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Synthesis of Pyrroles by Consecutive Multicomponent Reaction/[4 + 1] Cycloaddition of α-Iminonitriles with Isocyanides

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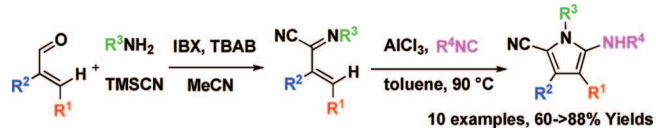
ABSTRACT



[4 + 1] Cycloaddition of α,β-unsaturated imidoyl cyanide (2-cyano-1-azadienes) with isocyanides in the presence of a catalytic amount of $AlCl_3$ afforded polysubstituted 2-amino-5-cyanopyrroles in good to excellent yields. In combination with the IBX/TBAB-mediated oxidative Strecker reaction, this important heterocycle is readily synthesized in two steps from simple starting materials.

Substituted 2-aminopyrrole is an important structural subunit found in natural products,[1] pharmacologically active molecules,[2] and molecular sensors.[3] Therefore, the development of a mild, efficient, and modular synthesis of this heterocycle is highly desirable.[4] Although a large number of new pyrrole syntheses have been reported in recent years that complement the classical approaches,[4] relatively few examples are known for the preparation of 2-aminopyrroles.[5−7] Recently, elegant three-component syntheses of 2-aminopyrroles have been developed by Nair[8] and Shaabani.[9,10] These reactions were nevertheless restricted to the highly reactive dimethylacetylenedicarboxylate as reaction partner, leading to 3,4-symmetrically substituted pyrroles. To the best of our knowledge, there is no convenient method for the preparation of unsymmetrical polysubsituted 2-aminopyrroles, particularly with regard to the availability of starting materials.

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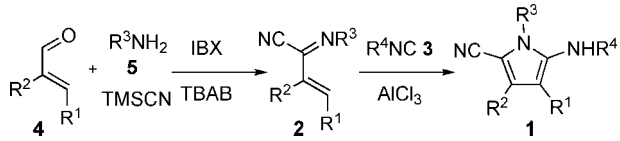
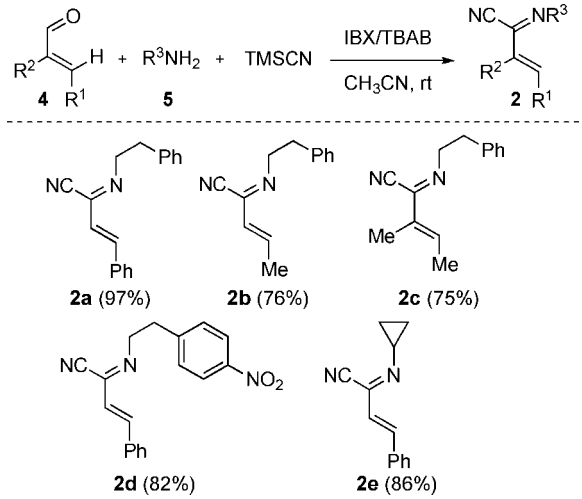
We have been working on heterocycle syntheses by developing novel multicomponent reactions (MCRs)[11] and by using MCRs/post-functionalization strategy.[12,13] In this context, we have recently initiated a research program aimed at developing oxidative MCRs[14] and have reported a three-component synthesis of α-iminonitriles.[15] Encouraged by the straightforward access to this otherwise difficultly accessible chemical entity, we were interested in the synthetic potentials offered by this unique functionality. We report herein the development of a novel synthesis of 5-amino-2-cyanopyrroles **1** by way of a $AlCl_3$-catalyzed [4 + 1] cycloaddition between α,β-unsaturated imidoyl cyanides (2-cyano-1-azadienes) **2** with isocyanides **3**.[16] In combination with the oxidative Strecker reaction, polysubstituted pyrroles **1** are readily synthesized in two steps from simple starting materials (Scheme 1).

Scheme 1. Sequential MCR/Cycloaddition Strategy



Under our previously developed conditions (IBX, TBAB, MeCN, rt),[15] the α-iminonitriles **2a**−**2e** were prepared in multigram scale from the respective α,β-unsaturated aldehydes **4**, amines **5**, and TMSCN (Scheme 2). The combined use of 2-iodoxybenzoic acid (IBX) and tetrabutylammonium bromide (TBAB) was crucial for the success of this oxidative Strecker reaction.

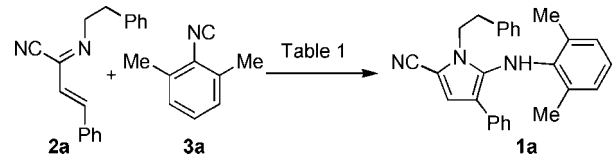
Scheme 2. Three-Component Synthesis of α,β-Unsaturated Imidoyl Cyanides



Synthesis of pyrroles by a formal [3 + 2] cycloaddition between α-isocyanoacetate and dipolarophiles is well established.[17,18] Morel and co-workers developed an alternative pyrrole synthesis by a [4 + 1] cycloaddition between simple 1-azadienes and isocyanides.[19−21] Although yields of this reaction remained moderate as a result of the presence of a number of side products, it provided incentive for our present studies. We reasoned that the presence of a nitrile group in **2** could (a) stabilize the enamine resulting from the initial 1,4-addition, thus avoiding the rearrangement reaction, and (b) deactivate the pyrrole ring, consequently inhibiting the subsequent Friedel−Crafts type reaction.

The reaction between **2a** and 2,6-dimethylphenyl isocyanide (**3a**) was selected for the survey of reaction conditions. The representative results are summarized in Table 1.

Table 1. Optimization of Reaction Parameters for the Synthesis of Pyrroles



entry	LA (equiv)	**3** (equiv)	concn (mol/L)	temp (°C)	time (h)	yield (%)[b]
1	none	1.1	0.3	60	15	
2	$AlCl_3$ (0.05)[a]	1.1	0.3	60	15	25
3	$AlCl_3$ (0.05)[a]	2.0	0.3	90	24	50
4	$GaCl_3$ (0.1)	1.1	0.7	90	15	
5	$AlCl_3$ (0.1)[a]	1.1	0.7	90	15	88

[a] Used $AlCl_3$ from Acros (98.5% purity). [b] Yields refer to chromatographically pure product.

Although no reaction took place in toluene under thermal conditions, the reaction performed in the presence of 5 mol% of $AlCl_3$ did provide the desired product **1a** in 25% yield together with the recovered **2a** (75%). Increasing the amount of isocyanide had only a marginal effect on the reaction

(10) Selected examples for multicomponent synthesis of pyrroles: (a) Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6234–6238. (b) Bossio, R.; Marcacini, S.; Pepino, R.; Torroba, T. *Heterocycles* **1999**, *50*, 463–467. (c) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3300. (d) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681–2684. (e) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468–469. (f) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813. (g) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem. Eur. J.* **2007**, *13*, 9973–9981. (h) St. Cyr, D. K.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449–452. (i) St. Cyr, D. K.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366–12367, and ref 4b.

(11) Selected examples: (a) Gámez-Montano, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351–6358. (b) Fayol, A.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3633–3635. (c) Janvier, P.; Bienayme, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291–4294. (d) Fayol, A.; Zhu, J. *Org. Lett.* **2005**, *7*, 239–242. (e) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145–4148. (f) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291–3295. (g) For an account: Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144.

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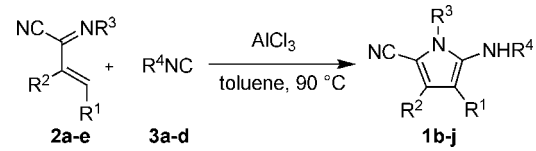
efficiency (entry 3). $GaCl_3$, the catalyst of choice for [4 + 1] cycloaddition between α,β-unsaturated carbonyl compounds and isocyanides,[20b] was found to be inefficient with iminonitrile **2a** (entry 4). Finally, heating a toluene solution of **3a** and **2a** (*c* 0.7 M) in the presence of 10 mol% of $AlCl_3$ at 90 °C was found to be optimum, providing pyrrole **1a** in 88% yield (Table 1, entry 5).

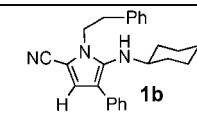
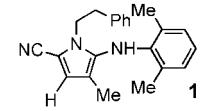
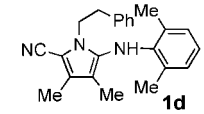
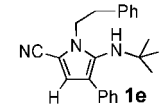
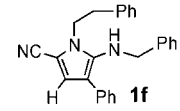
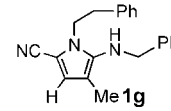
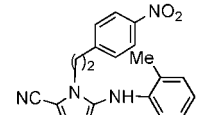
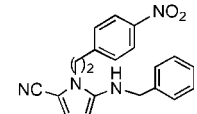
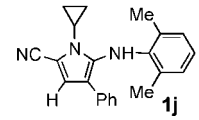
The scope of this novel synthesis of 2-amino-5-cyanopyrroles was next examined with different α,β-unsaturated imidoyl cyanides (**2a**−**e**) and isocyanides (**3a**−**d**). The results are depicted in Table 2. The reaction proceeded effectively with aromatic (**3a**) and aliphatic isocyanides (**3b**−**3d**) to give the corresponding 5-amino-2-cyanopyrroles (**1b**−**j**) in good to excellent yields. α,β-Unsaturated imidoyl cyanides bearing aromatic or aliphatic substituents at the α or β position react smoothly to give highly substituted pyrroles. The 2-cyano-1-azadiene **2c**, having substituents at both the α and β positions, was converted to the corresponding pentasubstituted 5-amino-2-cyanopyrrole **1d** in 74% yield (entry 3). Pyrroles **1h** and **1i**, having a *p*-NO_2-phenylethyl group at the N-1 position, were obtained in yields of 78% and 75%, respectively (entries 7 and 8). *N*-Cyclopropylated heterocycles are important structural units in medicinal chemistry; however, only limited synthetic methods are available.[22] It is thus interesting to note that the *N*-cyclopropyl iminonitrile **2e** participated readily in the reaction to afford directly the *N*-cyclopropyl pyrrole **1j** in 81% yield (entry 9). In all cases, pyrroles were obtained as a single product without concurrent formation of byproducts issued from the rearrangment of the nitrilium intermediate or isocyanide insertion to the resulting pyrrole.[19,23]

Removal of the *N*-*p*-NO_2-phenylethyl group from **1h** under thermal basic conditions[24] afforded a low yield of the desired *N*-unsubstituted pyrrole **6**. We found that under microwave irradiation conditions (DBU, MeCN, MW, 300 W), **1h** was

Table 2. $AlCl_3$-Catalyzed [4 + 1] Cycloaddition of α,β-Unsaturated Imidoyl Cyanides with Isocyanides[a]



2a-e 3a-d 1b-j

entry	2	R_4	product	yield (%)[b]
1	**2a**	*c*-Hex (**3b**)	 **1b**	73
2	**2b**	2,6-$Me_2C_6H_3$ (**3a**)	 **1c**	81
3	**2c**	2,6-$Me_2C_6H_3$ (**3a**)	 **1d**	74
4	**2a**	*t*-Bu (**3c**)	 **1e**	60
5	**2a**	Bn (**3d**)	 **1f**	88
6	**2b**	Bn (**3d**)	 **1g**	67
7	**2d**	2,6-$Me_2C_6H_3$ (**3a**)	 **1h**	78
8	**2d**	Bn (**3d**)	 **1i**	75
9	**2e**	2,6-$Me_2C_6H_3$ (**3a**)	 **1j**	81

[a] Reaction conditions: α,β-unsaturated imidoyl cyanides (1.0 mmol), isocyanide (1.1 mmol), $AlCl_3$ (0.1 mmol), toluene (1.4 mL), 90 °C. [b] Yield refer to chromatographically pure product.

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(16) Synthesis of pyrrole from α,β-unsaturated aldehydes: Fuchibe, K.; Ono, D.; Akiyama, T. *Chem. Commun.* **2006**, 2271–2273.

(17) (a) Van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; Van Leusen, D. *Tetrahedron Lett.* **1972**, *13*, 5337–5340. (b) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1098–1099. (c) Takaya, H.; Kojima, S.; Murahashi, S.-I. *Org. Lett.* **2001**, *3*, 421–424. (d) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (e) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246–1251. (f) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem. Eur. J.* **2009**, *15*, 227–236.

(18) For a review, see: Marcaccini, S.; Torroba, T. *Org. Prep. Proc. Int.* **1993**, *25*, 143–208.

(19) Marchand, E.; Morel, G.; Sinbandhit, S. *Eur. J. Org. Chem.* **1999**, 1729–1738.

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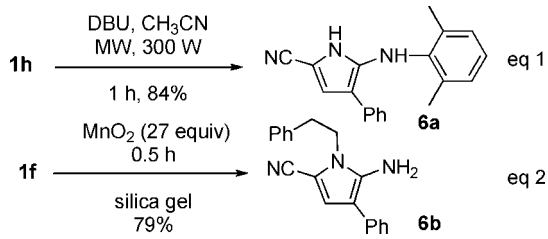
(21) Examples of [4 + 1] cycloaddition of nitroalkenes with isocyanides: (a) Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639–3644. (b) Person, H.; Del Aguila Pardo, M.; Foucaud, A. *Tetrahedron Lett.* **1980**, *21*, 281–284. (c) Saegusa, T.; Kobayashi, S.; Ito, Y.; Morino, I. *Tetrahedron* **1972**, *28*, 3389–3392. (d) Fédou, N. M.; Parsons, P. J.; Viseux, E. M. E.; Whittle, A. J. *Org. Lett.* **2005**, *7*, 3179–3182.

(22) (a) Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabé, F. *J. Am. Chem. Soc.* **2007**, *129*, 44–45. (b) Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. *Org. Lett.* **2008**, *10*, 1653–1655. (c) Bénard, S.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 6441–6444, and references therein.

deproteced efficiently to afford **6a** in 84% yield (eq 1, Scheme 3). On the other hand, deprotection of 2-benzylamine

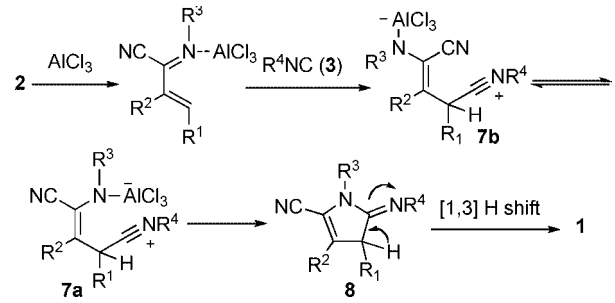
Scheme 3. Synthesis of 2-Amino-5-cyano-1*H*-pyrrole



in **1f** can also be realized by performing MnO_2-mediated oxidation followed by hydrolysis to afford **6b** in 79% yield (eq 2, Scheme 3).

A mechanistic rationale for the formal [4 + 1] cycloaddition is given in Scheme 4. Coordination of $AlCl_3$ to the

Scheme 4. Mechanistic Rational for the [4 + 1] Cycloaddition

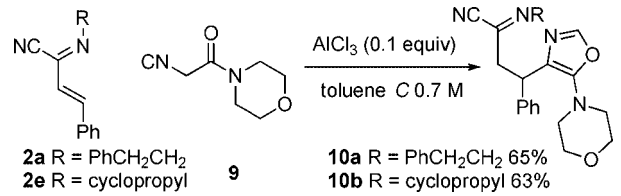


nitrogen atom of the iminonitrile **2** followed by 1,4-addition of isocyanide **3** could lead to the formation of two geometric isomers **7a** and **7b**. The nitrogen of isomer **7a** was properly positioned to attack the nitrilium to provide the primary cycloadduct **8**, which would then isomerize to the pyrrole **1** by a [1,3] H shift. We hypothesized that **7b**, if formed, could isomerize to **7a** via an imine intermediate.

Interestingly, when α-isocyanoacetamide **9** was allowed to react with **2a**, a completely different reaction occurred to afford oxazole **10a** in 65% yield. The ring connectivity of the resulting 5-aminooxazole indicated that the reaction was initiated by attack of the α-carbon of **9**, rather than the divalent carbon of isonitrile as was often observed.[25] We reasoned that in this case $AlCl_3$, being oxophilic, would coordinate preferentially to the amide oxygen of **9**, consequently increasing the acidity of its α-CH. The Michael addition of the resulting enolate onto the azadiene **2** followed by oxazole ring formation and enamine−imine tautomerization would then furnish the compound **10a**.[26] This reactivity profile seemed to be general since compound **10b** was similarly obtained from **2e** in 63% yield.

In summary, we have described an efficient synthesis of 2-amino-5-cyanopyrroles by an $AlCl_3$-catalyzed [4 + 1] cycloaddition between α,*β*-unsaturated imidoyl cyanides **2** and isocyanides **3**. Substituents at the C-3 and C-4 can be introduced as well by starting from the appropriately substituted iminonitrile **2**. Furthermore, the presence of a cyano group in the pyrroles makes them useful synthetic intermediates for the preparation of other nitrogen-containing heterocycles.[27] By combining this cycloaddition with the oxidative three-component synthesis of **2**, diversely substituted pyrroles are readily prepared in two steps from simple starting materials.

Scheme 5. Unusual Reactivity of α-Isocyanoacetamide



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Supporting Information Available: Experimental procedures, product characterization, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Note that reaction with **9** and aldehyde in the presence of $AlCl_3$ underwent Passerini-type reaction; see: Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, 4076–4080.

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