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Direct Solvent-Free Regioselective Construction of Pyrrolo[1,2-*a*][1,10]phenanthrolines Based on Isocyanide-Based Multicomponent Reactions

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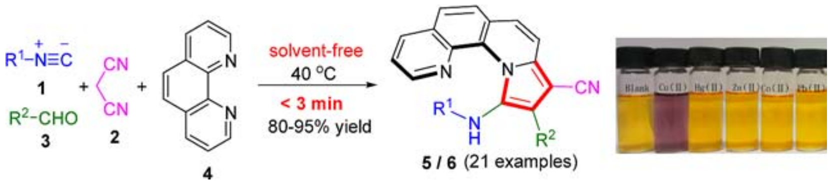
ABSTRACT



A novel efficient one-pot four-component regioselective synthesis of pyrrolo[1,2-*a*][1,10]phenanthrolines in excellent yields has been developed by 1,3-dipolar cycloaddition of aldehydes, malononitrile, and isocyanides with 1,10-phenanthroline under solvent-free conditions within 3 min without using any catalyst or activation. The products were preliminarily investigated as chromogenic and fluorescent sensors for Cu^{2+} ions.

Rapid synthesis of complex molecules in a single operation without isolation of intermediates is one of the current concerns of the scientific community that drives increasing efforts.[1] The multicomponent reaction (MCR) has thus emerged as a powerful tool for this purpose.[2] Isocyanide-based multicomponent reactions (IMCRs) are among the most popular multicomponent condensations due to their diversity of bond-forming processes, functional group tolerance, and high levels of chemo-, regio-, and stereoselectivities.[3] Apart from their well-known and much exploited reactivity in Passerini and Ugi reactions,[4] isocyanides are known to form zwitterions with activated acetylene compounds such as dimethyl acetylenedicarboxylate (DMAD) and develop novel protocols for the synthesis of heterocycles.[5] The success of these reactions provided us with a conceptual framework for designing novel multicomponent reactions.

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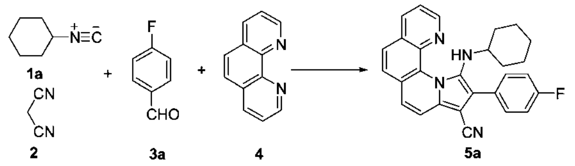
1,10-Phenanthroline and its derivatives possess a variety of uses, especially as biologically active compounds and chelating agents.[6] So far, pyrrolo[1,2-*a*][1,10]phenanthroline derivatives are mostly promising candidates for solid-state device technology,[7] particularly organic light emitting diodes (OLEDs);[8] no utility as a probe for metal ions has been reported. From a synthetic point of view, to date, methods for obtaining pyrrolo[1,2-*a*][1,10]phenanthrolines are very limited. The most useful synthetic approaches were based on 1,3-dipolar cycloaddition reactions of 1,10-phenanthrolinium *N*-ylides with activated alkynes and alkenes.[9] Considering the growing interest for these compounds, and based on our previous endeavors in exploring novel and practical multicomponent reactions,[10] herein, we report a novel displacement strategy involving the reactions of zwitterions generated in situ from isocyanides, aldehydes, and malononitrile with 1,10-phenanthroline to rapidly construct novel pyrrolo[1,2-*a*][1,10]phenanthrolines, which have not been so far reported as a selective chemosensor for determination of Cu^{2+}. To the best of our knowledge, this is so far the first synthetic application of isocyanides to construct pyrrolo[1,2-*a*][1,10]phenanthrolines.

Our investigation started with the reaction of isocyanocyclohexane **1a**, malononitrile **2**, 4-fluorobenzaldehyde **3a**, and 1,10-phenanthroline **4** at room temperature in acetonitrile. A variety of molecular ratios, temperature, solvents, and bases were screened (Table 1), and the results showed that protic solvents were less efficient (Table 1, entries 5–7); even in trifluoroethanol a complicated mixture was observed. Interestingly, when dichloromethane was accidentally decreased from 2 to 1 mL, the product **5a** was directly separated out in 82% yield within 10 h.

Inspired by this result, and considering that the solvent-free reaction (SFR)[3,4,11,12] is an important synthetic procedure from the viewpoint of green and sustainable chemistry, the solvent-free conditions at 40 °C in an oil bath were attempted. Excitingly, a breakthrough result was achieved; the starting materials were completely consumed in 2 min affording the desired compound **5a** in 95% isolated yield (Table 1, entry 9). The best results were obtained in the molecular ratio 1:1.2:1.2:1 for **1a/2/3a/4** at 40 °C under solvent-free conditions (for details, see Table S1 in the Supporting Information (SI)).

Table 1. Optimization of Reaction Conditions for **5a**[a]



entry	solvent	temp (°C)	*t* (h)	yield[b] (%)
1	CH_3CN	rt	16	72
2	CH_3CN	40	10	62
3	CH_3CN	rt	12	72[c]
4	CH_3CN	rt	12	71[d]
5	CH_3CH_2OH	rt	24	60
6	CH_3OH	rt	10	68
7	CF_3CH_2OH	rt	15	mixture
8	CH_2Cl_2	rt	10	82[e]
9	—[f]	40	2 min	95
10	—[f]	50	2 min	90

[a] Reaction of cycloisocyanide **1a** (1.0 mmol), malononitrile **2** (1.2 mmol), 4-fluoroaldehyde **3a** (1.2 mmol), and 1,10-phenanthroline **4** (1.0 mmol) was performed in 2 mL of solvent. [b] Isolated yield after washing with acetonitrile. [c] Et_3N was used as base. [d] PPh_3 was used as base. [e] In 1 mL of CH_2Cl_2. [f] Solvent-free conditions.

To generate a small library of functionalized pyrrolo[1,2-*a*][1,10]phenanthrolines, we next utilized a variety of substrates to explore the synthetic scope and generality of this accelerated one-pot Knoevenagel condensation–1,3-dipolar cycloaddition cascade reaction under the optimal conditions. Representative results are shown in Table 2.

Gratifyingly, the reactions of a wide range of aldehydes **3a–o** with isocyanocyclohexane **1a**, malononitrile **2**, and 1,10-phenanthroline **4** proceeded smoothly. The results showed that the process could tolerate both aromatic aldehydes with electronically different substituents (Table 2, entries 1–14) and heteroaromatic aldehydes such as furan-2-carbaldehyde (Table 2, entry 15). Unfortunately, some

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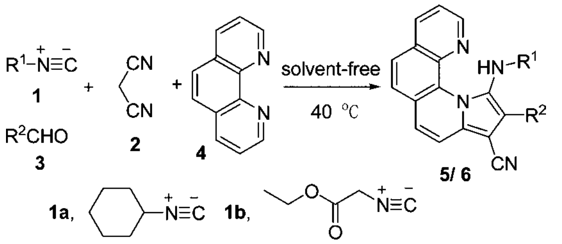
aliphatic aldehydes such as acetaldehyde, propionaldehyde, and butyraldehyde only gave trace products that could not be isolated.

Table 2. Exploration of Substrate Scope for Synthesis of **5/6**



entry	R^2	product	*t* (min)	yield^a (%)
1	4-FC_6H_4	**5a**	2	95
2	4-ClC_6H_4	**5b**	2	93
3	4-BrC_6H_4	**5c**	2	90
4	4-$NO_2C_6H_4$	**5d**	2.5	90
5	3-BrC_6H_4	**5e**	2	88
6	2-FC_6H_4	**5f**	2	90
7	2-ClC_6H_4	**5g**	2	90
8	2-BrC_6H_4	**5h**	2	86
9	2-$NO_2C_6H_4$	**5i**	2.5	88
10	C_6H_5	**5j**	2	85
11	4-MeC_6H_4	**5k**	3	84
12	4-$MeOC_6H_4$	**5l**	3	82
13	2-MeC_6H_4	**5m**	3	83
14	4-OHC_6H_4	**5n**	3	80^b
15	2-furnan	**5o**	2	90
16	2-ClC_6H_4	**6a**	2	93
17	4-ClC_6H_4	**6b**	2	94
18	4-BrC_6H_4	**6c**	2	92
19	4-$NO_2C_6H_4$	**6d**	2	90
20	C_6H_5	**6e**	2	89
21	4-$MeOC_6H_4$	**6f**	2	87

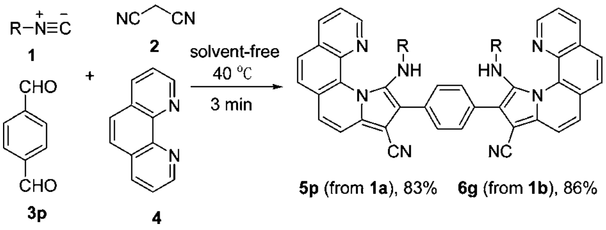
[a] Isolated yield after washing by EtOH. [b] Yield after purification via silica gel column chromatography.

Encouraged by the success of this reaction, we employed ethyl 2-isocyanoacetate **1b** instead of cyclohexylisocyanide **1a** to investigate this IMCR and found the reactions involving **1b** also proceeded well to afford the corresponding products **6** in excellent yields (Table 2, entries 16–21).

Subsequently, the difunctional group 1,4-phthaldehyde **3p** was also used to explore the scope of this reaction, and the results were still satisfactory even though low yields and a slightly longer reaction time were required (Scheme 1).

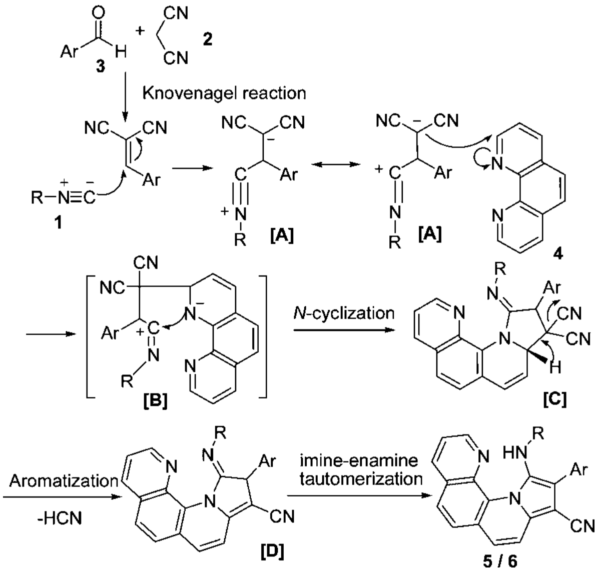
The above results revealed that the substituents on the aromatic aldehydes had some influence on the yields of products **5/6**. The aromatic aldehydes with electron-withdrawing groups such as fluoro, chloro, bromo, and nitro groups (Table 2, entries 1–9 and 16–18) reacted faster and gave higher yields than those with electron-rich groups such as methyl and methoxyl groups (Table 2, entries 11–13 and 20). However, the position of the substituents did not exhibit evident regularity in the reactivity of aromatic aldehydes.

Scheme 1. Exploration of 1,4-Phthaldehyde **3p** as Substrate



It is worth mentioning that this new domino multicomponent procedure might involve two directions of formation zwitterions. According to the Mironov reaction,[13] the zwitterion was generated from 2-arylidene malononitrile and 1,10-phenanthroline. However, in our investigation, the zwitterion was generated from 2-arylidenemalononitrile and an isocyanide, which was confirmed by the X-ray single crystal diffraction analysis of compounds **5l** and **6a** (Figure S1, SI).

Scheme 2. Plausible Mechanism



Although we have not experimentally established the mechanism of the reaction, based on the above experimental results, a plausible reaction scenario for the domino cyclocondensation is presented in Scheme 2. The first step is believed to be the Knoevenagel condensation between an aldehyde **3** and malononitrile **2** to generate 2-arylidenemalononitrile which reacts with an isocyanide **1** to give a highly reactive zwitterion intermediate **[A]**, followed by its trapping with 1,10-phenanthroline **4** to afford the intermediate **[B]**. Next **[C]** and **[D]** were obtained by N-cyclization and aromatization with loss of HCN. Finally, products **5/6** were received.

Selective detection of metal ions has been of great interest because of their importance in biological and

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environmental processes. However, an inherent problem exists in the detection of Cu^{2+} for fluorescent sensing because of the likely quenching of fluorescence.[14] Considering the great amount of interest in 1,10-phenanthrolines as a ligand for metal complexes, we preliminarily studied the photophysical behavior of representative compounds **5j** and **6e** in the presence of various metal ions in aqueous solution, such as Cu^{2+}, Hg^{2+}, Mg^{2+}, Ba^{2+}, Na^{+}, K^{+}, Ag^{+}, Ca^{2+}, Cd^{2+}, Ce^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}, and Al^{3+}, through UV/vis and fluorescence spectroscopy.

Figure 1. Visual appearance of solutions of **6e** (10 μM) with various metals (10 μM) in H_2O/CH_3CN (90:10 v/v) under ambient light.

From Figure 1, we can observe clearly the metal-dependent behavior of **6e**; the product **6e** showed strong Cu^{2+} selectivity with an evident color change from yellow to purple, while product **5j** had no response to all ions. The UV/vis absorption spectra of **6e** (10 μM) in CH_3CN and upon addition of 3 equiv of various perchlorate salts of metal ions (Figure S2, SI) show that **6e**–Cu^{2+} has a band in the visible region, λ_{max} = 549 nm, ε = 1.45 × 10^4 M^{-1} cm^{-1}. The IR and NMR spectra of the **6b**–Cu^{2+} complex suggested that compounds **6** could bind Cu^{2+} as a N,N,N ligand in a tridentate fashion, while the ester group did not participate in the coordination (Figure S3, SI). *N*-Cyclohexyl substituted pyrrolo[1,2-*a*]phenanthroline derivatives **5** could not act as a tridentate ligand to coordinate with Cu^{2+}, which may be due to the steric effect of the cyclohexyl group. A similar observation was obtained with compounds **6b** and **6f**, bearing an electron-withdrawing and -donating substituent on the 10-aryl ring, respectively. This feature of **6e** allows visual detection of Cu^{2+} under ambient light, configuring **6** as a potential sensor for the naked-eye detection of Cu^{2+}.

We next performed fluorescence emission experiments with compound **6e**. The results were consistent with the above observations. **6e** has almost no fluoresence, but the complex with Cu^{2+} shows an enhanced fluorescence (λ_{em} = 422 nm) with an emission maxima blue shift relative to **6e** (λ_{em} = 460 nm), which may be subject to that after the chelation with Cu^{2+} the lowest excited singlet state was changed to the $S_1(\pi\pi^*)$ state from $S_1(n\pi^*)$ of the **6e** molecule, while with other metal ions no evident relevant spectral changes were observed (Figure 2). The nonlinear fitting of the titration curve assumed a 1:1 stoichiometry for the **6e**–Cu^{2+} complex (Figure S4, SI). But **6e** is suitable for detecting the copper ion under the pH 6–7 conditions (Figure S5, SI). From the fluorescence emission experiments of **6b** and **6f**, it was found that the fluorescence intensity of complexes could be decreased by the introdution of either electron-withdrawing or -donating substituents compared to unsubstituted **6e** (Figure S6, SI).

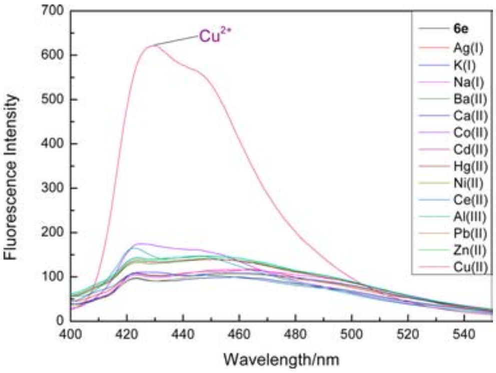

Figure 2. Fluorescence profiles of **6e** (10 μM) upon addition of various metal ions (3 equiv) in H_2O/CH_3CN (90:10 v/v) (λ_{ex} = 375 nm).

In summary, a novel rapid and direct synthesis of pyrrolo[1,2-*a*][1,10]phenanthrolines has been developed by cyclization of aldehydes, malononitrile with isocyanide, and 1,10-phenanthroline under solvent-free conditions within 3 min without using any catalyst or activation. This is the first example of a synthesis of pyrrolo[1,2-*a*]-[1,10]phenanthrolines involving the reactions of zwitterions generated in situ from isocyanides, aldehydes, and malononitrile with phenanthroline. Furthermore, our products **6** displayed a selective colorimetric and fluorescene change upon the addition of Cu^{2+} over a wide range of tested metal ions in H_2O/acetonitrile (90:10 v/v), indicating that compounds **6** could be used as a potential sensor for the naked-eye detection of Cu^{2+} and may contribute to the development of a more useful fluorescent sensor for Cu^{2+}.

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Supporting Information Available. Experimental and characterization details, ^1H and ^{13}C NMR spectra of all new compounds and complex **6b-**Cu^{2+}, UV/vis spectra of **6e** with metal ions, fluorescence emission spectra of **6e** upon titration with Cu^{2+}, and crystal data for **5l** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.