Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Allenamides by Copper-Catalyzed Coupling of Propargylic Bromides and Nitrogen Nucleophiles

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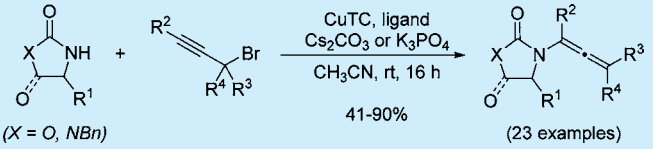
Supporting Information

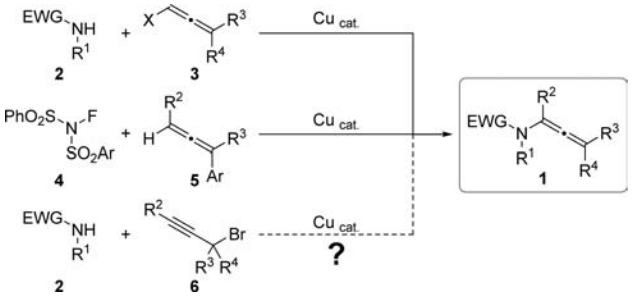
ABSTRACT: An efficient and general synthesis of allenamides derived from oxazolidinones and hydantoins is reported. Upon activation with a combination of a copper catalyst and a 2,2′-bipyridine derivative in the presence of an inorganic base, propargylic bromides were found to be suitable reagents for the direct allenylation of nitrogen nucleophiles by a formal copper-catalyzed S_N2' reaction. Besides the availability of the starting materials, notable features of this route to allenamides are its mild reaction conditions, the reaction being performed at room temperature in most cases, and its applicability to the preparation of mono-, di-, as well as trisubstituted allenamides.



Because of their higher stability compared to allenamines, allenamides **1** are clearly emerging as useful and versatile building blocks in organic synthesis.[1] These strongly polarized allenes have indeed been shown to be ideal substrates for an impressive number of transformations.[1,2] As additional evidence of their synthetic usefulness, they also began to appear in natural product synthesis[3] and medicinal chemistry.[4]

Despite a growing interest for the chemistry of allenamides, there is still a lack of general methods for their preparation. In addition to the classical route to allenamides based on the base-promoted isomerization of the corresponding propargylic derivatives,[5] which mostly provides an access to unsubstituted allenamides, they can also be prepared by sigmatropic rearrangements starting from propargylic alcohols.[6] These reactions, however, suffer from limitations such as low yields and poor substrate scopes or only allow the preparation of particular classes of allenamides. The major breakthrough for the synthesis of allenamides **1** was reported in 2005 by the Trost[7] and Hsung[8] groups, who developed the first general access to these building blocks based on the copper-catalyzed direct allenylation of nitrogen nucleophiles **2** with allenyl halides **3** (Scheme 1). While this reaction had a strong impact on the chemistry of allenamides and is still one of the most efficient routes to these building blocks, limitations remain, such as the impossibility of preparing trisubstituted allenamides with this method and the formation of dienes as byproducts. In addition, when the starting allenyl halides cannot be prepared or when their cross-coupling fails, there is no general alternative process available besides the recently reported direct radical amination of allenes **5** with *N*-fluorodiarenesulfonimides **4**, which despite its attractiveness, is limited to the synthesis of aryl-substituted allenamines bearing two sulfonyl groups on the nitrogen atom.[9] Therefore, a strong need remains for the development of robust and mild methods for the synthesis of allenamides from readily available starting materials.

Scheme 1. Previously Reported Direct Routes to Allenamides and Our Strategy for Allenylation with Propargyl Bromides



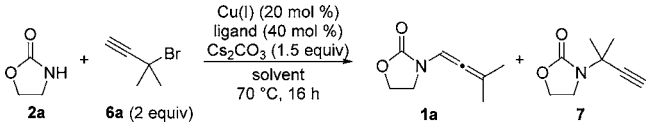
Based on our combined interest in copper catalysis[10] and the chemistry of heterosubstituted alkynes and alkenes,[11] we envisioned that an efficient entry to allenamides could rely on the use of propargylic bromides **6**. They could be potentially used for the direct allenylation of nitrogen nucleophiles **2**, provided they could be activated by a copper(I) complex and the formal S_N2' reaction could be favored over the direct S_N pathways.

The feasibility of this hypothesis based on an unprecedented copper-catalyzed S_N2' reaction involving a nitrogen nucleophile was therefore evaluated using oxazolidinone **2a** and 3-bromo-3-methylbut-1-yne **6a** (2 equiv) as model substrates. The efficiency of a set of representative bidentate ligands combined with cuprous iodide as the source of copper(I) in combination with cesium carbonate as the base in toluene at 70 °C was first evaluated (Table 1, entries 3−8). To our delight, we noted that the desired allenamide **1a** was formed in all trials, thereby validating our strategy and the use of propargyl bromides as

Received: February 5, 2016
Published: March 3, 2016

DOI: 10.1021/acs.orglett.6b00372
Org. Lett. 2016, 18, 1438−1441

Table 1. Optimization of the Copper-Catalyzed Allenylation



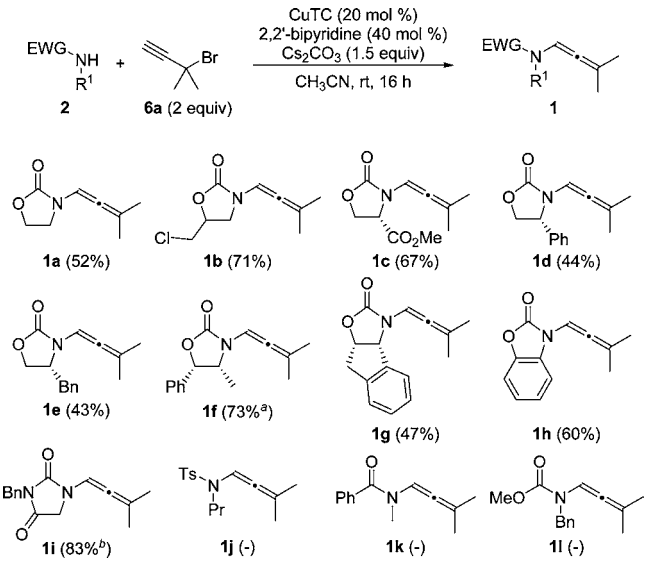
entry	Cu(I)	ligand	solvent	1a[a] (%)	7[a] (%)
1			toluene	11	50
2	CuI		toluene	20	
3	CuI	ethylene glycol	toluene	19	5
4	CuI	proline	toluene	12	3
5	CuI	isobutyrylcyclohexanone	toluene	19	6
6	CuI	DMEDA	toluene	13	18
7	CuI	1,10-phenanthroline	toluene	23	5
8	CuI	2,2′-bipyridine	toluene	33	6
9	CuCN	2,2′-bipyridine	toluene	21	12
10	CuCl	2,2′-bipyridine	toluene	23	0
11	CuTC	2,2′-bipyridine	toluene	56	0
12	CuTC	2,2′-bipyridine	dioxane	34	5
13	CuTC	2,2′-bipyridine	DMF	25	3
14	CuTC	2,2′-bipyridine	CH_3CN	69	3
15[b]	CuTC	2,2′-bipyridine	CH_3CN	64	3

[a]NMR yields using DMF as an internal standard. [b]At rt.

reagents for the allenylation of nitrogen nucleophiles, a reaction which mostly gave the propargylic oxazolidinone **7** in the absence of copper (Table 1, entry 1). Although the competitive reaction yielding **7** could not be totally suppressed at this stage of the optimization, 2,2′-bipyridine was found to be the best ligand in terms of efficiency and selectivity and was therefore chosen as the ligand for the rest of the optimization. Four copper(I) precatalysts were then evaluated in combination with 2,2′-bipyridine (Table 1, entries 8−11), and copper thiophene carboxylate (CuTC) was found to have a dramatic effect on the reaction since allenamide **1a** was formed in 56% yield without any competitive propargylation. Various solvents were finally evaluated for the allenylation, and acetonitrile was found to be superior to toluene, dioxane, and DMF (Table 1, entries 11−14), yielding the desired allenamide in 69% yield. While the use of other bases did not result in an improvement of the yield (data not shown), a brief examination of the influence of the reaction temperature revealed that heating the reaction mixture at 70 °C was actually not required for the allenylation to proceed since **1a** could be formed in 64% yield at room temperature without isomerization to the undesired diene (Table 1, entry 15), a common side reaction in the synthesis of allenamides. Due to the sensitivity of certain allenamides, we therefore chose to study the scope and limitation of our allenylation at room temperature.

Having in hand the optimized conditions for the allenylation with our model substrates, we next moved to the scope and limitation studies and first examined the allenylation of various representative nitrogen nucleophiles **2** with 3-bromo-3-methylbut-1-yne **6a** (Scheme 2). The synthesis of oxazolidinone-derived allenamides was found to proceed smoothly in most cases, giving the desired *N*-allenyloxazolidinones **1a−h** in fair to good yields at room temperature in most cases. Sensitive functional groups such as a chloride or epimerizable centers were found to be well-tolerated as well as the presence of bulky substituents close to the reacting center such as in **1d,e,g**. Importantly, the allenylation of chiral enantiopure oxazolidinones with this method provides a straightforward entry to the

Scheme 2. Scope of the Copper-Catalyzed Allenylation of Nitrogen Nucleophiles with 3-Bromo-3-methylbut-1-yne

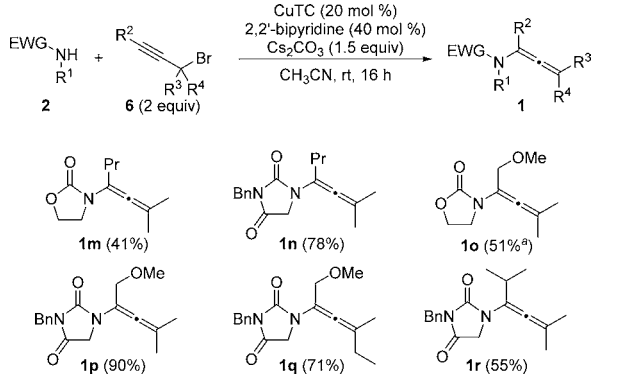


[a]Reaction performed at 70 °C. [b]4 equiv of **6a** was used.

corresponding chiral allenamides such as **1c−g**, useful building blocks in asymmetric synthesis. The allenylation could be further extended to the use of hydantoins provided that an excess of the propargylic bromide was used to drive the reaction to completion, which furnished the corresponding *N*-allenylhydantoin **1i** in 83% yield. However, and which probably represents the main limitation of our reaction that clearly must be mentioned, nitrogen nucleophiles such as sulfonamides, amides, or carbamates, coupling partners that usually perform well in the Hsung−Trost allenylation, were found to be reluctant substrates in our case, presumably due to lower coordination properties of these acyclic nitrogen nucleophiles.

After studying the influence of the nitrogen nucleophile, we then moved to the evaluation of the influence of the propargylic bromide. Since trisubstituted allenamides are the most challenging ones to synthesize, we first focused on their preparation starting from trisubstituted propargylic bromides **6** (Scheme 3). To our delight, the reaction proceeded smoothly at room temperature, except in the case of **1o**, which required a higher temperature (70 °C), providing an efficient entry to fully

Scheme 3. Synthesis of Trisubstituted Allenamides by Copper-Catalyzed Allenylation with Propargyl Bromides



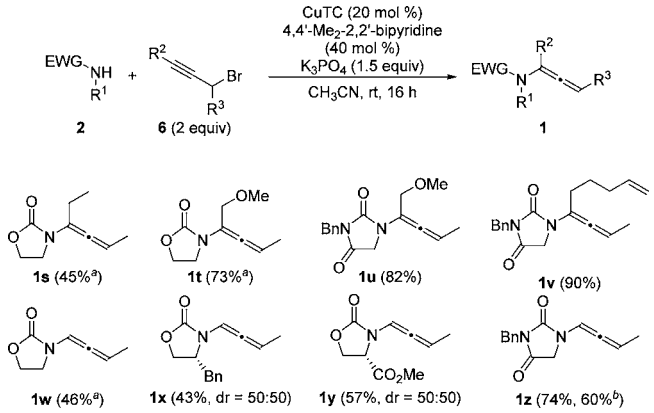
[a]Reaction performed at 70 °C.

DOI: 10.1021/acs.orglett.6b00372
Org. Lett. 2016, 18, 1438−1441

substituted allenamides **1m−r** which could be isolated in 41−90% yield.

Having demonstrated the efficiency of the cross-coupling of nitrogen nucleophiles with propargylic bromides for the preparation of 3,3-disubstituted as well as trisubstituted allenamides, we next investigated the extension of the formal S_N2' to the preparation of 1,3-disubstituted and 3-monosubstituted derivatives. The reaction turned out to be more sluggish in these cases, and the presence of a single substituent at the propargylic position seemed to have a dramatic impact on the activation of the starting propargylic bromide by the copper catalyst. This lack of reactivity could, however, be quite easily overcome by moving to a more electron-rich bipyridine ligand, and 4,4′-dimethyl-2,2′-bipyridine was found to be able to promote the allenylation. Replacing cesium carbonate by potassium phosphate further favored the reaction, which could then be readily applied to the preparation of a variety of 1,3-disubstituted **1s−v** and 3-monosubstituted **1w−z** allenamides in fair to good yields (Scheme 4). Interestingly, the reaction

Scheme 4. Synthesis of 3-Monosubstituted and 1,3-Disubstituted Allenamides by Copper-Catalyzed Allenylation with Propargyl Bromides



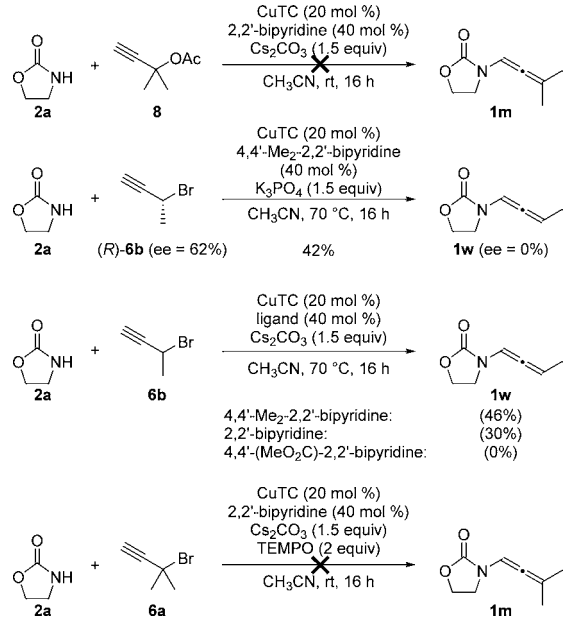
[a]Reaction performed at 70 °C. [b]Reaction performed on a gram scale.

could also be performed on a gram scale, which should demonstrate its potential use in the chemistry of allenamides. The absence of substituent at the propargylic position in the starting propargylic bromide was, however, found to be detrimental to the reaction, and in this case, the direct propargylation of the nucleophile could not be avoided.[12]

To gain insights into the mechanism of this formal copper-catalyzed S_N2' reaction, which can potentially proceed via a number of distinct reaction pathways, a series of test experiments, shown in Scheme 5, were performed. First, replacing the propargylic bromide by the corresponding acetate **8**[13] did totally suppress the allenylation, which was also shown to be not stereospecific since the cross-coupling between optically enriched bromide (*R*)-**6b**[14] and oxazolidinone **2a** resulted in the formation of racemic allenamide **1w**.[15]

Based on the reactivity of **8** and (*R*)-**6b**, a pure S_N2' mechanism can therefore be reasonably excluded. A mechanism in which the copper(I) catalyst would purely act as a Lewis acid activating the triple bond could also be excluded since the allenylation of **2a** with propargylic bromide **6b** in the presence of various bipyridines showed that electron-rich bipyridines, which form less Lewis acidic copper complexes, were more efficient, while an electron-poor one was totally inefficient.

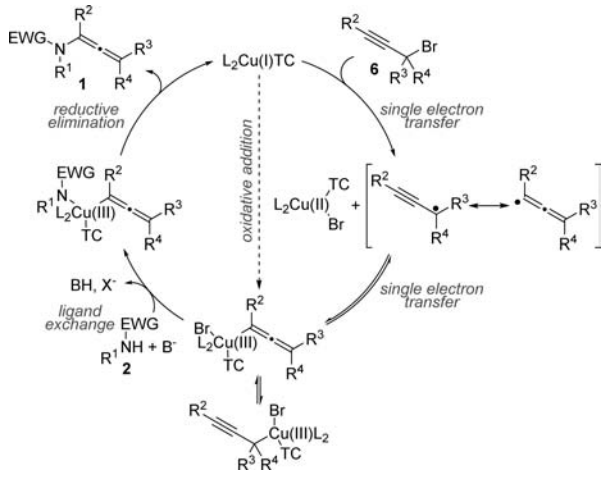
Scheme 5. Test Experiments To Gain Insights into the Mechanism of the Allenylation



Finally, we could demonstrate the intermediacy of a radical intermediate in this reaction since the addition of 2 equiv of TEMPO completely shut down the reaction (Scheme 5).

On the basis of these experiments, notably the use of stereochemical probes and radical inhibitors, it is reasonably safe to propose that the reaction involves radical species that could be generated by activation of the propargylic bromide **6** by the copper catalyst L_2CuTC through single-electron transfer (Scheme 6). This would initiate the homolysis of the C−Br

Scheme 6. Proposed Catalytic Cycle



bond and generate a propargylic radical, in resonance with an allenyl one, which could then directly evolve by formation of the coupled product and regeneration of the active catalyst or by a second single electron transfer followed by a reductive elimination step from a copper(III) intermediate in this case. Alternatively, a direct oxidative addition of L_2CuTC to the propargylic bromide would provide a propargylcopper(III) in which the stereochemistry would not be retained due to reversible propargyl/allenyl radical and copper(II) formation.

DOI: 10.1021/acs.orglett.6b00372
Org. Lett. 2016, 18, 1438−1441

Isomerization to allenylcopper(III) followed by ligand exchange and reductive elimination would then, as in the previous case, account for the formation of the final allenamide **1**.[16]

In conclusion, we have developed an efficient method for the synthesis of allenamides. Clear advantages of our procedure are the use of readily available propargylic bromides which were shown to be remarkably efficient allenylation reagents and the mild reaction conditions which are compatible with the allenamide moiety. Even trisubstituted allenamides, which are among the most challenging to prepare, are readily obtained using this cross-coupling, which should contribute to the chemistry of allenamides, together with bringing a useful addition to the ever-expanding copper-catalysis toolbox with this unprecedented copper-catalyzed formal S_N2' reaction between nitrogen nucleophiles and propargylic bromides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00372.

Detailed experimental procedures and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Our work was supported by the Université libre de Bruxelles (ULB), the FNRS (Incentive Grant for Scientific Research n° F.4530.13), and the Fédération Wallonie-Bruxelles (ARC Consolidator 2014-2019).

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(12) Under the reaction conditions shown in Scheme 4, the reaction between oxazolidin-2-one and 1-bromopent-2-yne gave a mixture of 3-(buta-2,3-dien-2-yl)oxazolidin-2-one (25%) and 3-(pent-2-yn-1-yl) oxazolidin-2-one (12%).

(13) The corresponding mesylate was found to be unstable under the reaction conditions, and its reactivity could therefore not be tested.

(14) Prepared from (*S*)-but-3-yn-2-ol and optical purity estimated according to: Claesson, A.; Olsson, L.-I. *J. Am. Chem. Soc.* **1979**, *101*, 7302. Its ee was estimated on the basis of its reaction with L-proline *tert*-butyl ester, which afforded an 81:19 ratio of diastereoisomers.

(15) The ee of **1w** was estimated by recording the ^{1}H NMR spectra of **1w** in the presence of 20 mol % of europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], which gave two signal of similar integrations for the allenamide methyl group.

(16) For an example of a copper-catalyzed S_N2' reaction involving cationic propargyl/allenyl copper as reactive intermediates instead of an *anti*-S_N2' pathway, see: Miyake, Y.; Ota, S.-i.; Shibata, M.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, *49*, 7809.

DOI: 10.1021/acs.orglett.6b00372
Org. Lett. 2016, 18, 1438–1441