

A Novel Cu-Assisted Cycloisomerization of Alkynyl Imines: Efficient Synthesis of Pyrroles and Pyrrole-Containing Heterocycles

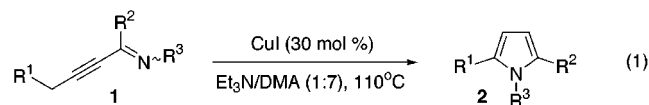
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Pyrroles are important heterocycles broadly used in material science¹ and found in naturally occurring and biologically important molecules.² Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles. Most known methods for the construction of the pyrrole ring proceed via various types of cycloaddition or cycloisomerization of acyclic precursors^{1,2a,3} and are most effective for forming 2,5-di- or polysubstituted pyrroles. To the best of our knowledge, there are no convenient methods for the formation of a mono-substituted pyrrole ring.⁴ Herein we wish to report a novel, general, and efficient method for the construction of 2-monosubstituted and 2,5-disubstituted pyrroles, as well as fused aromatic heterocycles containing a pyrrole ring, via the Cu-assisted cycloisomerization of readily available alkynyl imines.

First, it was found that *N*-butyl-substituted alkynyl imine **1a**⁵ in the presence of CuI (30 mol %) in Et₃N/DMA (1:7) at 110 °C underwent cycloisomerization to give pyrrole **2a** in 50% yield (eq 1, Table 1, entry 1). Replacement of the *n*-butyl group at



nitrogen with the *tert*-butyl group dramatically increased the efficiency of cycloisomerization providing the pyrrole **2b** in 86% yield (entry 2). Encouraged by this finding, we searched for another, potentially deprotectable group. This would allow access to synthetically more attractive N-unsubstituted pyrroles. We found that the trityl⁶ and the 3-(ethylbutyryl)⁷ (EB) groups perfectly serve these purposes: the corresponding alkynyl imines underwent smooth cycloisomerization to give the pyrroles **2c** and **2d**⁸ in 91% and 93% yields, respectively (entries 3 and 4). Naturally, most of our further cycloisomerization experiments

(1) For most recent work, see: Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992, and references therein.

(2) For a review see: (a) Gossauer, A. Pyrrole. In *Houben-Weyl*; Thieme: Stuttgart, 1994; E6a/1, p 556. See also: (b) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (c) Furstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (d) Sayah, B.; Pelloux-Leon, N.; Vallee, Y. *J. Org. Chem.* **2000**, *65*, 2824. (e) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587.

(3) For a review, see: (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. See also: (b) Tarasova, O. A.; Nedolya, N. A.; Vvedensky, V. Yu.; Brandsma, L.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 7241.

(4) For formation of the 2-monosubstituted pyrrole ring from γ -keto aldehydes or related precursors, see: (a) Reference 2a. See also: (b) Gadzhily, R. A.; Fedoseev, V. M.; Dzhafarov, V. G. *Chem. Heterocycl. Compd.* **1990**, *26*, 874. (c) Engel, N.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 676. For syntheses of 2-monosubstituted pyrroles via acylation-reduction or alkylation of pyrrole see, for example: (d) Garrido, D. O. A.; Buldain, G.; Frydman, B. *J. Org. Chem.* **1984**, *49*, 2619. (e) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203.

(5) For preparation of **1**, see Supporting Information (SI).

(6) For deprotection of the N-Tr-group in pyrroles, see: Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 93.

(7) For deprotection of the analogous group from pyrroles, see: Roder, E.; Wiedenfeld, H.; Bourauel, T. *Liebigs Ann. Chem.* **1985**, 1708.

(8) **2d** was deprotected into the corresponding N-H pyrrole quantitatively via retro-Michael protocol. See SI for details.

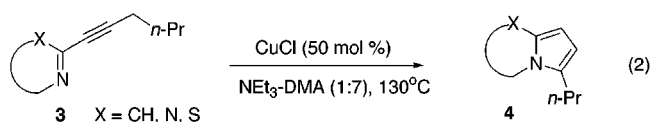
Table 1. Cu-Assisted Synthesis of Pyrroles **2**

entry	alkynyl imine 1			pyrrole 2	yield (%) ^a
	R1	R2	R3		
1	<i>n</i> -Bu	H	<i>n</i> -Bu (a)		50
2	<i>n</i> -Bu	H	<i>t</i> -Bu (b)		86
3	<i>n</i> -Bu	H	Tr (c)		91
4	<i>n</i> -Bu	H	(EB) (d)		93
5		H	<i>t</i> -Bu (e)		83
6	NC-	H	EB (f)		51
7	TBSO-	H	EB (g)		52
8	TBSO	H	EB (h)		79
9	H	<i>n</i> -Pr	EB (i)		71
10	H	Ph	Ph (j)		86
11	<i>n</i> -Pr	Me	EB (k)		87

^a Isolated yields.

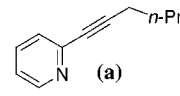
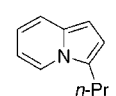
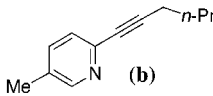
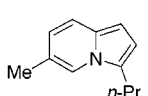
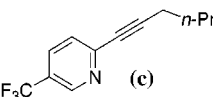
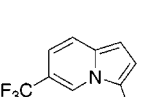
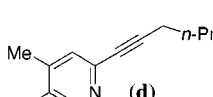
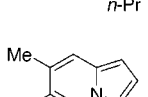
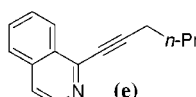
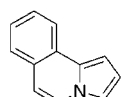
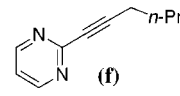
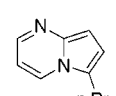
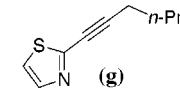

were performed with easily deprotectable *N*-EB-substituted alkynyl imines. This method was found to be rather general with respect to functional group compatibility: 5-pentenyl- (**1e**), 2-cyanoethyl- (**1f**), OTBS-methyl- (**1g**), and OTBS- (**1h**) substituted imines readily cycloisomerized to afford the corresponding pyrroles **2e–h** in reasonable to good yields (Table 1, entries 5–8). In all of the above examples, the monosubstituted pyrroles were synthesized from the alkynyl aldimines **1a–h**. Alternatively, the monosubstituted pyrroles **2i,j** can be efficiently synthesized from the corresponding propynyl ketimines **1i,j** (entries 9 and 10). Finally, the 2,5-disubstituted pyrrole **2k** was prepared in 87% yield from the ketimine **1k** (entry 11).

Inspired by the successful cycloisomerization of acyclic alkynyl imines to pyrroles, we attempted the cycloisomerization of the cyclic alkynyl imines **3**.⁹ We were pleased to find that 2-hexynyl pyridine **3a** in the presence of CuCl (50 mol %) at 130 °C underwent smooth cycloisomerization to give the indolizine **4a** in 91% yield (Table 2, entry 1). This approach proved to be general for the synthesis of various types of fused N-containing heteroaromatic compounds (eq 2, Table 2). Thus, a number of



heterocyclic alkynyl substrates, such as pyridines (entries 1–3), quinoline (entry 4), isoquinoline (entry 5), pyrimidine (entry 6),

Table 2. Cu-Assisted Synthesis of Fused Heterocycles 4

entry	alkynyl imine 3	product 4	yield (%) ^a
1	 (a)		91
2	 (b)		73
3	 (c)		73
4	 (d)		78
5	 (e)		74
6	 (f)		57
7	 (g)		57

^a Isolated yields.

and thiazole (entry 7), effectively participated in the cycloisomerization to give the corresponding fused heteroaromatic compounds **4** (eq 2, Table 2).

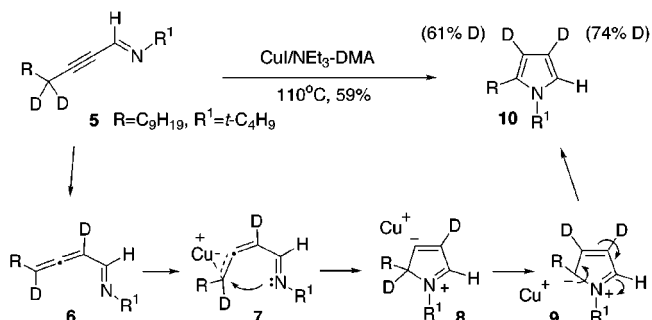
As a working hypothesis, we propose the following mechanism: first, **5** would undergo a base-induced propargyl–allenyl isomerization to form **6**; next, coordination of copper to the terminal double bond of the allene (intermediate **7**) would make it subject to intramolecular nucleophilic attack to produce a zwitterion **8**.¹¹ The latter would isomerize into the more stable zwitterionic intermediate **9**, which would transform to the pyrrole **10** (Scheme 1). In fact, the following observations provide certain support for the proposed mechanism. Significant deuterium loss, which occurred during the cycloisomerization of **5** into pyrrole **10**,¹² rules out possible involvement of “clean” H-shifts and does

(9) Cyclic alkynyl imines **3** were readily prepared by the Sonogashira protocol. For the original reference, see: Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

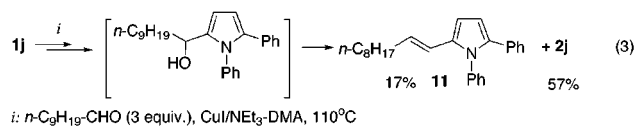
(10) 1,2-Unsubstituted indolizines are not available using common approaches, such as Tschitschibabin reaction. For the most comprehensive review, see: Behnisch, R.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. *Indolizine*. In *Houben-Weyl*; Thieme: Stuttgart, 1994; StuE6a/2a, p 323.

(11) A similar step has been proposed for the silver-assisted cycloisomerization of the allenyl ketones into furans, see: Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, 59, 7169.

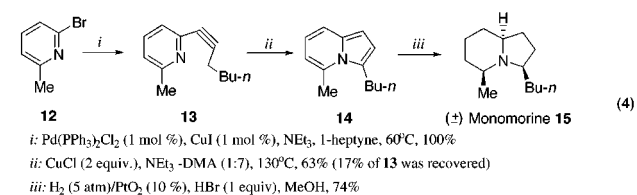
(12) A control experiment confirmed that **10** did not undergo any detectable change in the isotope composition upon the above-mentioned reaction conditions.

Scheme 1

not conflict with the proposed base-induced deprotonation–protonation sequence (Scheme 1). Furthermore, the cycloisomerization of **1j** in the presence of decanal provided **2j** along with 17% of the trapping product **11** (eq 3), thus supporting possible involvement of an anionic intermediate of type-**9** in the above cycloisomerization reaction (Scheme 1).¹³ As a further demonstra-



tion of the synthetic utility of this novel cycloisomerization methodology, we describe its application for an expeditious synthesis of (±) monomrine **15** (eq 4).¹⁴ The shortest synthesis of (±)**15** known involves six steps from noncommercially available starting material.^{14b} We found that (±)**15** can now be synthesized efficiently in three steps, in 47% overall yield, from the commercially available bromopyridine **12**. Thus, **12** was quantitatively converted into the alkynylpyridine **13**, which underwent the cycloisomerization to give the indolizine **14** in 63% yield. Catalytic hydrogenation of **14** gave (±) monomrine **15** in 74% yield (eq 4).



In conclusion, a novel, general, and efficient method, the Cu-assisted cycloisomerization of alkynyl imines into the pyrrole ring, has been developed. The generality and synthetic usefulness of this methodology was demonstrated in the efficient synthesis of pyrroles, various types of fused heteroaromatic compounds, and the expeditious synthesis of (±) monomrine **15**.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0058684

(13) A control experiment revealed no acylation reaction of **2j** with decanal under the same reaction conditions.

(14) For a review on the syntheses of monomrine and related indolizidine alkaloids, see: (a) Jefford, C. W. *Current Org. Chem.* **2000**, 4, 205. For the most efficient synthesis of (±)monomrine, see: (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *Helv. Chim. Acta* **1989**, 72, 1749.