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Construction of β-Haloenamides via Direct Copper-Promoted Coupling of Lactams with 2-Chloro and 2-Bromo Vinyliodides

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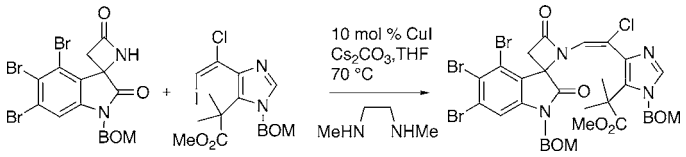
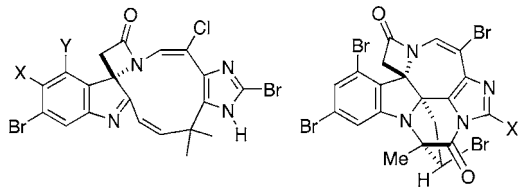
ABSTRACT



Cu(I)-catalyzed coupling of lactams with (*E*)-2-chlorovinyliodides or (*E*)-2-bromovinyliodides produces the corresponding β-haloenamides in moderate to excellent yields.

Several alkaloids isolated from the marine bryozoan *Chartella* papyracea incorporate an array of unusual functional groups, including a β-halogenated enamide moiety (Figure 1).[1] Due to their unique structures, both the chartellines (**1**−**3**)[2] and chartellamides (**4** and **5**)[3] have attracted attention as synthetic targets. However, little work to date has focused on formation of the β-chloroenamide moiety found in the chartellines and the β-bromoenamide of the chartellamides. We are currently exploring synthetic approaches to these marine metabolites and now describe some of our initial results for the efficient construction of the haloenamide portions of these natural products.

There has been a substantial amount of recent work dedicated to the synthesis of stereochemically well-defined enamides[4] and enamide-containing natural products[5] via metal-catalyzed coupling of vinyl halides with amides and lactams. Buchwald et al. have developed a mild and convenient improved procedure for the stereocontrolled *N*-vinylation of amides with vinyl halides using copper(I) catalysis with *N*,*N*′-dimethylethylenediamine as the ligand.[6]



1 chartelline A, X = Y = Br
2 chartelline B, X = H, Y = Br
3 chartelline C, X = Y = H

4 chartellamide A, X = H
5 chartellamide B, X = Br

Figure 1. The chartellines and chartellamides.

(1) (a) Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 5638−5639. (b) Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709−4712. (c) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, C.; Anthoni, U. *J. Am. Chem. Soc.* **1985**, *107*, 4542−4543. (d) Nielsen, P. H.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand.* **1988**, *B42*, 489−491.

(2) (a) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631−2633. (b) Lin, X. Ph.D. Thesis, The Pennsylvania State University, 2002. (c) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714−3717. (d) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025−2027. (e) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440−441. (f) Sun, C. Ph.D. Thesis, The Pennsylvania State University, 2005.

(3) Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141−4143.

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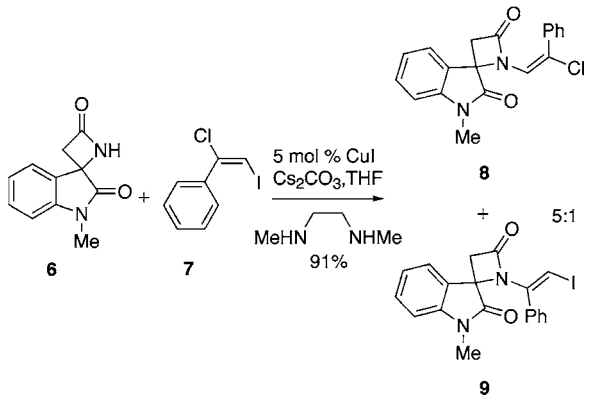
This methodology also allows the synthesis of 5−7-membered lactams via the intramolecular vinylation of amides.[7]

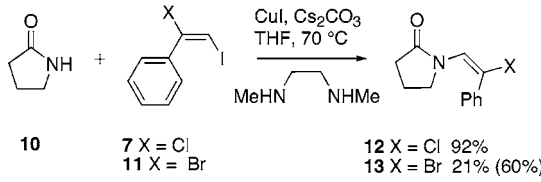
At the outset of our research, nothing had been reported on metal-induced couplings of amides or lactams with 1,2-dihaloalkenes.[8] During the course of the studies outlined here, however, the Isobe group described a single example of such a process. Thus, it was found that a 5:1 mixture of halogenated enamides **8** and **9** could be obtained via coupling of *β*-lactam **6** and *(E)*-*β*-chloro vinyliodide **7** with the Buchwald conditions (Scheme 1).[2e]

Scheme 1



Our initial investigations were aimed at both developing the chemistry required to construct the requisite haloenamide moieties and determining the functional group compatibility of this methodology. Therefore, known *(E)*-1-chloro-2-iodovinylbenzene (**7**)[9] and (*E*)-1-bromo-2-iodovinylbenzene (**11**)[10] were coupled with 2-pyrrolidinone (**10**) with use of the reaction conditions described by Buchwald for simple vinyl iodides (Scheme 2). Treatment of the chloro compound

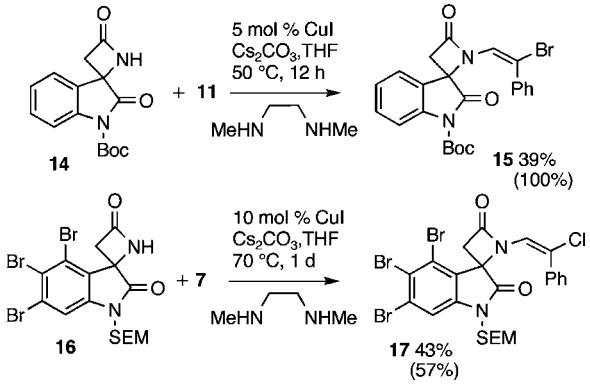
Scheme 2



7 and lactam **10** with 20 mol % of CuI, cesium carbonate, and *N*,*N*′-dimethylethylenediamine in THF at 70 °C produced the *β*-chloroenamide **12** in high yield as a single geometric isomer. Moreover, the reaction was completely iodide selective, and none of the coupling product analogous to **9** was detected in this case, or in any of the examples discussed below. In the case of bromo iodo compound **11**, however, the yield of coupled product **13** was significantly lower (21%; 60% based on recovered starting iodide).

We next investigated the coupling of some spiro-*β*-lactams structurally related to the chartellines with model dihalo substrates (Scheme 3). *β*-Lactam **14** reacted with iodo bromo

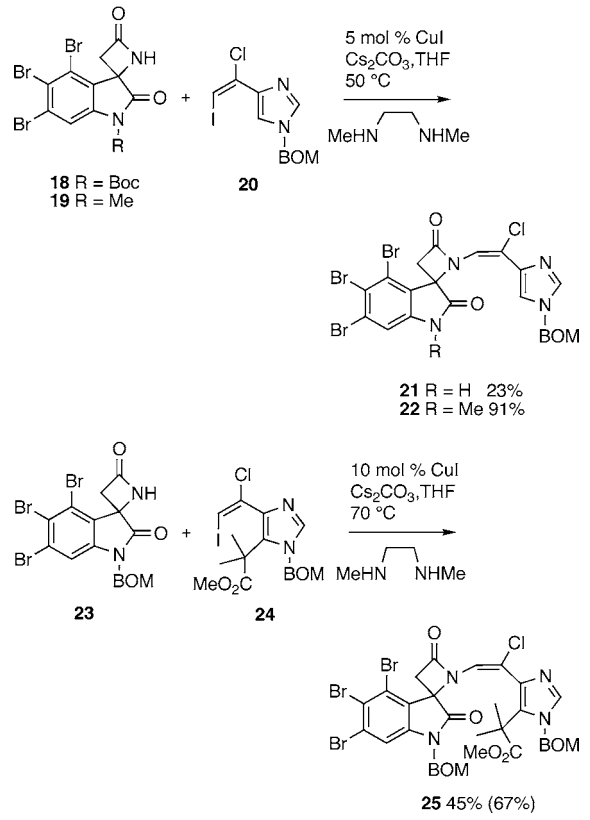
Scheme 3



compound **11** to give *β*-bromoenamide **15** in 39% isolated yield (100% based upon recovered iodide). We were pleased to find that tribrominated spiro-*β*-lactam **16**[11] coupled smoothly and chemoselectively with simple iodo chloro substrate **7** to produce *β*-chloroenamide **17** in moderate yield.

The couplings of some 4-dihalovinylimidazoles with tribromo spiro-*β*-lactam substrates were also investigated (Scheme 4). Reaction of the Boc-protected tribromo *β*-lactam **18** with imidazole **20** under the standard conditions resulted

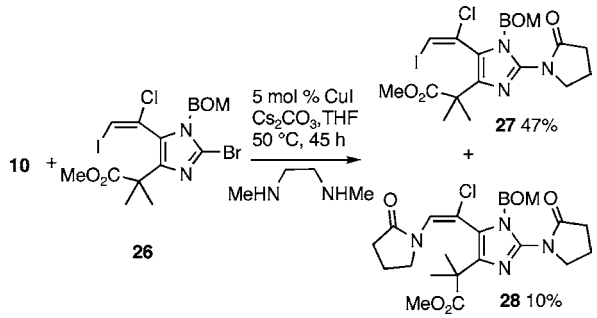
Scheme 4



in formation of the haloenamide **21** in low yield due to the lability of the protecting group in this system. However, the more stable methyl-substituted analogue **19** coupled in high yield with imidazole **20** to afford β-chloroenamide **22**. 5-Substituted imidazole **24** also reacted with BOM-protected lactam **23** to produce coupled product **25** in 45% isolated yield (67% based upon recovered **24**). This compound is a potentially useful intermediate for synthesis of chartelline A (**1**).

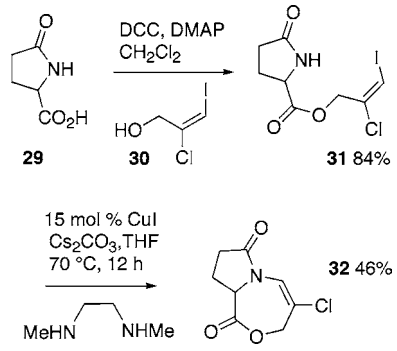
Since the chartellines and chartellamides contain a 2-bromoimidazole moiety, we decided to explore the compatibility of this functionality with the coupling methodology (Scheme 5). Thus, 2-pyrrolidinone (**10**) was coupled with 2-bromoimidazole **26** to afford the undesired lactam **27** as the major product, along with a small amount of bis-lactam **28**.

Scheme 5



Finally, it was found that this methodology can also be effected intramolecularly (Scheme 6). The cyclization precursor **31** was prepared via a DCC-mediated esterification[12] of pyroglutamic acid (**29**) with known (*E*)-1-iodo-2-chlorovinyl alcohol **30**.[13] Iodo lactam **31** was then subjected to the usual Buchwald conditions to afford seven-membered bicycle **32** in moderate yield.

Scheme 6



In conclusion, we have developed a simple, efficient method for the stereocontrolled synthesis of β-haloenamides in moderate to good yields via the copper-catalyzed halogen-selective *N*-vinylation of lactams with (*E*)-β-chloro and (*E*)-β-bromo vinyliodides. This methodology can also be effected intramolecularly, thereby providing interesting possibilites for the total synthesis of the chartellines **1**−**3** and chartellamides **4** and **5**.

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Supporting Information Available: Experimental procedures for preparation of new compounds including spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 676−680.

(10) Synthesized from phenylacetylene and IBr using a variation of the methodology of Uemura.[9] See the Supporting Information for experimental details.

(11) For synthesis of the β-lactam and imidazole substrates see ref 2f, and: Sun, C.; Lin, S.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, *ASAP*.

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