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Direct Synthesis of Pyrroles from Imines, Alkynes, and Acid Chlorides: An Isocyanide-Mediated Reaction

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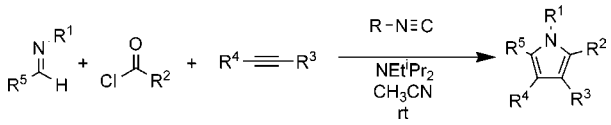
ABSTRACT



A direct synthesis of pyrroles from imines, acid chlorides, and alkynes mediated by isocyanides is reported. This reaction proceeds with a range of each of these three substrates, providing a method to generate families of pyrroles in high yield. Mechanistic studies suggest this process proceeds via the generation of imino analogues of münchnones, which can undergo in situ coupling with alkynes to liberate isocyanate and form the pyrrole product.

The pyrrole core is found in a diverse array of structures, including biologically active agents,[1] components in polymers,[2] and intermediates in organic synthesis.[3] This utility has driven the search for efficient methods to construct pyrroles. A number of classic methods exist for the synthesis of these heterocycles, such as the Knorr,[4] Paal−Knorr,[5] and Hantzsch syntheses.[6] These methodologies typically require the initial synthesis of the correctly substituted precursor(s) prior to cyclization, which can complicate both the synthesis and structural modification of substituted pyrroles. This has stimulated significant interest in the design of new routes to pyrroles, including several efficient multicomponent[7] and metal-catalyzed routes.[8]

An alternative to the multistep synthesis of pyrroles would be to assemble structures directly from several readily available and easily diversified building blocks. We have recently reported a reaction of this type, where the pyrrole core can be considered to be the product of three simple building blocks: imines, alkynes, and acid chlorides (Figure 1, Scheme 1), brought together by palladium catalysis.[9] Considering the nature of the building blocks employed, this

(1) Representative examples: (a) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671. (b) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109. (c) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. For reviews: (d) Rossi, R.; Bellina, F. *Tetrahedron* **2006**, *62*, 7213. (e) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. *Nat. Prod. Rep.* **2006**, *23*, 517. (f) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; Vol. 2, p 207. (g) Jones, R. A. *Pyrroles, Part II*; Wiley: New York, 1992. (h) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier S. W., Ed.; Pergamon: Elmsford, NY, 1999; Vol. 13, p 238.

(2) (a) Skotheim, T. A., Elsenbaumer, R. L., Reynolds, J. R., Eds. *Handbook of Conducting Polymers*, 2nd ed.; Marcel Dekker: New York, 1998. (b) Ramanavicius, A.; Ramanaviciene, A.; Malinauskas, A. *Electrochem. Acta* **2006**, *51*, 6025.(c) Novak, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207.

(3) For example: Boger, D. L.; Boyce, C. W.; Labrilli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.

(4) Knorr, *L. Chem. Ber* **1884**, *17*, 1635.

(5) Paal, C. *Chem. Ber.* **1885**, *18*, 367.

(6) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.

(7) Recent examples: (a) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (b) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (c) Bharadwaj, A. R; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (d) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390. (e) Ranu, B. C.; Dey, S. S. *Tetraherdron Lett.* **2003**, *44*, 2865. (f) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Heterocycles* **1999**, *50*, 463.

(8) Recent examples: (a) Braun, R. U.; Zietler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (b) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (c) Shiraishi , H.; Nishitani , T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6234. (d) Gorin, D. J.; Davis, N. R.; Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (e) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (f) Declerk, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372. (g) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (h) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664.

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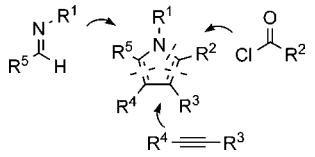
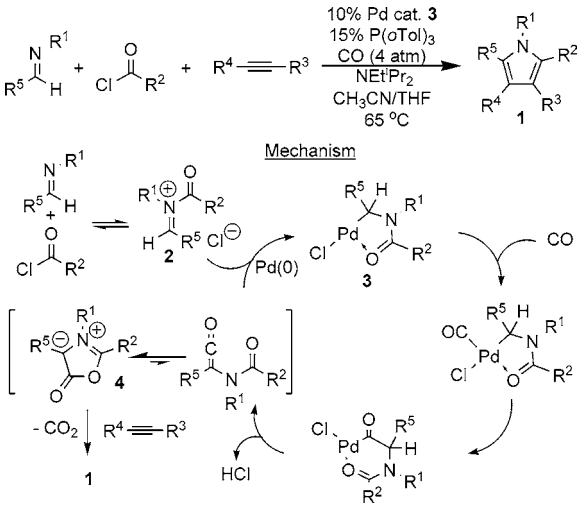


Figure 1. Direct approach to pyrroles.

is not only straightforward to perform, but holds the potential to provide a general route to variously substituted pyrroles.

Scheme 1. Palladium-Catalyzed Pyrrole Synthesis



However, there are certain limitations to this palladium catalyzed approach to pyrroles. This includes a relatively slow rate of catalysis (ca. 16 h at 65 °C) which precludes the use of a number of less stable substrates. For example, while stable imines of aromatic aldehydes are viable reagents, many simple alkyl-substituted imines or acid chlorides (e.g., enolizable substrates) instead undergo more rapid decomposition. As such, we became interested in developing alternative routes to couple these units into pyrroles. We describe herein that this assembly of pyrroles can be mediated, instead of via palladium-catalyzed carbonylation, by the simple use of isocyanides. This not only provides a non-palladium-based route to assemble pyrroles but occurs under very mild conditions and is compatible with a diverse range of imine and acid chloride substrates.

In considering the palladium-catalyzed pyrrole synthesis (Scheme 1), we noted from the mechanism that the role of the catalyst is to mediate the coupling of an in situ generated *N*-acyliminium salt (**2**) with CO to form a münchnone **4**, which is subsequently trapped with alkynes to form pyrroles and liberate CO_2. Since CO is not incorporated into the final product, the efficiency of this synthesis might potentially be increased by simply replacing the CO reagent. Isocyanides are well-known to display similar reactivity to carbon monoxide, albeit with a higher nucleophilicity. Our attempt to employ isocyanides instead of carbon monoxide in this process was probed with the reaction of imine (**5a**), acid chloride (**6a**), and alkyne (**7a**) followed by *tert*-butyl isocyanide and diisopropylethylamine. As shown in Table 1, even in the absence of a palladium catalyst, this reaction leads to the formation of pyrrole **1a** in 62% yield after 20 h at 55 °C (entry 1).

Examination of the product solution of this reaction by ^{1}H NMR spectroscopy reveals the formation of ^{t}BuNCO at the same time as **1a**, suggesting that pyrrole is generated via a mechanism similar to that with carbon monoxide, where in this case an imino analogue to a münchnone (**4**) is generated. In order to probe the mechanism, the reaction was performed in a stepwise fashion. The mixing of imine and acid chloride followed by *tert*-butyl isocyanide leads to the rapid formation of **8a**, presumably via the nucleophilic attack of ^{t}BuNC on *N*-acyliminium salt[10] **2a**. This reaction is similar to the initial stages of the Ugi and related multicomponent reactions,[11] wherein isocyanides are postulated to react with iminium salts, followed by rearrangement and hydrolysis to form α-amino acid derivatives. It is also analogous to reported formal [4 + 1]-cycloaddition of isocyanides to heterodienes, including that with thioiminium salts.[12,13] In this case, by operating under non-hydrolytic conditions, **8a** can be observed in 92% yield by ^{1}H NMR analysis. Subsequent addition of base leads to the immediate formation of the münchnone analogue **9a**. The addition of DMAD to **9a** leads to the generation of pyrrole **1a** over the course of 20 h at 50 °C (84% by ^{1}H NMR analysis), via the established dipolar cycloaddition to the **9a**, followed by retrocycloaddition to eliminate an isocyanate.[14] Considering the slow rate of pyrrole formation from **9a**, this cycloaddition appears to be the rate-determining step in the overall synthesis.

A useful feature of isocyanides is that their reactivity can be modulated by changing the substitutent on nitrogen. As shown in Table 1, less sterically encumbered isocyanides form pyrroles much more rapidly (i.e., ambient temperature for entries 2−6), implying the slow cycloaddition to **9a** is likely the result of steric encumberance. However, the yields of pyrole with these isocyanides are low. Considering that control experiments demonstrate each step in this process (Scheme 2) proceeds efficiently, the yield of pyrrole with

(9) (a) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (b) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474.

(10) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

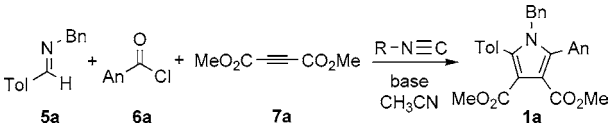
(11) (a) Ugi, I. *Angew. Chem., Int. Ed.* **1962**, *1*, 8. (b) Diaz , J. L.; Miguel, M.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550.

(12) For related [4 + 1] cycloadditions: (a) Morel, G.; Marchand, E.; Benjelloun, A. T.; Sinbandhit, S.; Guillou , O.; Gall, P. *Eur. J. Org. Chem.* **1998**, *11*, 2631. (b) Marchand, E.; Morel, G. *Tetrahedron Lett.* **1993**, *34*, 2319. (c) Berthet, J.-C.; Nierlich, M.; Ephritikhine, M. *Eur. J. Org. Chem.* **2002**, *2*, 375. (d) Deyrup, J. A.; Killion, K. K. *J. Heterocycl. Chem.* **1972**, *9*, 1045.

(13) (a) Berree, F.; Morel, G. *Tetrahedron* **1995**, *51*, 7019. (b) Berree, F.; Malvaut, Y.; Marchand, E.; Morel, G. *J. Org. Chem.* **1993**, *58*, 6022.

(14) (a) Gribble, G. W. *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*; Palmer, D. C., Ed.; Wiley: New York, 2003; Vol. 60, Chapter 4, p 473. (b) Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., William, W. H., Eds.; Wiley: New York, 2002; Vol. 59, Chapter 10, p 681. (c) McEwen, W. E.; Kanitkar, K. B.; Hung, W. M. W. *J. Am. Chem. Soc.* **1971**, *93*, 4484.

Table 1. Isocyanide-Mediated Pyrrole Synthesis[a]

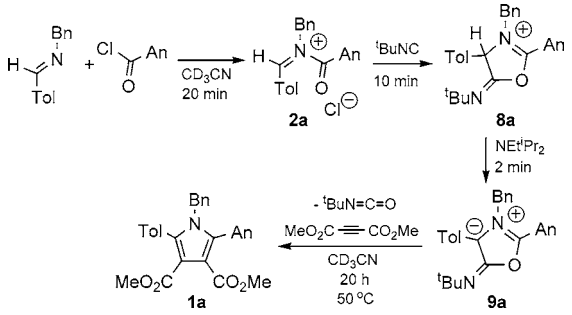


entry	isocyanide	base	T (°C)	yield[b] (%)
1[c]	^{t}BuNC	NEt^{i}Pr$_2$	55	62
2	pentylNC	NEt^{i}Pr$_2$	rt	29
3	benzylNC	NEt^{i}Pr$_2$	rt	33
4	p-$CH_3OC_6H_4NC$	NEt^{i}Pr$_2$	rt	11
5	o-$CH_3C_6H_4NC$	NEt^{i}Pr$_2$	rt	27
6	CyNC	NEt^{i}Pr$_2$	rt	57
7	CyNC	NEt_3	rt	58
8[d]	CyNC	K_3PO_4	rt	59
9	CyNC	DBU	rt	27
10[e]	CyNC	NEt^{i}Pr$_2$	rt	70

[a] **5a** (0.50 mmol), **6a** (0.75 mmol), **7a** (0.75 mmol)), RNC (0.55 mmol), and base (0.55 mmol) mixed in 2 min intervals in 0.5 mL of CH_3CN; stir for 6 h. Tol = *p*-tolyl; An = *p*-methoxyphenyl; Cy = cyclohexyl. [b] NMR yields vs an internal standard. [c] 3 equiv of **7a** for 20 h. [d] 3 equiv of K_3PO_4. [e] CyNC added after 20 min, followed by NEt^{i}Pr$_2$ after 10 min.

isocyanide can be improved by adding the isocyanide after **2a** has formed, followed by base. Overall, this provides an ambient temperature route to construct pyrrole **1a** in good yield (70%, entry 10).

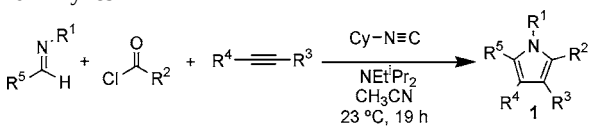
Scheme 2. Mechanism for the Isocyanide-Mediated Pyrrole Synthesis

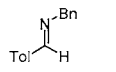
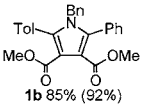
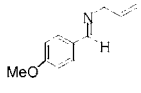
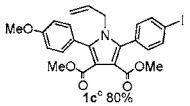
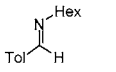
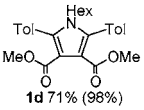
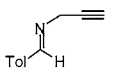
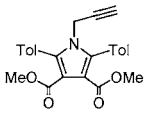
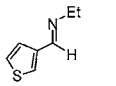
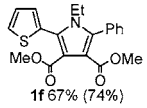
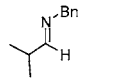
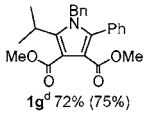
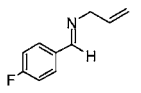
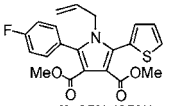
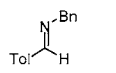
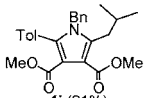
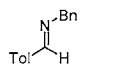
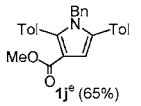
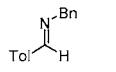
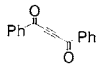
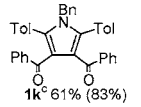
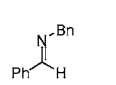
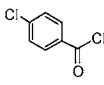
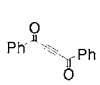
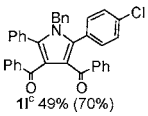


This approach can be used to generate a range of variously substituted pyrroles (Table 2). This includes the use of imines of aromatic and heteroaromatic aldehydes (**1b**−**f**), including those with alkene and alkyne substituents. A range of acid chlorides can also be employed, including those with aryl, heteroaryl, alkyl, and functionalized substituents. In addition to DMAD, other electron-poor alkynes are compatible with the reaction (**1j**−**l**); however, more electron-rich alkynes do not react with the relatively nucleophilic münchnone analogue **9**.

In contrast to palladium catalysis, enolizable alkylimines are also viable substrates with this isocyanide-mediated reaction.[15] The latter results from the mechanism of the coupling, where the rapid nucleophilic attack of isocyanides upon the in situ generated *N*-acyliminium salt can compete

Table 2. Diversity of Pyrroles from Imines, Acid Chlorides, and Alkynes[a]



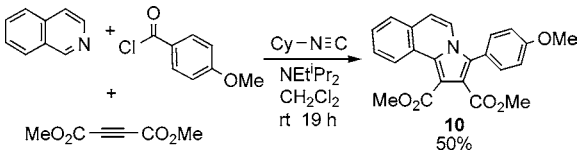
imine	acid chloride	alkyne	1 (%)[b]
	PhCOCl	MeO_2C — CO_2Me	 **1b** 85% (92%)
		MeO_2C — CO_2Me	 **1c**[c] 80%
	TolCOCl	MeO_2C — CO_2Me	 **1d** 71% (98%)
	TolCOCl	MeO_2C — CO_2Me	 **1e** 57% (80%)
	PhCOCl	MeO_2C — CO_2Me	 **1f** 67% (74%)
	PhCOCl	MeO_2C — CO_2Me	 **1g**[d] 72% (75%)
		MeO_2C — CO_2Me	 **1h** 65% (95%)
		MeO_2C — CO_2Me	 **1i** (81%)
	TolCOCl	— CO_2Me	 **1j**[e] (65%)
	TolCOCl		 **1k**[c] 61% (83%)
			 **1l**[c] 49% (70%)

[a] Table 1, entry 10 procedure. [b] Yields in parentheses when adding CyNC 30 min after imine/acid chloride and EtN^iPr$_2$ and alkyne after 1 h. [c] In $CHCl_3$. [d] Imine/acid chloride mixed at −15 °C in CH_2Cl_2, followed by CyNC at 0 °C. [e] K_3PO_4 (1.5 mmol) as base.

with enamide generation. Thus, performing the coupling at −15 °C leads to the generation of **1g** in 72% yield. Similarly, enolizable acid chlorides can also be employed in this chemistry (**1i**).

The rapid attack of isocyanides on the in situ formed iminium salts suggested that this reaction may not be limited

to imines, and other less reactive C═N π-bonded reagents could also participate in the coupling. For example, aromatic heterocycles such as isoquinoline contain a C═N π-bond reasonance structure and are known to intereact with acid chlorides in a similar fashion to imines. As shown below, these heterocycles are also amenable to cyclization with CyNC to form **10**. Such polyaromatic pyrroles are similar to those found in the Lamellarin class of natural products which have shown anticancer and antiviral activity[16] and are accessible in this case directly from available isoquinoline, *p*-methoxybenzoyl chloride, and DMAD.



In conclusion, we have demonstrated a new isocyanide-mediated synthesis of pyrroles from imines, acid chlorides, and alkynes. Considering the availablility of the starting materials, the simple room-temperature procedure, and the robust nature of this chemical process, this provides a very straightforward route to construct variously substituted pyrroles without metal catalysts. Studies directed toward the further generalization of this approach, as well as the application of this method to other heterocycles, are underway.

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Supporting Information Available: Synthesis and spectral data for pyrrole products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Enolizable iminium salts readily form enamides, which do not provide pyrroles under palladium catalysis (ref 9).

(16) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363.