ORGANIC LETTERS

2007
Vol. 9, No. 6
973−976

Copper-Catalyzed Vinylation of Hydrazides. A Regioselective Entry to Highly Substituted Pyrroles

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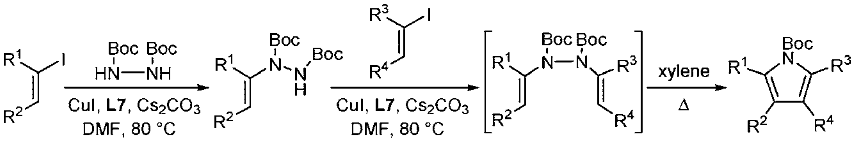
Received December 8, 2006

ABSTRACT

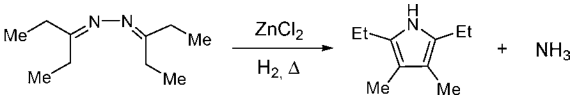


A modular route to highly substituted pyrroles has been developed. This transformation consists of two sequential copper-catalyzed vinylations of bis-Boc-hydrazine followed by thermal rearrangement/cyclization. A wide variety of functionalized pyrroles can be prepared in a selective manner from simple and easily accessible precursors.

The pyrrole ring is an important heteroaromatic system found in many natural products and bioactive molecules.[1] Furthermore, pyrroles are widely used in materials science and as structural elements in molecular recognition studies.[2] Classical methods for the synthesis of these nitrogen heterocycles include the Knorr,[3] Hantzsch,[4] and Paal−Knorr[5] reactions.[6] However, these approaches usually present significant limitations in terms of substituents that can be introduced, the substitution pattern, or regioselectivity. Although several novel synthetic strategies have been described in recent years,[7] a general, regioselective approach to generate pyrroles with a wide functional group tolerance from readily available precursors is still lacking.

More specifically, access to highly substituted electron-rich pyrroles is particularly limited. The Piloty−Robinson synthesis[8] (Scheme 1), consisting of a [3,3]-rearrangement of ketazines followed by ring formation, represents an interesting approach to these kinds of systems. Despite the potential utility of this transformation, it has only been rarely

Scheme 1. Piloty−Robinson Pyrrole Synthesis[8a]



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[2] (a) Custelcean, R.; Delmau, L. H.; Moyer, B. A.; Sessler, J. L.; Cho, W.-S.; Gross, D.; Bates, G. W.; Brooks, S. J.; Light, M. E.; Gale, P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2537. (b) Domingo, V. M.; Aleman, C.; Brillas, E.; Julia, L. *J. Org. Chem.* **2001**, *66*, 4058.

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[4] (a) Hantzsch, A. *Ber.* **1890**, *23*, 1474. For recent examples: (b) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Comp.* **2004**, *40*, 1218. (c) Calvo, L.; González-Ortega, A.; Sañudo, M. C. *Synthesis* **2002**, 2450. (d) Trautwein, A. W.; Süβmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2381.

[5] (a) Paal, C. *Ber.* **1885**, *18*, 367. (b) Knorr, L. *Ber.* **1885**, *18*, 299. For recent examples: (c) Chen, J.; Wu, H.; Zheng, Z.; Jin, C.; Zhang, X.; Su, W. *Tetrahedron Lett.* **2006**, *47*, 5383. (d) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277. (e) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. K. *Tetrahedron Lett.* **2005**, *46*, 2643.

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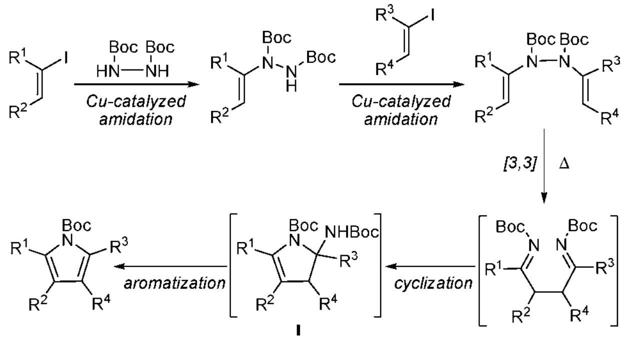
10.1021/ol062978s CCC: $37.00

used due to the strongly acidic conditions (e.g., HCl gas or $ZnCl_2$, 180−220 °C) required for the reaction. Milder variations based on the prior formation of the intermediate bisene-hydrazides by acylation of the starting azines have been reported.[9] However, these approaches are still extremely limited in scope and functional group compatibility. More importantly, unsymmetrical ketazines are not practical substrates in the transformation because the initial tautomerization could occur at either of the α-positions, affording mixtures of isomers. Therefore, the development of a new method to obtain alkenyl hydrazides in a selective fashion would dramatically increase the utility of the Piloty−Robinson reaction.

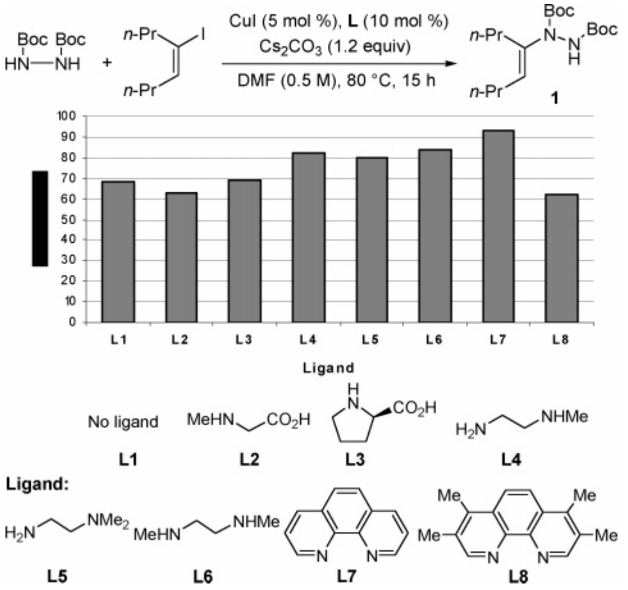
Recently, our research group disclosed the copper-catalyzed coupling of bis-Boc-hydrazine with 1-iodo-1-en-2-ynes and its application to the synthesis of pyrazoles.[10] On the basis of these results, we envisioned taking advantage of a metal-catalyzed C−N bond-forming reaction[11] as a new means to prepare bisene-hydrazides which would overcome the lack of regio- and stereoselectivity of classical methods. Herein, we describe a convenient and selective procedure for the synthesis of highly substituted pyrroles by two sequential Cu-catalyzed vinylations of bis-Boc-hydrazine[12] followed by cyclization (Scheme 2).

Scheme 2. Synthesis of Pyrroles through a Sequential Cu-Catalyzed Vinylation of the Bis-Boc-hydrazine/Cyclization Strategy



Reaction conditions for the initial copper-catalyzed C−N bond-forming reaction were explored using (*E*)-4-iodo-4-octene as the coupling partner (Scheme 3). A ligand screen was carried out using CuI as a precatalyst and Cs_2CO_3 as a base in DMF at 80 °C. Among the ligands examined, a catalyst based on 1,10-phenanthroline (**L7**) showed the highest activity giving the desired hydrazide **1** in excellent yield. It is important to note that double vinylation was not observed in the formation of compound **1** under these conditions. Reasonable results can also be achieved using a ligandless catalytic system (**L1**).

Scheme 3. Ligand Screen



As shown in Table 1, a variety of vinyl hydrazides can be prepared employing these optimized conditions.[13] We were pleased to find that α-, *β*-, and disubstituted vinyl iodides are all viable substrates. Different substituents on the alkene, including alkyl, aryl, and heteroaryl moieties, as well as several functional groups, are tolerated in the process. Although the reaction of (*Z*)-4-iodo-4-octene did not proceed under the optimized conditions, the use of a more activated (*Z*)-alkenyl iodide afforded the desired hydrazide in moderate yield (entry 5).[14] As summarized below, the method shows excellent selectivity; only a small amount of the double vinylation product was obtained when activated vinyl iodides were employed (entries 2 and 5).

With these alkenyl hydrazides in hand, we next studied their further coupling reaction with vinyl halides (Scheme 4). Although the second vinylation proceeds slowly, the

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(7) For recent syntheses of pyrroles: (a) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (b) Fuchibe, K.; Ono, D.; Akiyama, T. *Chem. Commun.* **2006**, 2271. (c) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560. (d) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (e) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (f) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (g) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.

(8) (a) Piloty, O. *Ber.* **1910**, *43*, 489. (b) Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1918**, *43*, 639.

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(10) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 7079.

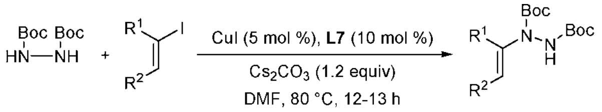
(11) For recent reviews on palladium-catalyzed C−N bond-forming reactions: (a) Hartwig, J. F. *Synlett* **2006**, 1283. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 699.

(12) For recent reviews on Cu-catalyzed C−N bond-forming reactions: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(13) Two examples for the metal-catalyzed syntheses of monosubstituted vinyl hydrazides from alkenyl boronic acids have been previously reported in the literature: (a) Uemura, T.; Chatani, N. *J. Org. Chem.* **2005**, *70*, 8631. (b) Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, *5*, 4129. During the revision process of this manuscript, the Pd-catalyzed coupling between *tert*-butyl carbazate and vinyl halides was reported: (c) Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C. *Org. Lett.* **2007**, *9*, 275.

(14) NOESY experiments for compounds in entries 3 and 5 (Table 1) indicate that the double bond geometry of the starting vinyl iodides is retained in the product.

Table 1. Cu-Catalyzed Coupling of Vinyl Iodides with Bis-Boc-hydrazine[a]



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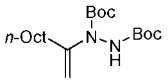
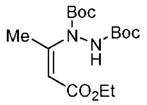
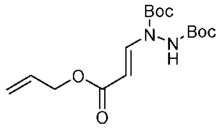
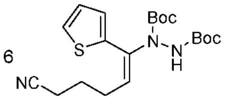
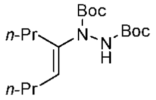
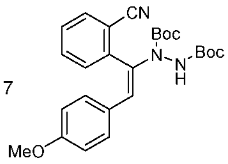
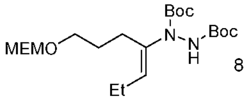
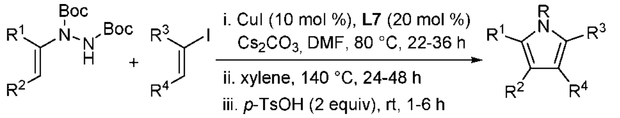
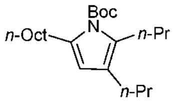
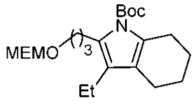
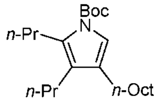
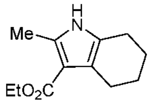
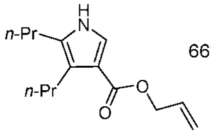
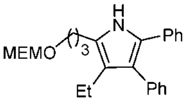
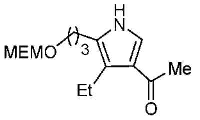
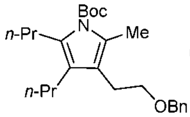
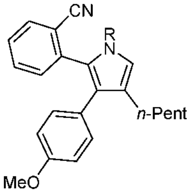
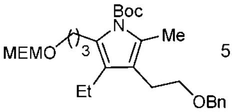
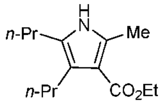
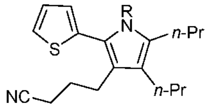
1		75%	5		64%[c,e]
2		70%[c,d]	6		85%
3		87%	7		94%
4		85%			

[a] Reaction conditions: 5 mol % of CuI, 10 mol % of 1,10-phenanthroline, 1 equiv of vinyl iodide, 1.2 equiv of hydrazide, 1.2 equiv of Cs_2CO_3, DMF (0.5 M in vinyl iodide), 80 °C. [b] Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^1H NMR and/or combustion analysis. [c] 2 equiv of bis-Boc-hydrazine were employed. [d] A 96:4 ratio of mono- and double-vinylation products was observed by ^1H NMR analysis of the crude reaction mixture. [e] A 91:9 ratio of mono- and double-vinylation products was observed by ^1H NMR analysis of the crude reaction mixture.

Table 2. Synthesis of Pyrroles through Sequential Cu-Catalyzed Vinylation of Hydrazides/Cyclization[a]



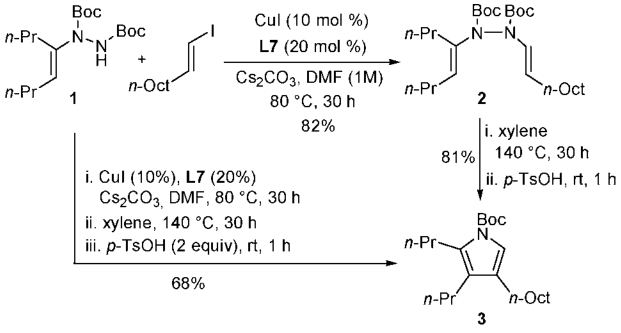
entry	product	yield[b]	entry	product	yield[b]
1		62%	7		61%[c]
2		68%	8		48%
3		66%[c]	9		60%[c]
4		49%[c]	10		61%
5		54%[d]	11		55%[c]
6		59%	12		60%[e]

[a] Reaction conditions: (i) 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, 1 equiv of vinyl iodide, 1 equiv of vinyl hydrazide, 1.2 equiv of Cs_2CO_3, DMF (1 M), 80 °C; (ii) *m*-xylene (0.25 M), 140 °C; (iii) 2 equiv of *p*-TsOH·H_2O, room temperature. [b] Isolated overall yields (average of two runs) of compounds estimated to be >95% pure as determined by ^1H NMR and/or combustion analysis. [c] Addition of *p*-TsOH·H_2O was not necessary. For details, see Supporting Information. [d] Combined yield: R = Boc 38%, R = H 16%. [e] Combined yield: R = Boc 21%, R = H 39%.

reaction between **1** and (*E*)-1-iodo-1-decene takes place in good yield by utilizing 10 mol % of CuI and 20 mol % of **L7** and increasing the concentration of vinyl iodide to 1 M. The resulting bisene-hydrazide **2** was then subjected to thermal cyclization.[15] After refluxing a solution of **2** in xylene for 30 h, total consumption of the starting material was observed. However, further acidic treatment at room temperature was necessary to achieve complete aromatization of intermediate **I** (Scheme 2) to the pyrrole.[16]

Pyrrole **3** could also be obtained from **1** without purification of the intermediate bisene-hydrazide. Once the vinyl iodide was consumed, filtration of the crude product from the copper-catalyzed reaction through Celite followed by a solvent exchange and subjecting the solution to rearrangement/cyclization conditions afforded the pyrrole in an overall yield similar to that for the stepwise process.

Scheme 4. Cu-Catalyzed Synthesis of Bisene-hydrazides and Further Cyclization Reaction



With these results, we examined the scope and generality of this new protocol. As shown in Table 2, the standard reaction conditions are applicable to the synthesis of a wide variety of pyrroles. Both alkyl- and aryl-substituted vinyl

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(15) The use of several Lewis acids to catalyze the [3,3] rearrangement was tested. However, only decomposition products were obtained.

(16) For the isolation of similar intermediates in the Fischer indole synthesis: (a) Tullberg, E.; Schacher, F.; Peters, D.; Frejd, T. *Synthesis* **2006**, 1183. (b) Miyata, O.; Kimura, Y.; Naito, T. *Synthesis* **2001**, 1635.

iodides can be used to build the pyrrole framework. Moreover, a wide range of functional groups, such as alkenes, alkyl or benzyl ethers, ketones, esters, and nitriles, are tolerated in the reaction. Another important feature of this route is that it provides access not only to electron-rich pyrroles but also to derivatives bearing electron-withdrawing groups. The procedure allows easy and complete control over the installation of substituents around the heterocyclic core, by choosing the appropiate starting vinyl iodides.[17]

Although addition of *p*-TsOH is necessary to obtain pyrrole **3** (Scheme 4), in some instances thermal treatment gives rise directly to the aromatic heterocycle without further addition of acid (entries 3, 4, 7, 9, and 11). In general, when electron-withdrawing groups are attached to the pyrrole framework, cleavage of the carbamate group takes place under the reaction conditions, affording the deprotected products (entries 3, 4, 6, 8, and 9), although in some cases mixtures of free and Boc-protected pyrroles are obtained (entries 5 and 12).

In summary, we have improved the utility of the Piloty–Robinson reaction, allowing the flexible and regioselective preparation of pyrroles through a sequential Cu-catalyzed vinylation of bis-Boc-hydrazine/cyclization strategy. This synthetic route accommodates a variety of substituents in the heterocyclic ring, providing modular access from simple and readily available precursors.

Acknowledgment. Generous financial support from the National Institutes of Health (GM058160) is gratefully acknowledged. M.R.R. thanks the Spanish Ministerio de Educación y Ciencia for a Postdoctoral Fellowship. Chemetall is acknowledged for a gift of Cs_2CO_3. We are indebted to Merck, Amgen, and Boehringer-Ingelheim for unrestricted support.

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

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[17] Starting vinyl iodides were readily prepared, generally in one or two steps, from commercially available materials. For details, see the Supporting Information.