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Efficient synthesis of polysubstituted pyrrole-3-carbonitriles via reactions of 1,1-dicyano-2,3-diarylcyclopropanes with aromatic imines

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$Co(ClO_4)_2$ smoothly catalyzed the reactions of 1,1-dicyano-2,3-diarylcyclopropanes with aromatic imines to give the novel polysubstituted pyrrole-3-carbonitriles bearing an 2-arylidenimino group in good to high yields in refluxing THF.

During the last two decades, the activated cyclopropanes have attracted much attention and are widely used as the versatile three carbon building blocks due to the broad scope of reactivity and ease of preparation.[1,2] The presence of electron-donating groups and electron-withdrawing groups increases the reactivity of cyclopropane toward the electrophiles and nucleophiles.[3,4] The cycloaddition reactions of the donor–acceptor cyclopropanes with various dienophiles such as aldehydes, imines, isocyanate, nitrones, acetylenes and nitriles have been demonstrated to form valuable five-membered heterocycles.[5–12] At present most of the reported works were focused on the cycloadditions of donor–acceptor cyclopropanes having at least one unsubstituted methylene unit in order to finish the ring-opening of cyclopropyl moiety in mild condition, while the reactivity of the sterically hindered polysusbstituted cyclopropanes was rarely investigated.[13] Our group has recently developed an efficient method for the preparation of diverse 1,1-dicyano-2,3-diarylcyclopropanes from readily available regents via multicomponent reaction.[14] It is very interesting to examine the combining reactivity of cyano group and cyclopropyl moiety in ring-opening reaction toward the electrophiles and nucleophiles. In this work we wish to report the preliminary results on the reactions of 1,1-dicyanocyclopropanes with aromatic imines.

There have been several reports about Lewis acid catalyzed reactions of imines as dipolarophiles with the activated cyclopropane to form pyrrolidine derivatives.[8–12] These led us to focus our early efforts to use transition metal perchlorides as Lewis acid catalyst in the ring-opening of 1,1-dicyano-2,3-diarylcyclopropanes. At first the reaction conditions were examined on the reaction of 1,1-dicyano-2-*p*-methoxyphenyl-3-*p*-nitrophenylcyclopropane **1c** with *p*-methoxybenzylidene *p*-toluidine **2a**. The catalytical effect of several transition metal perchlorides ($Cu(ClO_4)_2$, $Ni(ClO_4)_2$, $Co(ClO_4)_2$, $Mn(ClO_4)_2$, $Zn(ClO_4)_2$) were tested. We are pleased to find that the best catalyst is $Co(ClO_4)_2$, which gave satisfactory yield of the ring-opening product. Then the solvents were also examined. Product **3c** was hardly obtained in the solvent such as chloroform, acetonitrile and toluene. The reaction could proceed smoothly in ethanol and DMF, but the yields of **3c** were lower than that in THF. Thus we established the optimal conditions as the reaction of cyclopropanes **1** with aromatic imines **2** in refluxing THF with $Co(ClO_4)_2$ as catalyst for 30–48 h.[15] The results are summarized in Table 1. Cyclopropanes having different kinds of groups such as alkyl, alkoxyl, chloro and bromo groups were used in reactions, from which polysubstituted pyrrol-3-carbonitriles **3a–3o** were obtained in good yields (65–80%). On the other hand aromatic imines devised from aldehydes and amines bearing either electron-donating or electron-withdrawing substituents showed similar reactivity and reacted efficiently to yield the desired products. These results showed that this reaction is quite general and has a very broad substrate scope. The structures of the prepared products **3a–3o** were fully characterized by ^1H and ^{13}C NMR, MS, IR spectra, and were further confirmed by single-crystal X-ray diffraction studies performed for three representatives compounds **3c** (Fig. 1), **3j** and **3m**.[16] The most unusual feature of the structure of **3a–3o** is the fact that one arylidenimino group is formed at the 2-position of pyrrole ring.

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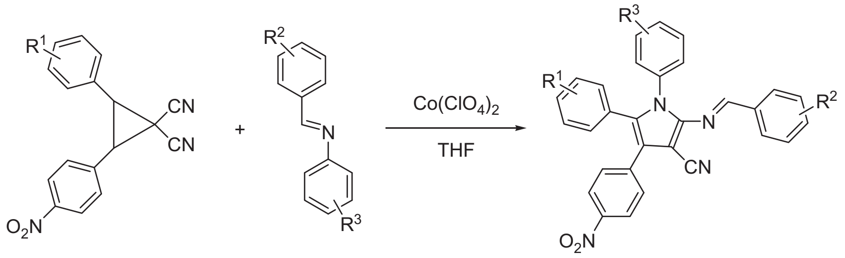
Table 1
The synthesis of polysubstituted pyrrole-3-carbonitriles



Entry	Compd	R^1	R^2	R^3	Yield[a,b] (%)
1	**3a**	H	p-CH_3O	p-CH_3	76
2	**3b**	p-CH_3	p-CH_3O	p-CH_3	80
3	**3c**	p-CH_3O	p-CH_3O	p-CH_3	82
4	**3d**	p-CH_3CH_2	p-CH_3O	p-CH_3	73
5	**3e**	p-$(CH_3)_3C$	p-CH_3O	p-CH_3	71
6	**3f**	m-Cl	p-CH_3O	p-CH_3	78
7	**3g**	p-Br	p-CH_3O	p-CH_3	68
8	**3h**	H	m-Cl	p-CH_3	70
9	**3i**	p-CH_3	m-Cl	p-CH_3	75
10	**3j**	p-CH_3O	m-Cl	p-CH_3	78
11	**3k**	p-$(CH_3)_3C$	m-Cl	p-CH_3	65
12	**3l**	m-Cl	m-Cl	p-CH_3	68
13	**3m**	p-CH_3	p-Br	p-CH_3O	71
14	**3n**	p-CH_3O	p-Br	p-CH_3O	66
15	**3o**	m-Cl	p-Br	p-CH_3O	63

[a] Isolate yields.

[b] Cyclopropane (1.0 mmol), imine (1.0 mmol), $Co(ClO_4)_2$ (0.2 mmol), THF, reflux, 30 h.

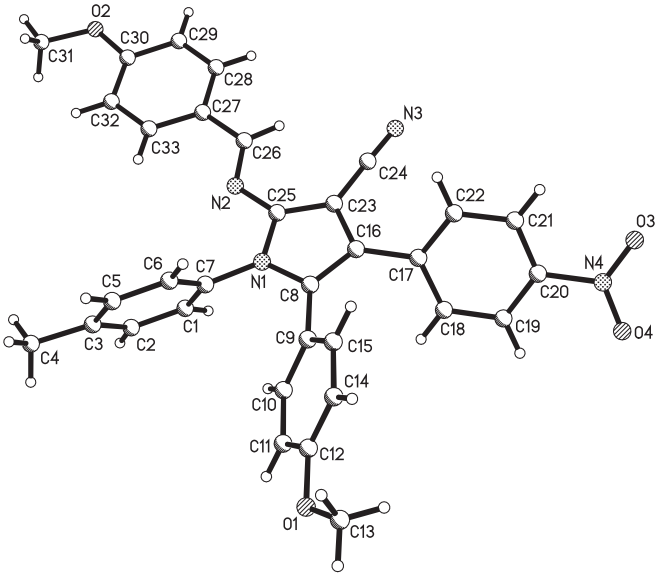


Figure 1. The molecular structure of compound **3c**.

Although no detailed mechanism and experimental investigation are carried out in this letter, a plausible reaction course for the formation of pyrrol-3-carbonitriles was proposed in Scheme 1 on the basis of the established ring-opening reaction of the donor–acceptor substituted cyclopropanes.[10–12] Firstly the aromatic imine **2** was decomposed to give aromatic aldehyde and amine.[17] The two stronger electron-withdrawing cyano groups and one p-nitrophenyl groups in cyclopropane **1** greatly activate the cyclopropyl moiety. Thus the nucleophilic amine attacks the cyclopropyl ring **1** to give the ring-opening intermediate (**A**).[16] Then intramolecular addition of the amino group to one of cyano group yielded the ring intermediate (**B**). The 2-aminodihydropyrrole (**C**) was formed by the imine–enamine tautomerization, which in turn was oxidized in air to give the 2-aminopyrrole (**D**). At last the condensation of the 2-aminopyrrole (**D**) with aromatic aldehyde gave the 2-arylideniminopyrrolecarbonitrile **3** as the final product. It should be pointed out that when the reactions were carried out in ethanol the 2-aminopyrrole (**D**) could be separated in lower yields due to existing water in ethanol causing the partial hydrolysis of the arylidenimine group.

In order to shine more light on the proposed reaction mechanism for the formation of pyrrole-3-carbonitriles, the three-component reactions of aromatic aldehydes, arylamines and 1,1-dicyano-2,3-diarylcyclopropanes (Table 2) were carried out under similar reaction conditions. The expected pyrrole-3-carbonitriles were also obtained in similar yields. It should be pointed that the compounds **3c** and **3i** have already been prepared by directly using imines in the reactions (Table 1). The compounds **3p–3r** are obtained only by the three-component reactions. This result also supported our above proposed reaction mechanism, in which the aromatic imine **2** was decomposed to give aromatic aldehyde and amine, which in turn took part in the sequential reactions.

In conclusion an efficient synthetic procedure for the polysubstituted pyrrole-3-carbonitriles was developed by Lewis acid catalyzed ring-opening reaction of the sterically hindered cyclopropane with aromatic imines. This protocol not only provides an effective methodology for the preparation of functionalized pyrroles, but also opens a brand way for employing the sterically hindered cyclopropane to design the new ring-opening reaction. Further expansion of the reaction scope and synthetic applications of this methodology are in progress in our laboratory.