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Exploitation of Dual Character of CN Moiety in the Synthesis of Uniquely Decorated 3*H*-Pyrroles: A Rare Observation

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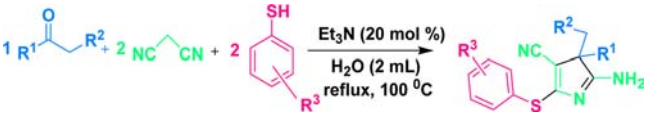
ABSTRACT

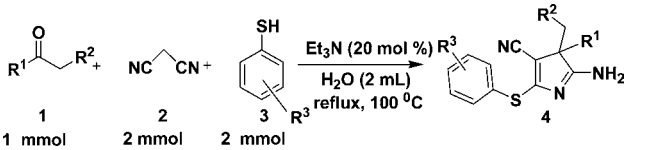


This is the first report of an innovative, one-pot, organocatalyzed, multicomponent synthesis of 3*H*-pyrroles from ketones, thiols, and malononitrile in ecofriendly solvent water. The approach to 3*H*-pyrroles presented herein offers, for the first time, an unprecedented coupling which leads to the construction of the nitrogen containing ring without starting from any amine moiety. In this context, cyanide-based multicomponent reactions involving the dual nature of the CN moiety has blossomed in an unprecedented way.

3*H*-pyrrole is a little known ring system with a potentially rich chemistry in terms of rearrangement, addition, and cycloaddition reactions.[1] Some 3*H* compounds showed antimicrobial activity against Gram-positive bacteria, and some have antitumor activity.[2] Unlike other pyrrole compounds, relatively little attention is paid in the synthesis of 3*H*-pyrroles presumably because of difficulties associated with the synthesis of these compounds. Only a few novel unconventional routes are reported for their synthesis which involve reaction of electrophiles with 1*H*-pyrroles;[3] cyclization of open-chain compounds;[4] 1,3 dipolar cycloadditions using nitrile ylides; etc.[5−7] However, the reaction conditions are often inconvenient and the starting materials are not easily accessible. Therefore, an alternative way would be to assemble structures directly from several readily available and easily diversified building blocks in a one-pot multicomponent fashion and preferably using organocatalysis.

We thus wish to disclose the one-pot, organocatalyzed synthesis of 3*H*-pyrrole from ketones, a sulfur nucleophile, and malononitrile in an environmentally benevolent solvent (Scheme 1).

Scheme 1. Synthesis of 3*H*-Pyrrole (**4**)



In this present synthesis, cyanide-based multicomponent reactions (CMCRs) involving the dual nature of the CN^- (both as a carbon center nucleophile and an electrophile) moiety blossomed in an unprecedented way, thanks to the

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versatility of cyanide chemistry. The most exciting feature of this communication is its mechanism, that we postulated here involving the dual nature of CN moiety.

Mechanistically, it is conceivable that the aromatic ketones first undergo a Knoevenagel condensation reaction with malononitrile which is a very characteristic reaction of carbonyl compounds in the presence of a base.[8] This is evident from the NMR spectrum of the major product [(**5**), (R = 4′-Cl-C_6H_4-)] isolated after 30 min. This intermediate (**5**) underwent nucleophilic attack by thiols on −CN functionality to give the in situ intermediate **6** (Scheme 2). Intermediate **6** undergoes cheletropic addition with a cyanide ion to give an amidine species (**7**) that tautomerizes to yield an amino-3*H*-pyrrole (**4**). A highly reactive cyanide species was presumed to be formed by the nucleophilic attack of thiols on malononitrile by a mechanism drawn in Scheme 2. This proposition was further supported by the isolation of the byproduct, 2-(phenylthio)-acetonitrile (**8**), formed by the nucleophilic attack of PhSH on malononitrile which furnishes cyanide ions for the reaction. Thus, malononitrile acts as a nontoxic cyanide source in this reaction.

Here, despite Knoevenagel condensation being a net dehydration of the water molecule, the reaction is favored in an aqueous medium. A plausible explanation is that water aids in better contact between the catalyst (Et_3N) and the active methylene compounds through hydrogen bonding.[8b,9] Thus, realizing environmental concerns, as well as the vast utility and scope of reactions carried out in water, we established water to be the preferred solvent.

The reaction between acetophenone (**1a**), malononitrile (**2**), and thiophenol (**3a**) was selected for the survey of reactions. The yield decreased substantially with stronger base catalysts instead; significant tarring was observed (Table 1, entries 1 and 2) probably due to the self-condensation of the carbonyl compounds at high temperature with stronger bases.[8] Importantly, no product was observed when a background reaction was carried out without any catalyst (Table 1, entry 3). Interestingly, the basicity of the common organic bases did not assert any obvious effect on the product yield. However, pyridine and Et_3N afforded a slightly better yield than DBU, guanidine, or piperidine presumably due to the lesser extent of polymerization of the ketones with weaker bases such as pyridine and Et_3N. However pyridine is potentially harmful to the experimentalist.[8a] Therefore, Et_3N was our obvious choise of catalyst. Again, temperature played a significant role since there was only a 62% yield at 60 °C compared to the 94% yield at 100 °C (Table 1, entries 7 and 8). Albeit the reaction was successful in common high boiling point organic solvents such as toluene, DMSO, DMF, etc., the isolated yields were comparatively low (Table 1, entries 10−12). The reaction in low boiling point solvents (DCM, MeOH) afforded poor yields of **4aa** (Table 1, entries 15, 16). However comparatively better yields were obtained in EtOH and acetonitrile (Table 1, entries 13, 14).

With the optimized conditions in hand, to delineate this approach, the scope and generality of this protocol was next assessed by employing various ketones, thiols, and

Scheme 2. Proposed Mechanism

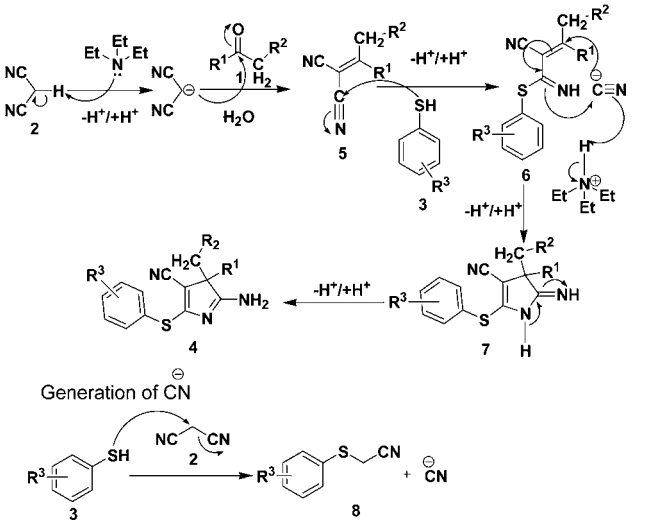
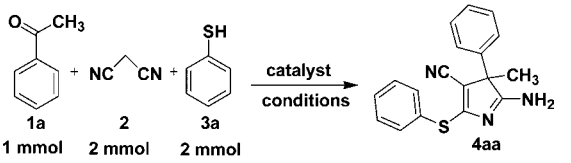


Table 1. Optimization of Reaction Conditions for the Multicomponent Coupling Reactions[a]



entry	amount of catalyst (mol %)	catalyst	solvent	temp (°C)/ time (h)	yield of **4aa** (%)[b]
1	10	NaOH	H_2O	100, 2	22
2	10	K_2CO_3	H_2O	100, 2	47
3	–	–	H_2O	100, 20	–
4	20	guanidine	H_2O	100, 3	86
5	20	DBU	H_2O	100, 3	88
6	20	piperidine	H_2O	100, 3	89
7	20	Et_3N	H_2O	60, 10	62
8	20	Et_3N	H_2O	100, 3	94
9	20	pyridine	H_2O	100, 3	91
10	20	Et_3N	toluene	100−110, 3	84
11	20	Et_3N	DMSO	120−130, 3	74
12	20	Et_3N	DMF	120−130, 3	79
13	20	Et_3N	ACN	70−80, 3	64
14	20	Et_3N	EtOH	70−80, 3	65
15	20	Et_3N	MeOH	50−60, 3	41
16	20	Et_3N	DCM	30−35, 3	21

[a] Reaction conditions: Acetophenone (1 mmol), malononitrile (2 mmol), thiophenol (2 mmol), different catalysts, different solvents, different temperatures, different times. [b] Isolated yields.

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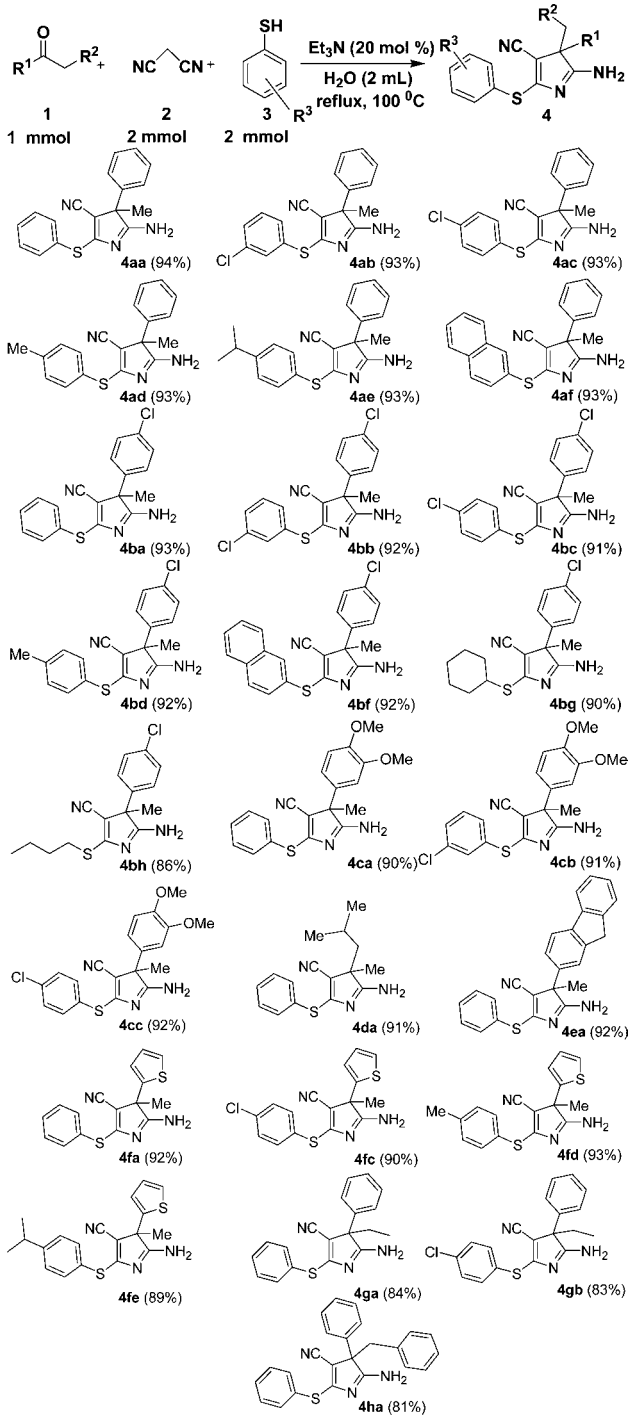
Scheme 3. Diversity of Uniquely Decorated 3*H*-Pyrrole[a]



[a] Reaction conditions: Ketones (1 mmol), malononitrile (2 mmol), thiols (2 mmol), Et_3N (20 mol %), reflux in water at 100 °C for 3 h.

malononitrile. An assembly of 25 compounds was synthesized using this protocol (Scheme 3). Aromatic, alicyclic (**4bg**), and alkyl thiols (**4bh**) all afforded good to excellent yields. It was pleasing to find that sterically bulky naphthalene-2-thiol also reacted very efficiently with no side reactions (**4af**, **4bf**). To further expand the scope of the reaction the use of different ketones was investigated. Despite the

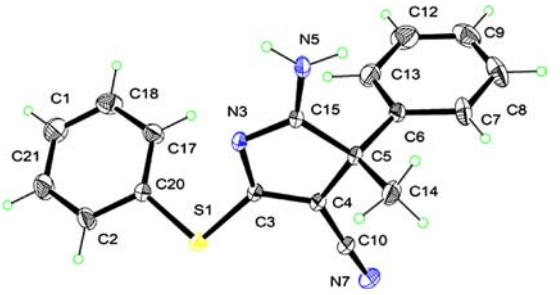
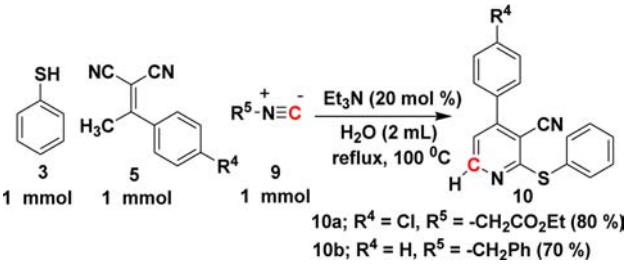


Figure 1. ORTEP representation of **4aa** (CCDC 952788).

Scheme 4. Synthesis of Unexpected Pyridine (**10**)[a]



[a] Reaction conditions: Knoevenagel product (**5**) (1 mmol), thiophenol (1 mmol), isocyanide (1 mmol), Et_3N (20 mol %), reflux in water at 100 °C for 3 h.

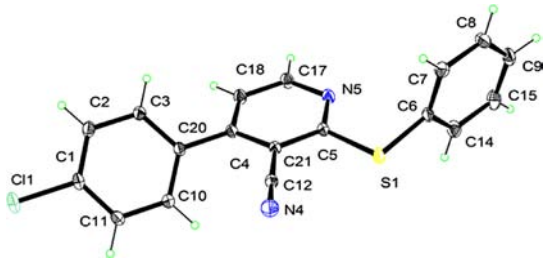
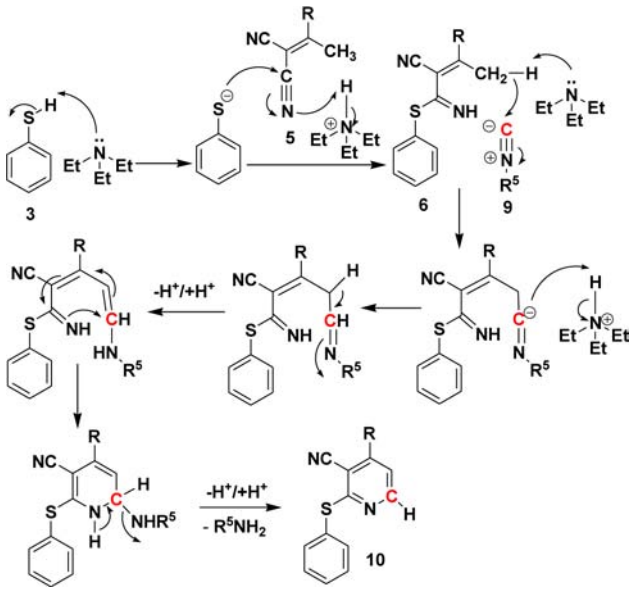


Figure 2. ORTEP representation of **10a** (CCDC 965798).

difficulty of a Knoevenagel condensation reaction with electron-rich ketones, the reaction occcured successfully with 3′,4′-dimethoxy acetophenone (**4ca**–**4cc**). In addition, the use of aliphatic ketones was also examined (**4da**). The modularity of this pyrrole- forming reaction sequence was further demonstrated by the use of heteroaryl ketones (**4fa**–**4fe**). It is important to mention that, in addition to methyl ketones, other substituted alkyl ketones (e.g., ethyl phenyl ketone and 1,2-diphenylethanone) reacted smoothly under the present conditions. The low reactivity of substituted alkyl ketones (**4ga**–**4ha**) in this reaction which is also reflected in the reaction yield may be due to the steric crowding among the substituents.

The structures of the compounds were confirmed unambiguously from X-ray single crystal analysis of four

Scheme 5. Mechanism of Pyridine Formation



distinct compounds **4aa**, **4ab**, **4bb**, **4ha**. An ORTEP plot of **4aa** is given in Figure 1, and plots of the other compounds are in the Supporting Information.

After the mechanism of 3*H*-pyrrole formation was realized, the question remained regarding what would be the product if instead of using 2 equiv of malononitrile, the Knoevenagel product of ketone and malononitrile (intermediate **5**) is allowed to react with thiophenol and isocyanide compounds under the same reaction conditions. We could not isolate the corresponding pyrrole. However instead of the anticipated 3*H*-pyrrole we generated an unexpected pyridine compound (**10**) according to Scheme 4. The structure of **10a** was confirmed by X-ray single crystal analysis (Figure 2).

It is worth mentioning that the mechanism of this reaction is a special case which depicts the incorporation of only one carbon atom from isocyanide to pyridine (Scheme 5).

In conclusion, this present approach to 3*H*-pyrroles depicted herein offers for the first time an unprecedented coupling of ketones, thiols, and malononitrile which leads to the construction of the nitrogen-containing ring without starting from any amine moiety. Thus, this newly developed protocol is a significant proof of the fact that nitrile is one of the most versatile functional groups, as it can be readily transformed into various other functional groups or reactive intermediates. This novel 3*H*-pyrrole synthesis describes an entirely new approach involving the dual role of the CN moiety (as both a carbon center nucleophile and an electrophile), an area that remains elusive in current organic research. Moreover it opens a brand new way to build C−C, C−S, and C−N bonds in a single operation. All of the cycloadducts were quite stable and easy to handle under standard conditions. Furthermore, the presence of a cyano group in the pyrroles makes them useful synthetic intermediates for the preparation of other nitrogen-containing heterocycles.[10] It is hoped that this methodology will be embraced by the synthetic organic community at large.

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Supporting Information Available. Experimental procedures and full spectroscopic data. 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.