, the avoidance of prolonged heating (as required for challenging ynamide C–N couplings) and the use of readily available Grignard/organozinc reagents (which obviates the need to preform haloalkene/alkyne coupling partners) enhances the range of functionality that can be introduced and affords opportunities to develop novel ynamide reactivity. For instance, tolerance of nitro and fluoro substituents in the formation of ynamide **1s** enabled a concise synthesis of aminoindole **8** (Scheme 1) via S$_N$Ar/cyclization.

Scheme 1. Synthesis of an Aminoindole from Ynamide 1s



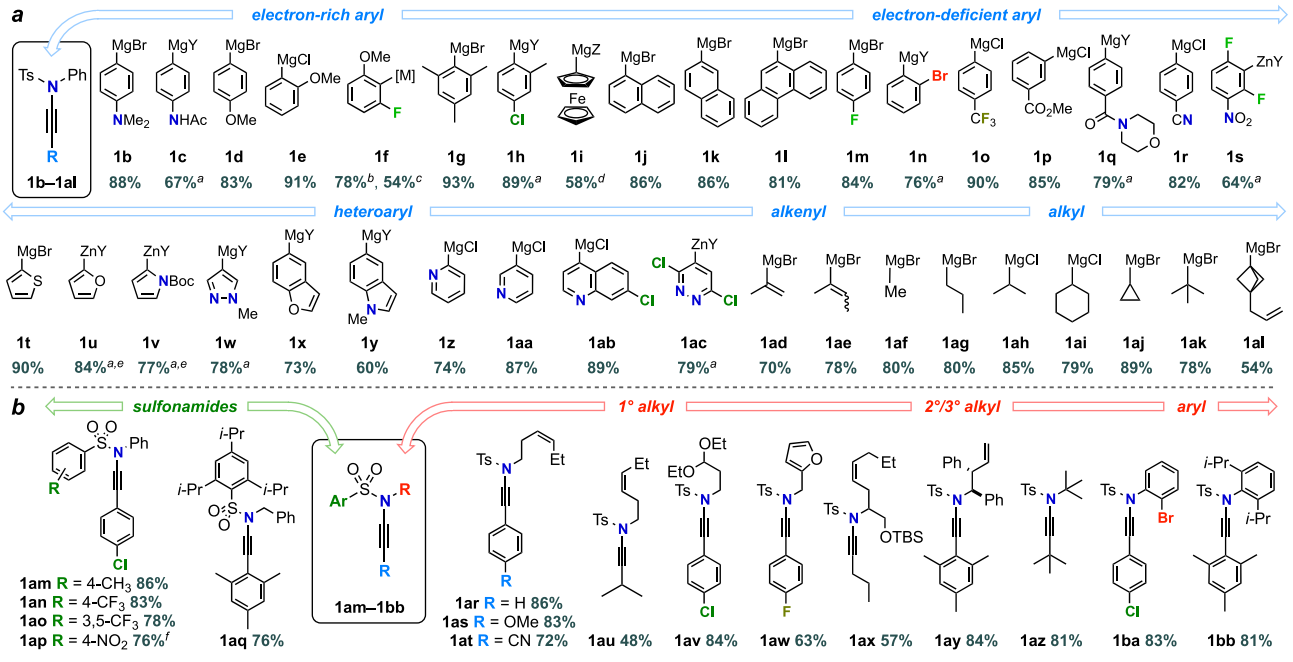


Figure 3. Synthesis of sulfonamide ynamides. (a) Scope of organometallic coupling partners. (b) Scope of sulfonamide. All reactions were conducted on 500 mg (1.46 mmol) scale using RMgX (1.03 equiv), [CuCN·2P(OMe)$_3$] (1.25 mol %), TBME (0.34 M), 21 °C, 10 min–1 h, unless otherwise stated. [a] Y = Cl·LiCl. [b] ArMgBr·LiBr was used. [c] ArZnCl·LiCl was used. [d] Z = TMP·LiCl. [e] TMEDA (1.3 equiv) was added. [f] Ar$_2$Zn was used.

DOI: 10.1021/acs.orglett.9b00971
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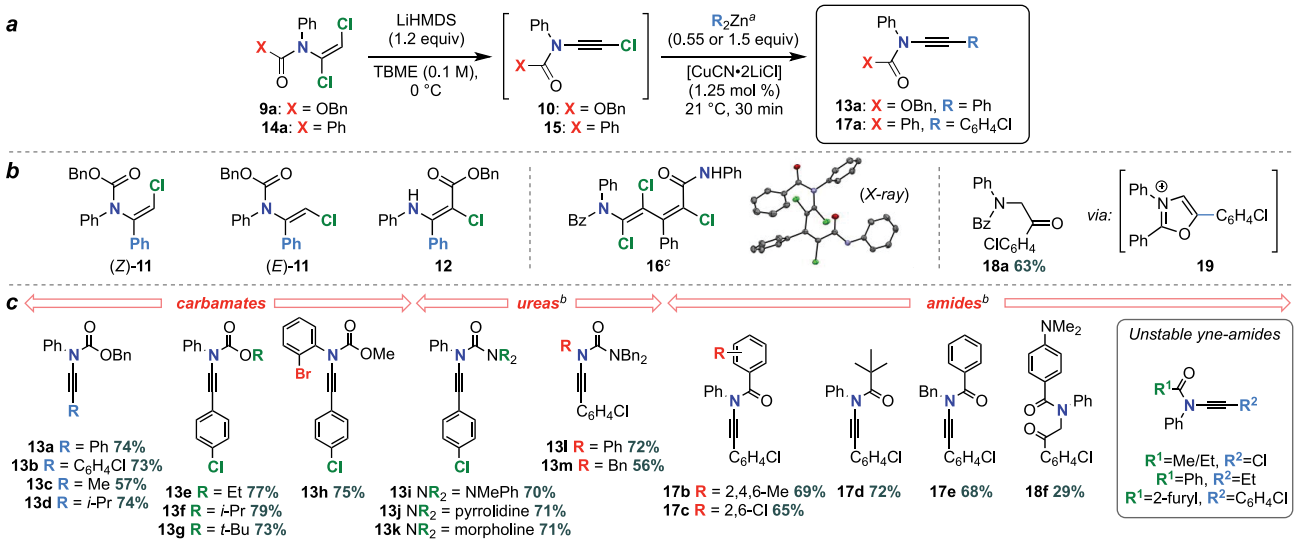

Figure 4. (a) Synthesis of carbonyl ynamides. (b) Reaction byproducts. (c) Reaction scope. [a] Ar_2Zn prepared using a 2:1 ratio of ArMgBr (in toluene or Et_2O) and $ZnCl_2$, Ar = Ph or 4-ClC_6H_4. [b] TMEDA (10 equiv) was added. The crystal molecular structure of **16** is displayed at 50% probability;[15] hydrogen atoms are omitted for clarity.

With the scope of the organometallic partner established, we next tested a selection of *N*-sulfonyl dichloroenamides to explore variation of the sulfonamide, and the steric/functional group tolerance of the nitrogen substituent (Figure 3b). Efficient reactions were observed irrespective of the nature of either the sulfonyl motif (**1am**−**1aq**) or the nitrogen atom substituent (**1ar**−**1bb**); particularly notable are ynamides **1aq**, **1ay**, **1az**, and **1bb** featuring bulky substituents on both the nitrogen and alkyne (76−84%), and electron-deficient sulfonamides **1ao** and **1ap** (78% and 76%).

Having developed a general approach to sulfonyl ynamides, we decided to challenge the robustness of the transformation by targeting acyclic carbonyl ynamides, which have otherwise proven difficult to make. Carbamate dichloroenamide **9a**, which was readily prepared on multigram scale (42 mmol/12 g, 89%), was used as a test substrate (Figure 4a). Chloroynamide formation (**10**) was achieved in 80−85% yield; however, its coupling with PhMgBr led to significant amounts of chloroenamides (*Z*)- and (*E*)-**11** and (*E*)-chloroester **12**, in addition to the desired ynamide **13a** (Figure 4b). These byproducts likely arise from competing addition of the Grignard to the intermediate chloroynamide,[16] but could be suppressed through the use of diarylzinc reagents (prepared by salt metathesis of the Grignard reagent with zinc(II) chloride). The addition of TMEDA was also found to be beneficial for the formation of urea-ynamides, and under these reoptimized conditions, a range of carbamate and urea dichloroenamides underwent smooth conversion to ynamides **13a**−**m** (Figure 4c). These couplings were complete within 30 min—a time scale that compares favorably with other carbonyl-ynamide synthesis routes—with both diaryl and dialkylzinc reagents proving effective.[16]

Acyclic amide substrates presented a significantly greater challenge, with both reaction intermediates and products displaying heightened reactivity compared to other derivatives. For example, the conversion of dichloroenamide **14a** to chloroynamide **15** was accompanied by the unexpected formation of **16** (Figure 4b), which likely arises from reaction of **15** with the lithiated dichloroenamide.[13] This side reaction, which was not observed with any other substrate class, could be minimized by conducting the elimination at room temperature, enabling rapid coupling of chloroynamides to give amide-ynamides **17b**−**e** in good yields (Figure 4c).

In certain cases, the amide-ynamide products were prone to hydration upon concentration, or during chromatography on neutralized silica gel, giving δ-ketoamides (**18a**/**f**). This remarkable β-hydration of the ynamide may be explained by a 5-*endo*-*dig* cyclization[22] to oxazolium ion **19** and subsequent hydrolysis, and was particularly apparent for *N*-phenylamide derivatives.[23] In contrast, *N*-benzyl benzoyl ynamide **17e** was comparatively stable (68%), as were amide-ynamides featuring bulky substituents (**17b**−**d**) where adoption of the conformation required for cyclization to the oxazolium ion may be disfavored. It is surprising that these amide-ynamides are somewhat fragile, given that equivalent carbamate- and urea-ynamides are not; for example, urea **13l** withstood heating in ethanol during recrystallization. Although amide-ynamides have been prepared sporadically in the past,[10] it is clear that the nature of the electron-withdrawing group and the second nitrogen substituent are very important in modulating the stability and reactivity of these compounds.

In summary, we have established a new strategy to access ynamides from readily available dichloroenamides, in which intermediate chloroynamides act as electrophilic components in coupling with carbon-based nucleophiles. The reaction shows broad scope, accommodating a wide range of Grignard and organozinc reagents, and tolerating a diverse range of functionality, electronic character, and steric bulk on both coupling partners. This chemistry also offers a general route to acyclic carbonyl-based ynamides and affords valuable insight into their stability and reactivity. In overcoming many previous limitations, this method provides a wealth of opportunities for the development of new ynamide chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00971.

DOI: 10.1021/acs.orglett.9b00971
Org. Lett. 2019, 21, 2918−2922

Full optimization details, experimental procedures, copies of ^{1}H and ^{13}C NMR spectra and crystallographic data (PDF)

Accession Codes

CCDC 1895057−1895071 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

S.J.M. is grateful for support from an Oxford R. E. Jones Scholarship, and the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1), generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. R.C.S. thanks the SBM CDT for the industrial partnership. E.A.A. thanks the EPSRC for additional support (EP/M019195/1).

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DOI: 10.1021/acs.orglett.9b00971
Org. Lett. 2019, 21, 2918–2922