ORGANIC LETTERS

2008
Vol. 10, No. 11
2307−2310

Low Temperature Organocopper-Mediated Two-Component Cross Coupling/Cycloisomerization Approach Toward N-Fused Heterocycles

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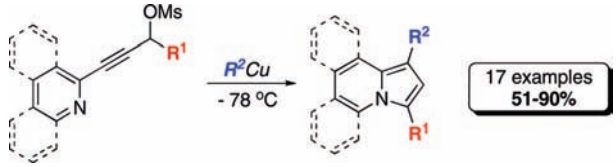
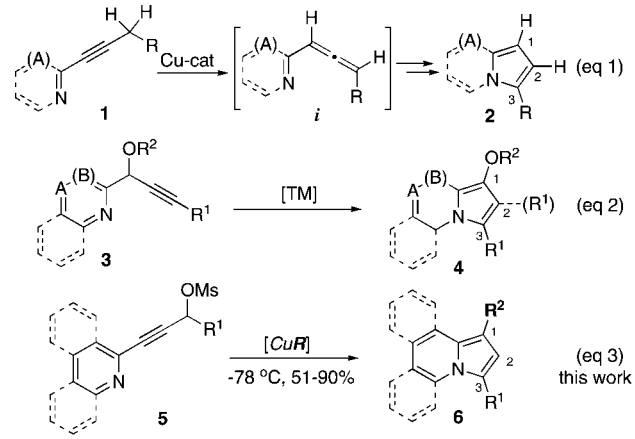
Received April 15, 2008

ABSTRACT



Organocopper reagents smoothly react with heterocyclic propargyl mesylates at low temperature to produce N-fused heterocycles. The copper reagent plays a "double duty" in this novel cascade transformation, which proceeds via an S_N2' substitution followed by a subsequent cycloisomerization step.

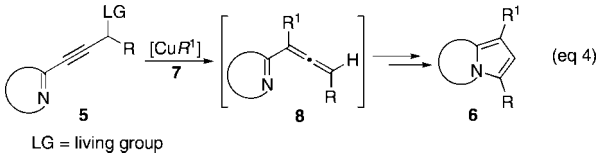
The transition metal-catalyzed cycloisomerization approach is a powerful tool for the assembly of diverse heterocyclic frameworks.[1] We have developed the base-assisted Cu-catalyzed cycloisomerization of conjugated alkynylpyridines **1** into monosubstituted N-fused heterocycles **2**[2] (eq 1). Later, our group and others reported alternative methods for cycloisomerization of skipped propargyl imines **3** into 1,2- or 1,3-disubstituted N-fused heterocycles **4**[3] (eq 2). Although both approaches are quite general with respect to the heterocyclic cores, they still have certain boundaries. Thus, the former method is restricted to the synthesis of heterocycles which do not possess substituents at the C-1 and C-2 positions, whereas the latter approach is limited to the oxygen-based substituents at C-1 (OR^2), as these propargylic precursors **3** are normally prepared from the corresponding heterocyclic aldehydes. Accordingly, development of more general methodologies toward multisubstituted N-fused heterocyclic scaffolds is desirable. Herein, we wish to report the copper-mediated coupling/cyclization cascade reaction of propargyl mesylates **5** toward N-fused heterocyclic frameworks **6** (eq 3). Not only does this method give access to C-1 alkyl- or aryl-substituted heterocycles, unavailable by existing cycloisomerization techniques, but it also holds a promise for a quick assembly of libraries of heterocyclic compounds via the two-component coupling/cycloisomerization strategy.



It was suggested that the copper-catalyzed cycloisomerization of **1** into the monosubstituted heterocycles **2** proceeds

10.1021/ol8008705 CCC: $40.75
Published on Web 05/08/2008

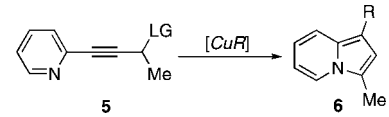
via a 1,3-disubstituted allenyl intermediate *i* (eq 1).[2] Accordingly, we aimed at the analogous 1,1,3-trisubstituted allenyl intermediates en route to 1,3-disubstituted N-fused heterocyclic cores. Likely, these reactive allenyl intermediates **8** can be generated in situ via the S_N2'-substitution[4] of the corresponding propargyl esters **5** (eq 4).



We chose to employ the organocopper nucleophiles,[5] based on the reasoning that, potentially, the copper reagent (or the copper byproduct) can also mediate the subsequent cycloisomerization step of *v* into the heterocycle **6**, thus playing a "double duty" in this transformation.[6]

To this end, a possible substitution/cycloisomerization cascade of pyridyl-containing propargyl alcohol derivatives **5** with various copper reagents[7] has been examined (Table 1). It was found that the higher order alkyl cuprate reagents were not efficient in this transformation (entries 1−3). In contrast, the lower order cyanocuprate (MeCu(CN)Li) reacted with mesylate **5** very smoothly, affording the C-1 alkylated indolizine derivative **6a** in 90% yield (entry 5)! Attempts to substitute mesylate with another leaving group[8] were not successful (entries 6−12).

Table 1. Optimization of Reaction Conditions



run	[CuR][a]	LG	solvent	yield %[b]
1	*s*-Bu(Me)Cu(CN)Li_2	OMs	Et_2O	11
2	*n*-Bu_2Cu(CN)Li_2	OMs	Et_2O	traces
3	Me_2Cu(CN)Li_2	OMs	THF	0
4	MeCu(CN)Li	OMs	Et_2O	8
5	**MeCu(CN)Li**	**OMs**	THF	**90**
6	MeCu(CN)Li	OAc	THF	21
7	MeCu(CN)Li	OTFA	THF	16
8	MeCu(CN)Li	OC(O)OEt	THF	0
9	MeCu(CN)Li	OP(O)OEt_2	THF	27
10	MeCu(CN)Li	OTf	THF	5
11	MeCu(CN)Li	OBs	THF	traces
12	MeCu(CN)Li	ONs	THF	traces
13	Ph_2Cu(CN)Li_2	OMs	Et_2O	traces
14	Ph_2Cu(CN)Li_2/BF_3•Et_2O	OMs	Et_2O-THF	9
15	PhCu(CN)Li	OMs	Et_2O	0
16	**PhCu**[c]	**OMs**	**THF**	**71**

[a] Reactions were carried out with 1.0 mmol of **5** and 1.2 mmol of copper reagent at −78 °C for 1 h, then at rt for 1 h. [b] Isolated yield. [c] Prepared by mixing PhMgBr with CuBr•SMe_2 complex.

Short optimization indicated that employment of a phenyl copper reagent was resonably efficient for the construction of C-1 phenyl-substituted indolizine **6** (entry 16). Importantly, in all cases, the corresponding allenes **8** were detected at early stages of the reaction, thus confirming for the first time that the cycloisomerizations of propargyl imines, indeed, proceed via allenic intermediates *i*[2,3] (eq 1) and **8** (eq 4).

Next, the generality of the substitution/cycloisomerization cascade of differently substituted propargyl mesylates **5** was examined (Table 2). Thus, secondary alkyl-susbtituted mesylates **5a** and **5b** underwent smooth cyclization upon treatment with primary (**7a**−**c**), secondary (**7d**), and tertiary (**7e**) lower order cyanocuprates to produce the corresponding indolizines **6** in good to excellent yields (Table 2, entries 1−7). Noteworthy, primary mesylate **5d** can also be employed in this reaction, giving access to monosubstituted indolizine **6ga**, a heterocycle, which can be further elaborated at C-3 via a direct C−H functionalization protocol.[9] The secondary aryl-substituted mesylates **5e**−**i** were also efficient in this cyclization, producing C-3 arylated indolizines in good yields. Notably, ester (entry 10), chloro (entry 11), cyano (entry 12), and nitro (entry 13) functionalities were perfectly

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(2) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638. (c) Kim, J. T.; Gevorgyan, V *J. Org. Chem.* **2005**, *70*, 2054. (d) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868.

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(4) For a general review, see: (a) Krause, N.; Hashmi, S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; p 1143. See also: (b) Krause, N.; Hoffmann-Roeder, A. *Tetrahedron* **2004**, *60*, 11671. (c) Krause, N.; Hoffmann-Roeder, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933.

(5) For recent examples on synthesis of allenes using copper reagents via S_N2' substitution approach, see: (a) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3931. (b) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (c) Dieter, R. K.; Chen, N.; Gore, V. K. *J. Org. Chem.* **2006**, *71*, 8755. (d) Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, *7*, 1267. (e) Dieter, R. K.; Chen, N.; Yu, H.; Nice, L. E.; Gore, V. K. *J. Org. Chem.* **2005**, *70*, 2109. (f) Regás, D.; Afonso, M. M.; Rodríguez, M. L.; Palenzuela, J. A. *J. Org. Chem.* **2003**, *68*, 7845. (g) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855.

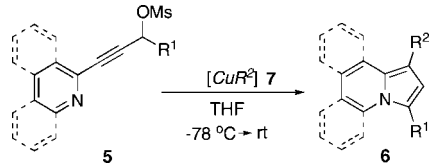
(6) For copper-mediated cascade transformations, see for example: (a) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573. (b) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896.

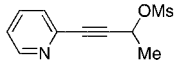
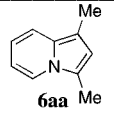
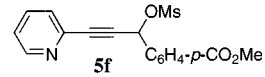
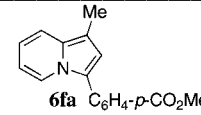
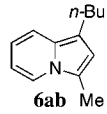
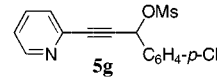
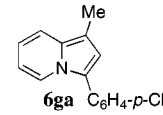
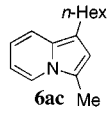
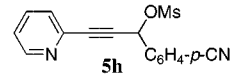
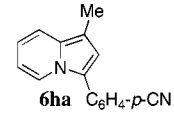
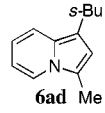
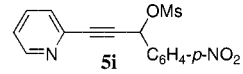
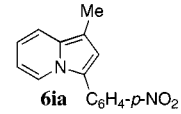
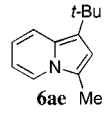
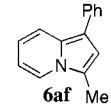
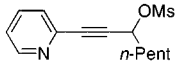
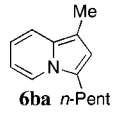
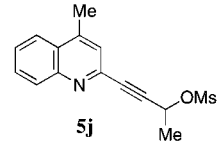
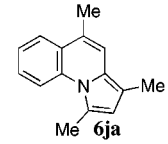
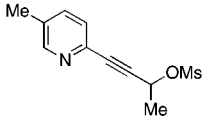
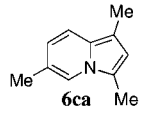
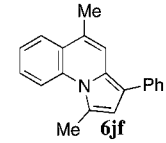
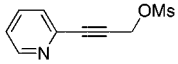
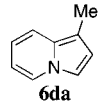
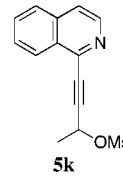
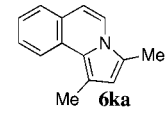
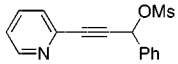
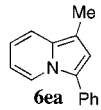
(7) For general reviews on copper reagents, see: (a) Lipshutz, B. H. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; Wiley-VCH: Weinheim, Germany, 1994; pp 283−376. (b) Krause, N. *Modern OrganocopperChemistry*; Wiley-VCH: Weinheim, Germany, 2002. (c) Caprio, V. *Lett. Org. Chem.* **2006**, *3*, 339. (d) Nakamura, E.; Seiji, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750. (e) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393. (f) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186. (g) Taylor, R. J. K.; Casy, G. In *Organocopper Reagents−A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994.

(8) It was also recently reported by Krause that the lower order cyanocuprates provide high selectivity in S_N2'-substitution reaction employing propargyl acetates. See: (a) Jansen, A.; Krause, N. *Inorg. Chem. Acta* **2006**, *359*, 1761. (b) Jansen, A.; Krause, N. *Synthesis* **2002**, 1987.

(9) For a review, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. For a direct arylation of indolizines, see: (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. For a direct alkynylation of indolizines, see: (c) JSeregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742.

Table 2. Organocopper-Mediated Synthesis of N-Fused Heterocycles[a]



entry	starting material[b] **5**	[CuR^2] **7**	product **6**	yield[c] %	entry	starting material[b] **5**	[CuR^2] **7**	product **6**	yield[c] %
1	 **5a**	MeCu(CN)Li (**7a**)	 **6aa**	90	10	 **5f**	**7a**	 **6fa**	62
2	**5a**	*n*-BuCu(CN)Li (**7b**)	 **6ab**	89	11	 **5g**	**7a**	 **6ga**	74
3	**5a**	*n*-HexCu(CN)Li (**7c**)	 **6ac**	81	12	 **5h**	**7a**	 **6ha**	63
4	**5a**	*s*-BuCu(CN)Li (**7d**)	 **6ad**	82	13	 **5i**	**7a**	 **6ia**	77
5	**5a**	*t*-BuCu(CN)Li (**7e**)	 **6ae**	79	14	**5a**	PhCu (**7f**)	 **6af**	71
6	 **5b**	**7a**	 **6ba**	70[d]	15	 **5j**	**7a**	 **6ja**	65
7	 **5c**	**7a**	 **6ca**	80[e]	16	**5j**	**7f**	 **6jf**	51
8	 **5d**	**7a**	 **6da**	61	17	 **5k**	**7a**	 **6ka**	66
9	 **5e**	**7a**	 **6ea**	75					

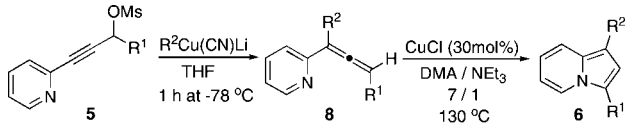
[a] Reaction carried out in 1.0 - 1.5 mmol scale. [b] Mesylate prepared in situ. [c] Isolated yields. [d] Additionally, 14% of allene was isolated. [e] Additionally, 4% of allene was isolated.

tolerated under these reaction conditions. It was also shown that pyrroloquinoline (entries 15 and 16) and pyrroloisoquinoline (entry 17) cores can efficiently be assembled via this protocol. As discussed above, phenyl copper-mediated cyclization of **5a** produced C-1 aryl-substituted indolizine **6af** in 71% yield. Likewise, application of the same reagent to cyclization of **5j** led to formation of arylated pyrroloquinoline **6jf**, albeit in 51% yield (entry 16, Table 2).

We also investigated the efficacy of a possible stepwise approach toward N-fused heterocycles **6** (Table 3). It was found that addition of cuprate reagents to the mesylates **5** at −78 °C in 1 h led to formation of the allenes **8** in varying yields (27−89%).[10] The next step, cycloisomerization of allenes **8** under the standard conditions,[2a] was even less efficient, producing trace to low yields of indolizines **6** (Table 3). Evidently, due to low stability of the pyridyl allenes **8** and low yields of their cyclization under the catalytic cyclization conditions,[2a] the two-step process is much less

(10) See Supporting Information for complete experimental data.

Table 3. Attempts at the Stepwise Synthesis of N-Fused Heterocycles



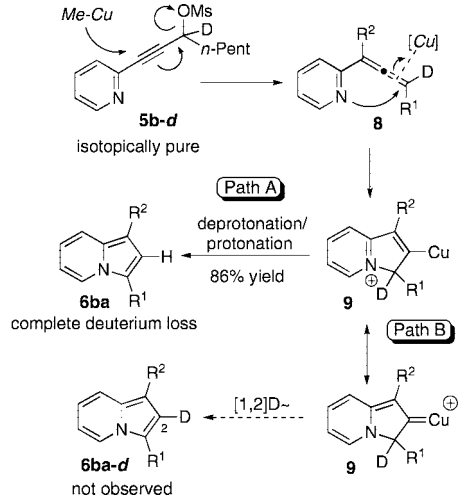
run	R^1	R^2	yield[a] % **8**	yield[a] % **6**	overall yield[b] % **6**
1	H	Me	27[c]	0	trace (61)
2	Me	*s*-Bu	89	42	37 (82)
3	C_6H_4-*p*-CO_2Me	Me	34	27	9 (62)

[a] Isolated yield. [b] Overall isolated yield for a stepwise process. Yield for cascade transformation from Table 2 is given in parentheses. [c] Trace amounts of **6** were also isolated.

efficient compared to the cascade substitution/cycloisomerization process (Table 2).

We propose the following mechanism for the substitution/cycloisomerization cascade of propargyl mesylates **5** with copper reagents into N-fused heterocycles **6** (Scheme 1). First, S_N2'-substitution of mesylate in **5** leads to allene **8**, which, upon intramolecular nucleophilic attack of pyridyl nitrogen at the Cu-activated double bond of allene, produces cyclic intermediate **9**. The latter can transform into product **6** either via the deprotonation−protonation sequence (Path A) or through the 1,2-hydride shift in the carbenoid intermediate **9** (Path B). To verify which mechanism operates, we performed a deuterium-labeling experiment. Indeed, if the reaction proceeds via Path A, then cyclization of **5b**-*d* should produce **6ba**, a product with significant or total deuterium loss.[11]

Scheme 1. Proposed Mechanism for Cascade Cyclization



In contrast, the end-game via Path B would give **6ba**-*d* with complete preservation of the deuterium label.[12] It was found that, under the standard cyclization conditions, the reaction of isotopically pure **5b**-*d* produced indolizine **6ba** with total deuterium loss, thus strongly supporting Path A.

In summary, we have developed a novel organocopper-mediated two-component coupling/cycloisomerization cascade transformation. This mild and efficient method allows for easy synthesis of C-1 alkyl- and aryl-substituted N-fused heterocycles, such as indolizines, pyrroloquinolines, and pyrroloisoquinolines, from easily available starting materials. It deserves mentioning that these important heterocyclic scaffolds[13] with an alkyl or aryl substituent at C-1 are not available via the existing cycloisomerization methods.

Acknowledgment. Financial support from the National Institutes of Health (GM-64444) is gratefully acknowledged.

Supporting Information Available: Preparative procedures, analytical and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For substantial deuterium loss in the Cu-mediated cycloisomerization, see ref 2a.

(12) For complete preservation of the deuterium label in the cycloisomerization proceeding via a 1,2-deuterium shift in carbenoid intermediate, see: (a) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (b) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440.

(13) For biological activity of N-fused pyrroloheterocycles, see for example: (a) Fujita, T.; Matsumoto, Y.; Kimura, T.; Yokota, S.; Sawada, M.; Majima, M.; Ohtani, Y.; Kumagai, Y. *Br. J. Clin. Pharmacol* **2002**, *54*, 283. (b) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392. (c) Reddy, M. V.; Rao, M. R.; Rhodes, D.; Hansen, M. S.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901. (d) Østby, O. B.; Dalhus, B.; Gundersen, L.-L.; Rise, F.; Bast, A.; Haenen, G. R. M. M. *Eur. J. Org. Chem.* **2000**, 3763. (e) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.