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The trifluoromethyl transformation synthesis, crystal structure and insecticidal activities of novel 2-pyrrolecarboxamide and 2-pyrrolecarboxlate

Yongqiang Li, Pengxiang Zhang, Qiaoqiao Ma, Haibin Song, Yuxiu Liu *, Qingmin Wang *

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

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ABSTRACT

Two series of 2-phenylpyrroles: 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxamide (**5a**–**5d**) and 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxylate (**6a**–**6c**) were synthesized by a novel trifluoromethyl transformation. The result of insecticidal bioassays indicated that **6a**–**6c** had moderate larvicidal activity against oriental armyworm and **6b** also had good acaricidal activity, so 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxylate derivatives were expected to become lead compounds for new pesticides.

Dioxapyrrolomycin (Fig. 1) was isolated from a *Streptomyces* strain by the researchers from American Cyanamid Co. in 1980s and found to have insecticidal and acaricidal activities.[1] It has also reported as an antibiotic in Japan.[2,3] It was not developed as a candidate pesticide because of its super high toxicity to mammals. Extensive structural modification was used to overcome the defect of toxicity. Afterwards, series of compounds were synthesized, of which compound **1** possessed outstanding insecticidal activity against tobacco cutworm, two-spotted spider mite and potato leafhopper, etc.[4] However, evaluation of bioactivity showed compound **1** had intolerable toxicity to crops. An ethoxymethyl group was introduced onto the nitrogen atom of compound **1**, therefore got rid of the undesirable phytotoxic properties but retained high insecticidal activity.[5–8] This compound was finally commercialized as an insecticide/acaricide by American Cyanamid Co. with its trade name as Chlorfenapyr.

We have been focusing on novel Chlorfenapyr analogues as substitute for years. In our previous work, we paid more attention on modifying substituent on the nitrogen atom of pyrrole **1** and found some of the compounds **A** and **B** exhibited excellent insecticidal activities.[9,10] After that, we turned our direction onto the substituent on other positions of compound **1**. Recently, we happened to find a novel synthetic method that can convert trifluoromethyl group to the corresponding carboxamide, thus the method was applied to synthesize a series of 2-pyrrolecarboxamide and 2-pyrrolecarboxlate (**3**–**6**). Herein, we report the synthesis of the compounds and speculated mechanism. Furthermore, their insecticidal activities against oriental armyworm (*Mythimna separata*) and acaricidal activities against eggs, larvae and adults of spider mite (*Tetranychus cinnabarinus*) were assayed and discussed.

As illustrated in Scheme 1, the initial aim of the reaction of 4-bromo-2-(4-bromophenyl)-5-(trifluoromethyl)pyrrole-3-carbonitrile (**2**) with aniline in the presence of CuI was to prepare diphenyl amine via Ullmann coupling reaction,[11] which was carried out in microwave synthesizer to shorten the reaction time. However, the Ullmann coupling product was not formed, while unexpected *N*-phenyl 5-(4-bromophenyl)-3-cyanopyrrole-2-carboxamide (**3a**) was separated, and its structure was verified by NMR, high resolution mass spectrum and the X-ray single-crystal diffraction (Fig. 2).[12]

Similarly, the reaction of compound **2** or **1** with 4-trifluoromethylaniline afforded pyrrolecarboxamide **3b** or **4**, respectively. In all these reactions the original 5-trifluoromethyl group of pyrrole of **2** or **1** was replaced by carboxamide, and the original bromide at the 4-position of pyrrole (i.e., 3-position in compound **3** or **4**) was missing. The drop of bromine can be explained as CuI-catalyzed debromonation. As expected, in the absence of CuI, compounds 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxamides (**5a**–**5d**) and 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxamides (**6a**–**6c**) were prepared from compound **1** with corresponding amines or alcohols under similar condition (Scheme 2).

As far as we know, the reaction that converting trifluoromethyl group to corresponding carboxamide or carboxylate has seldom been reported so far. In 2010, Gavin O'Mahony reported

* Corresponding authors. Tel./fax: +86 22 23503952.
E-mail addresses: wang98h@263.net, wangqm@nankai.edu.cn (Q. Wang).

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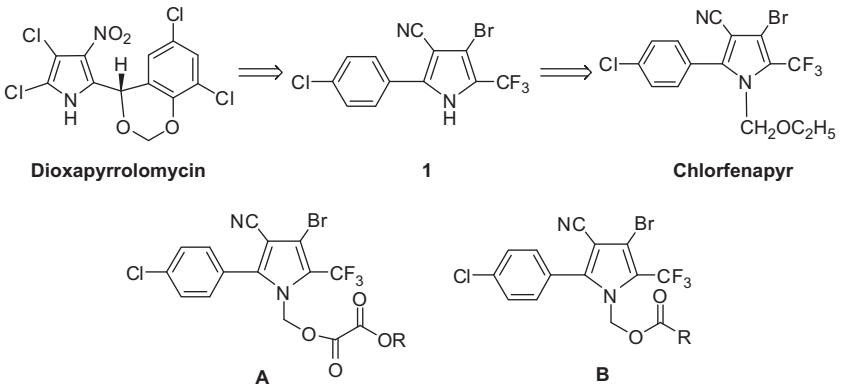
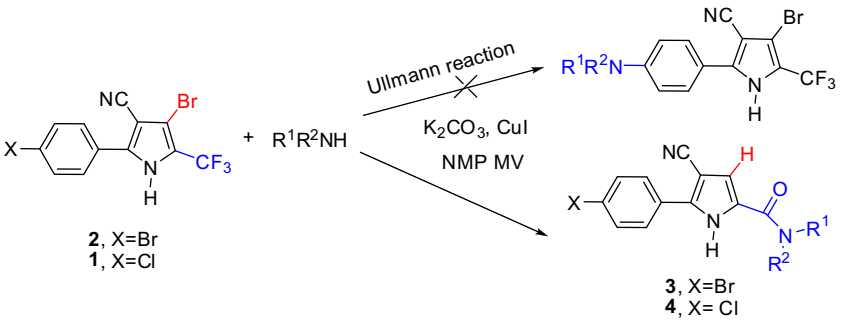


Figure 1. Chlorfenapyr and related compounds.



Scheme 1. Synthetic route of the compounds **3** and **4**.

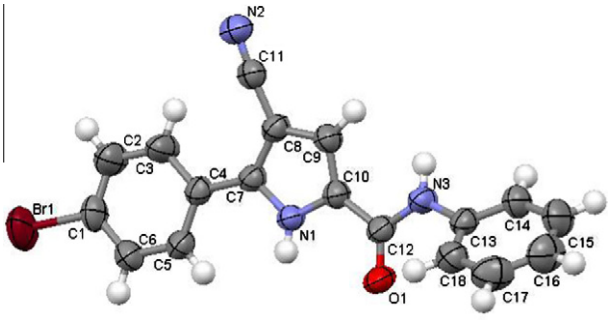
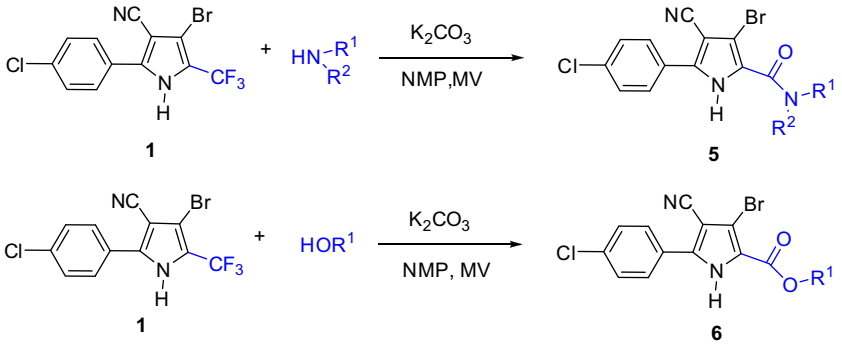
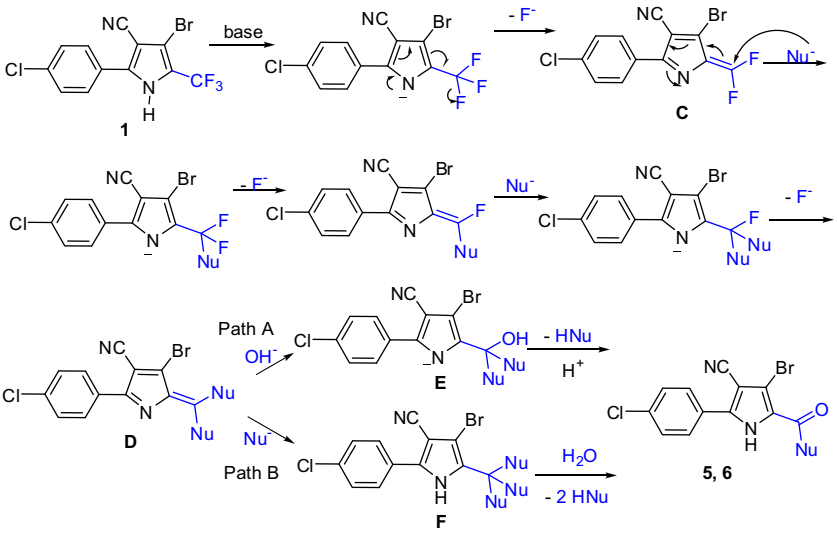


Figure 2. Molecular structure of compound **3a**.

CF_3-substituted anilines, phenols and 2-phenyl-4(5)-trifluoromethyl imidazoles could afford corresponding amide in the presence of alkaline.[13] Heidelberger[14] and Terenin[15] also reported the aminolysis of trifluoromethyl-substituted deoxyuridine or 3,4-dihydropyrrolo-[1,2-*a*] pyrazines but with low yields. Comparably more literature can be found on the alkaline hydrolysis of trifluoromethyl group to carboxylic acid or alcoholysis to orthoester if the trifluoromethyl group is at a proper position of the benzene or heteroaromatic ring.[16–30] Theoretically carboxamide or carboxylate should be the hydrolysis product of trisubstitutedamino methyl or trialkoxy methyl group. But C–F bond has great bond energy, so the F atom in the CF_3 group is difficult to be substituted via an SN_2-type mechanistic pathway. Based on the literature mentioned above, the reaction process of compound **1** to **5** or **6** was proposed and illustrated in Scheme 3. Under microwave irritation



Scheme 2. Synthetic route of the compounds **5** and **6**.



Scheme 3. Proposed formation of **5** and **6**.

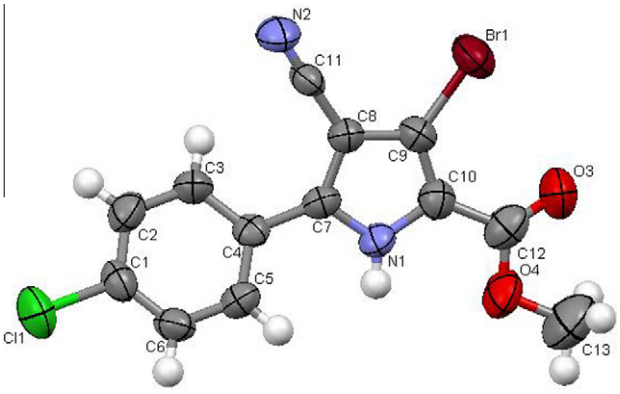


Figure 3. Molecular structure of compound **6a**.

or higher temperature and in the presence of Na_2CO_3, trifluoromethyl pyrrole compound **1** firstly undergoes an elimination of hydrogen fluoride by an E1cB mechanism assisted by the N atom of pyrrole ring to afford an electrophilic intermediate **C**, then it is attacked by a nucleophile to restructure pyrrole ring; by repeating process, the reaction gives compound **D**, which can be attacked either by OH^- (Path A)[13] or by Nu^- (Path B)[31], and then the resulting trisubstituted compound **E** or **F** is converted to amide or carboxylate by elimination of HNu.

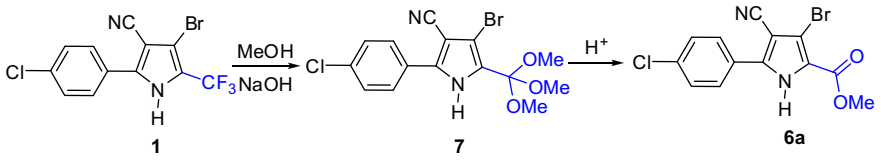
Of the two paths, we are more apt to agree with path B. Though we did not separate **F** from the reaction mixture irritated by microwave, we did get the trimethoxymethyl pyrrole **7** when compound **1** was refluxed in methanol in the presence of sodium hydroxide. The orthoester **7** converted to methyl carboxylate **6a** in the later hydrolysis, the structure of which was verified by the X-ray single crystal diffraction (Fig. 3).[12] Therefore we verified our assumption and provide an alternative method to prepare pyrrolecarboxylate **6** (Scheme 4).

Synthesized compounds **3**–**6** and reference compound Chlorfenapyr and **1** were tested for their insecticidal activity against oriental armyworm and acaricidal activities against spider mite according method described in literature.[9,10,32]

The data in Table 1 show that pyrrolecarboxamide compounds **3b**, **4**, **5a, 5c** and **5d** had no insecticidal activity against oriental armyworm at 200 mg L^{-1}, which indicates that when trifluoromethyl group was changed to amide group, the bioactivity dramatically decreased whatever bromine atom is at the 3-position of pyrrole ring or not. The substituent on the amide nitrogen plays an important role on the activity; though **5a, 5c** and **5d** gave no insecticidal activity at 200 mg L^{-1}, *N*-cyclohexyl compound **5b** showed 80% insecticidal activity at the same concentration. The pyrrolecarboxylate compounds **6b** and **6c** exhibited relatively good activity against oriental armyworm at high concentrations (200 mg L^{-1}, 100 mg L^{-1}); at lower concentration (50 mg L^{-1}), compound **6c** still remained 100% insecticidal activity; but all the activity dropped to 0 at the concentration of 25 mg L^{-1} whereas the commercial Chlorfenapyr and compound **1** remaining 100%.

Just like the insecticidal activity against oriental armyworm, the acaricidal activities of most of compounds also vanished when CF_3 group was replaced by amide or ester. Ethyl ester compound **6b** gave better acaricidal activity than methyl ester **6a** and benzyl ester compound **6c** but much lower than compound **1**, which indicates that the substituent at 2-position of pyrrole is very important for the compounds' activity.

In summary, we have developed a new organic synthetic method about trifluoromethyl group converting to corresponding carboxamide or carboxylate, and this method has been used to yield a series of 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carbox-



Scheme 4. Alternative method for **6a**.

Table 1
Insecticidal and acaricidal activities of compounds **3–6** against oriental armyworm, spider mite, larvae of spider mite, and eggs of spider mite (Mortality (%) at concentration (mg kg^{-1}).)

	R^1	R^2	Oriental armyworm				Spider mite		Larvae of spider mite		Eggs of spider mite	
			200	100	50	25	200	100	200	100	200	100
3b	H	*p*-CF_3-phenyl	0	—	—	—	0	—	0	—	0	—
4	H	*p*-CF_3-phenyl	0	—	—	—	0	—	0	—	0	—
5a	H	*p*-CF_3-phenyl	0	—	—		0	—	0	—	0	—
5b	H	Cyclohexyl	80	—	—	—	0	—	0	—	0	—
5c	Ethyl	Ethyl	0	—	—	—	0	—	0	—	0	—
5d	H	Benzyl	0	—	—	—	0	—	0	—	0	—
6a	Methyl	—	100	100	40	0	60	—	40	—	0	—
6b	Ethyl	—	100	100	60	0	78	40	76	52	81	54
6c	Benzyl	—	100	100	100	0	0	—	0	—	0	—
1	—	—	100	100	100	100	100	100	100	100	100	100
Chlorfenapyr			100	100	100	100	100	100	100	100	100	100

amide derivatives (**5a–5d**) and a series of 3-bromo-5-(4-chlorophenyl)-4-cyanopyrrole-2-carboxylate derivatives (**6a–6c**) in relatively mild reaction conditions. Their structures were characterized by ^{1}H NMR spectroscopy, elemental analysis, high-resolution mass spectrometry or X-ray diffraction. The results of bioassays indicated when CF_3 was changed to carboxamide, the bioactivity seriously decreased. But pyrrole-2-carboxylate **6** had moderate larvicidal activity against oriental armyworm and certain acaricidal activity, so pyrrole-2-carboxylate was expected to become precursors which could be modified for new pesticides.

Acknowledgments

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Supplementary data

Supplementary data (experimental detail, characterization of target compounds, X-ray diffraction data and bioassay method were provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.09.036.

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