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Highly Efficient Chemoselective Synthesis of Polysubstituted Pyrroles via Isocyanide-Based Multicomponent Domino Reaction

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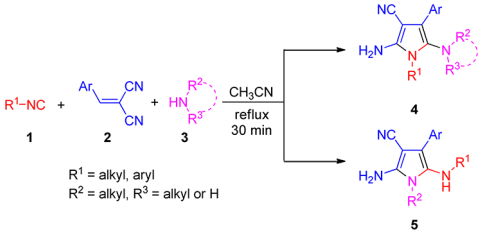
ABSTRACT



A multicomponent domino reaction for the chemoselective, catalyst-free synthesis of polysubstituted pyrroles from readily available isocyanides, primary or secondary amines, and *gem*-diactivated olefins has been developed. Structurally diverse pyrroles were obtained in moderate to good yields under mild conditions.

Efficient construction of complex molecules from inexpensive, readily available starting materials via the generation of several bonds in a single process is a major challenge[1] in modern organic chemistry. For this purpose, multicomponent domino reactions[2] are considered to be an ideal tool. These reactions[3] can efficiently furnish complex structures of chemical and pharmaceutical interest in a single operation by means of a cascade of processes without the need for protection/deprotection of functional groups or time-consuming and costly operations.

Many natural products, biologically important molecules,[4] and pharmaceuticals (e.g., Lipitor)[5] contain a pyrrole core (Figure 1). Pyrroles are also versatile as components of polymers[6] and as synthetic intermediates for many kinds of pharmaceuticals.[7]

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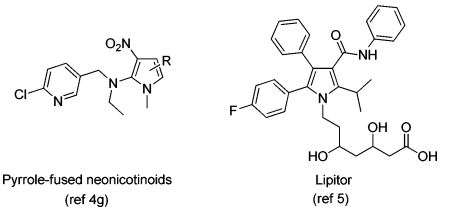
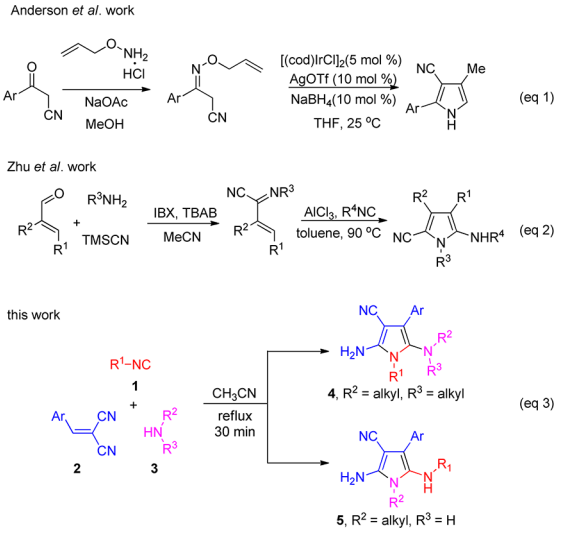


Figure 1. Biologically active pyrrole-containing products.

Traditional methods for pyrrole synthesis include the Knorr,[8] Paal–Knorr,[9] and Hantzsch[10] syntheses, which generally require the initial preparation of an intermediate that subsequently undergoes a cyclization reaction. Thus, the development of new, single-process routes to construct the pyrrole skeleton from simple starting materials is highly desired.

Some interesting new approaches to pyrroles have recently been developed, including multicomponent reactions (MCRs)[11] and metal-catalyzed routes.[12] For example, Anderson et al.[13] recently reported an iridium-catalyzed two- or three-step method for the synthesis of substituted pyrroles from ketones and allyl hydroxylamine. Zhu et al.[14] reported an oxidative Strecker reaction (mediated by 2-iodoxybenzoic acid and tetrabutylammonium bromide) followed by a [4+1]-cycloaddition of the resulting α,β-unsaturated imidoyl cyanides (2-cyano-1-azadienes) with various isocyanides to provide polysubstituted 2-amino-5-cyanopyrroles (Scheme 1). However, some of these new approaches

Scheme 1. Methods for the Construction of Cyano-Substituted Pyrroles



have significant limitations, such as the need for expensive catalysts, harsh reaction conditions, and tedious workup procedures, and poor selectivity and low yield.

MCRs involving isocyanides have become an important area of research in modern organic chemistry.[15] The isocyanide functional group is an extraordinarily useful synthon for the design of novel MCRs. The most commonly used isocyanide-based MCR is the Ugi-4CR, which involves an aldehyde, an amine, a carboxylic acid, and an isocyanate.[16] Ugi-4CR-type reactions in which malononitrile is used instead of an amine, have also been described; these reactions, which are always terminated by water as a nucleophile, can be considered as variants of the Ugi-4CR.[17] Over the past several years, various other nucleophiles have also been used in these reactions, including phenol[18] and thiophenol.[19] However, the use of amines as nucleophiles in these reactions is rare. In this paper, we report a novel one-pot isocyanide-based multicomponent domino reaction for the catalyst-free synthesis of polysubstituted pyrroles from simple and readily available isocyanides, amines, and gem-diactivated olefins with high chemoselectivity and moderate to good yields (Scheme 1).

We started by studying the three-component reaction of *tert*-butylisonitrile **1a** (1 mmol), 2-benzylidenemalononitrile **2a** (1 mmol), and piperidine **3a** (1 mmol) in EtOH under reflux conditions for 30 min. To our delight, the reaction afforded 2-amino-1-(*tert*-butyl)-4-phenyl-5-(piperidin-1-yl)-1*H*-pyrrole-3-carbonitrile **4a** in 42% yield. Polysubstituted

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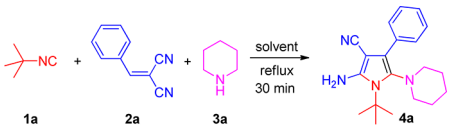
Table 1. Optimization of the Solvent for the MCR[a]



entry	solvent	**4a**, yield[b] (%)
1	1,4-dioxane	24
2	toluene	27
3	EtOH	42
4	MeOH	35
5	MeCN	74

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), solvent (2 mL). [b] Isolated yield.

pyrrole **4a** was fully characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. To determine the ideal solvent for the transformation, we investigated this model reaction in various other solvents (Table 1). The desired product **4a** was obtained in all the tested solvents, but MeCN gave the best isolated yield (74%), (Table 1, entry 5).

Using the optimized solvent conditions, we evaluated the substrate scope of the reaction by using readily available starting materials (Scheme 2). The reaction of isocyanides **1** with primary or secondary amines **3** and various substituted gem-diactivated olefins **2** afforded the desired polysubstituted pyrroles **4** in moderate to good yields, in most cases. The structure of **4k** was confirmed by single-crystal X-ray diffraction.

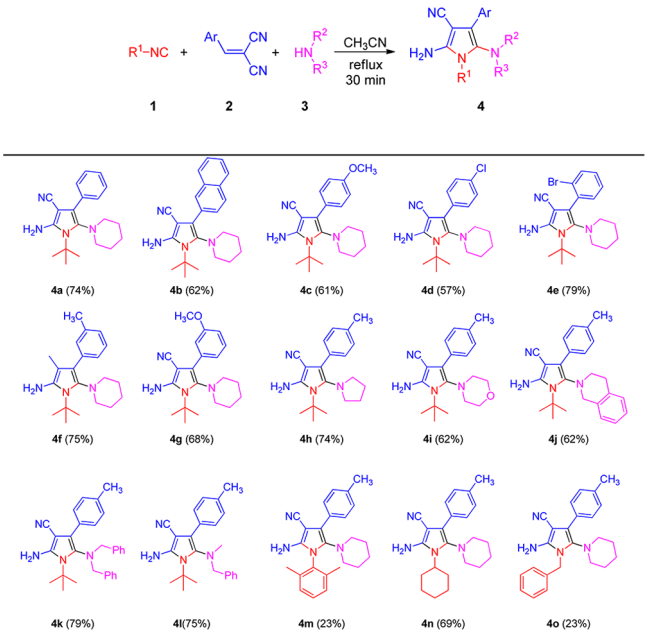
Notably, 2-benzylidenemalononitrile substrates with a strongly electron-donating substituent (−OCH_3, **2c**) or an electron-withdrawing substituent (−Cl or −Br, **2d** or **2e**) afforded desired products **4c**−**e** in 61%, 57%, and 79% yields, respectively.

Reactions of a variety of substituted secondary amines **3** with *tert*-butylisonitrile **1a** and 2-(4-methylbenzylidene)-malononitrile **2h** were also surveyed. When cyclic secondary amines pyrrolidine, morpholine, and 1,2,3,4-tetrahydroisoquinoline were used in the reaction, the desired products (**4h**, **4i**, and **4j**, respectively) were obtained in moderate yields (62%−74%). When acyclic secondary amines *N*-methyl-1-phenylmethanamine and dibenzylamine were used, the desired products **4l** and **4k**, respectively, were also obtained in good yields (75% and 79%).

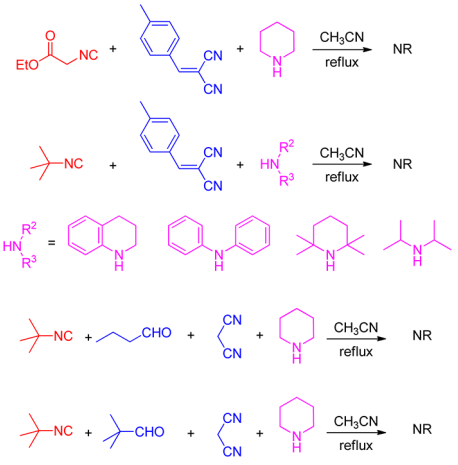
When *tert*-butylisonitrile **1a** was replaced with 2-isocyano-1, 3-dimethylbenzene **1b**, which possesses methyl substituents at the ortho positions of the aryl ring, and was used in the reaction with 2-(4-methylbenzylidene)malononitrile and piperidine **3a** under the optimized conditions, the desired polysubstituted pyrrole derivative **4m** was obtained in 23% yield; and the reaction of isocyanocyclohexane **1c** and benzylisocyanide **1d** afforded polysubstituted pyrrole derivatives **4n** and **4o** in 69% and 23% yield, respectively.

However, when isocyanoacetate was employed in this reaction, no desired product was obtained. Other secondary amines, such as 1,2,3,4-tetrahydroquinoline

Scheme 2. Construction of Polysubstituted Pyrroles **4**



Scheme 3. Substrate Limitations of the MCR

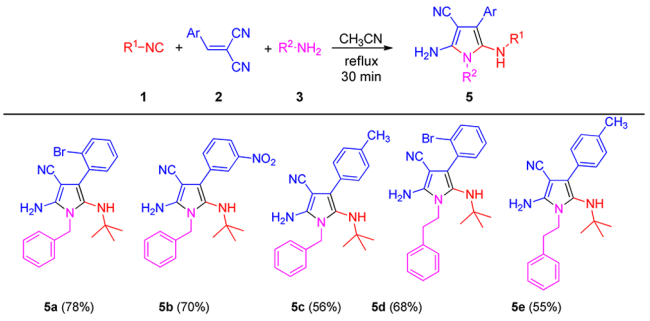


and diphenylamine, did not afford the corresponding pyrrole products, perhaps owing to the low nucleophilicity of these amines. Sterically hindered amines such as 2,2,6,6-tetramethylpiperidine and diisopropylamine were also unsuitable. When aliphatic aldehydes, such as *n*-butyraldehyde and pivalaldehyde, were used, the corresponding polysubstituted pyrroles were not obtained (Scheme 3).

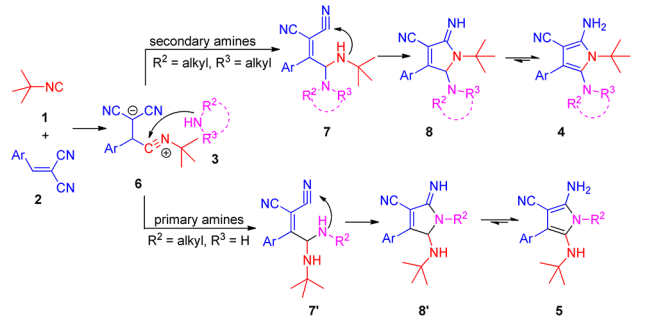
We also surveyed reactions of benzylamine, a primary amine, with *tert*-butylisonitrile **1a** and various *gem*-diactivated olefins **2** (Scheme 4). Notably, olefins bearing an electron-donating group or an electron-withdrawing group at various positions on the aryl ring provided the desired polysubstituted pyrrole products **5a**−**c** in moderate to good yields (56%−78%). When phenylethylamine was used instead of benzylamine, polysubstituted pyrrole

derivatives **5d** and **5e** were obtained in 68% and 55% yields, respectively.

Scheme 4. Construction of Polysubstituted Pyrroles **5**



Scheme 5. Proposed Mechanism for the Formation of Pyrroles **4** and **5**



On the basis of the above-described results, we propose that this multicomponent domino reaction proceeds by the mechanism shown in Scheme 5. First, isocyanide **1** undergoes nucleophilic addition to gem-diactivated olefin **2**, and the resulting intermediate undergoes nucleophilic attack by the amine to afford intermediate **7** in the case of secondary amines or **7′** in the case of primary amines. Then the cyano group of **7** undergoes nucleophilic attack by the nitrogen atom derived from the isocyanide group to afford polysubstituted pyrroles **4**, and the cyano group of **7′** undergoes nucleophilic attack by the nitrogen atom derived from the primary amine to afford polysubstituted pyrroles **5**. The difference between the behaviors of **7** and **7′** may be due to the steric bulk of the *tert*-butyl group. The density functional theory calculations on **5a** are consistent with the experimental results in this transformation (**7′** to **8′** vs **7** to **8**).[20]

In conclusion, we have developed a novel catalyst-free multicomponent domino reaction for the construction of polysubstituted pyrroles from readily available isocyanides, primary or secondary amines, and *gem*-diactivated olefins. The reaction proceeded under mild conditions and afforded the desired products in moderate to good yields.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds and X-ray crystallographic details of **4k** (CIF; atomic coordinates, displacement parameters, bond lengths and angles, and torsion angles). This material is available free of charge via the Internet at http://pubs.acs.org.

(20) For details, see the Supporting Information.

The authors declare no competing financial interest.