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Synthesis of functionalized 2,2′- and 2,3′-bipyrroles via 3-imino-3*H*-pyrrolizine-2-carbonitriles

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ABSTRACT

A novel strategy for the synthesis of 4-amino-3-cyano-2,2′- and 5′-amino-4′-cyano-2,3′-bipyrroles via readily available 1-amino-3-imino-3*H*-pyrrolizine-2-carbonitriles has been developed. The rearrangement leading to 5′-amino-4′-cyano-2,3′-bipyrroles involves formation of the intermediate aziridine, which undergoes other side ring-opening.

The bipyrrole scaffold occurs in many natural products,[1,2] pigments, porphyrin mimics,[3] compounds used for anion recognition and in the design of self-assembly systems.[4] Bipyrroles have sparked interest as building blocks for the synthesis of isomeric and expanded forms of porphyrins such as rubyrin, rosarin,[4] *meso*-substituted [34]octaphyrin(1.1.1.0.1.1.1.0) and cyclo[8]pyrroles.[5] They also attract attention as a synthetic intermediate towards antitumor medicines (prodigiosins,[6] sapphyrins[7]), radiation sensitizers[7,8] photodynamic cancer therapy and antimalarial agents.[9]

The strong interest in this structural unit has resulted in the development of a vast amount of synthetic research in this area. Classic approaches to 2,2′-bipyrrole syntheses include oxidative,[10] Ullman-type homocouplings[10a,11] or the condensation of pyrrolinones with pyrroles.[12] The first two methods are limited to the preparation of symmetrical 2,2′-bipyrroles, while the third one allows a few unsymmetrical 2,2′-bipyrroles to be synthesized. The latter were sporadically obtained by Paal-Knorr condensation,[13] Suzuki coupling,[6a,d,9] aza-Nazarov[14] and Trofimov reactions,[15] from 2-cyanopyrroles and substituted cyclopropanes,[16] or from pyrrolylbutenyl ketones.[6b]

In contrast to the numerous syntheses of 2,2′-bipyrroles, fewer methods for the preparation of 2,3′-bipyrroles, mostly in low yields, are known to date.[9,10b–e,17–21] The most efficient of these include a phenyliodine(III) bis(trifluoroacetate)-induced oxidative coupling of *N*-substituted pyrroles,[10b–e] the 1,3-dipolar cycloaddition of *N*-protected 2-nitrovinylpyrroles with unsymmetrical 1,3-oxazolium-5-olates,[20] the Suzuki coupling of 4-bromo-pyrrole-2-carboxaldehydes with *N*-Boc-2-pyrroleboronic acid,[9] and the reaction of (1-methoxy-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-yn-1-yl)lithium with isothiocyanate.[21] Most of these were of narrow substrate scope.

It is important for this communication to note that only one protocol for the synthesis of bipyrroles with an amino group has been described,[22] but none for a cyano substituent and, moreover, for the combination of these two functionalities. The synthesis of bipyrroles with amino substituents includes multi-step procedures starting from 4-oxo-*N*-(PhF)prolinate. It is important to emphasize that bipyrroles, both 2,2′- and 2,3′-bearing neighboring amino and cyano functions, might be precursors of purine analogues, including pyrrolotetrazines,[23] pyrrolotriazines,[24] pyrrolopyridines,[25] pyrrolopyrimidines,[26] and in this case, for their unknown families with a second pyrrole ring.

Herein, we describe a convenient strategy for the synthesis of 2,2′- and 2,3′-bipyrroles with neighboring amino and cyano groups. This is a continuation of the previously developed carbodithioation of substituted pyrroles with CS_2 in a KOH/DMSO system.[27] The pyrrole-2-carbodithioates obtained were then easily transformed into 1-amino-3-imino-3*H*-pyrrolizines (Scheme 1).[28,29]

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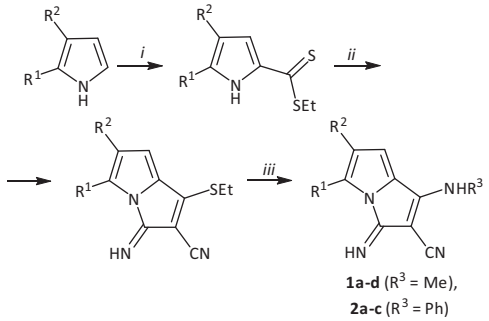
0040-4039/



Scheme 1. Synthesis of 1-amino-3-imino-3*H*-pyrrolizines **1a**–**d** and **2a**–**c**. Reagents and conditions: *i*: (a) CS_2, KOH/DMSO, (b) EtI; *ii*: (a) $CH_2(CN)_2$, KOH/DMSO, (b) EtI; *iii*: R^3NH_2.

The readily accessible pyrrolizines **1a**–**d**, **2a**–**c** served as starting materials for the synthesis of functionalized 2,2′- and 2,3′-bipyrroles.

When 1-methylamino-3-imino-3*H*-pyrrolizines **1a**–**d** were treated with 1-chloroacetophenone, 2,2′-bipyrroles **3a**–**d** were formed in yields of 20–54% (Table 1).

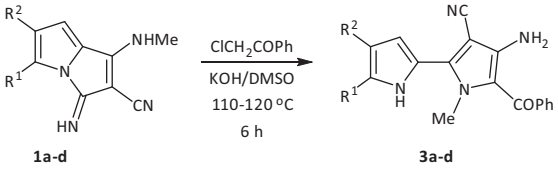
The reaction was carried out by the portion-wise addition of 1-chloroacetophenone (1.75 equiv) to a stirred suspension of pyrrolizine **1a**–**d** (1 equiv) and KOH (1.5 equiv) in DMSO over 4 h, followed by stirring for an additional 2 h. The excess of 1-chloroacetophenone and its gradual addition were found to be crucial to avoid the undesirable conversion of α-halo ketones in the presence of base.[30]

Surprisingly, when the methylamino substituent in the pyrrolizine ring was replaced by a phenylamino group, 2,3′-bipyrroles **4a**–**c**, instead of the expected 2,2′-bipyrroles, were isolated in yields of 5–10% (Table 2).

In this case, along with 2,3′-bipyrroles, 1-anilino-2,2-dicyanoethenylpyrroles **5a**–**c** and 3-imino-1-[(2-oxo-2-phenylethyl)anilino]-3*H*-pyrrolizine-2-carbonitriles **6a**–**c** were also formed in yields of 35–41% and 14–15%, respectively (Fig. 1).

The ketones **6a**–**c** are likely to be intermediates in the synthesis of 2,3′-bipyrroles since their further heating (110–120 °C) in

Table 1
Synthesis of 2,2′-bipyrroles **3a–d** from pyrrolizines **1a–d** and 1-chloroacetophenone



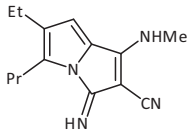
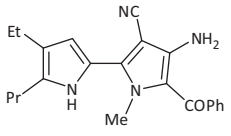
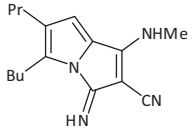
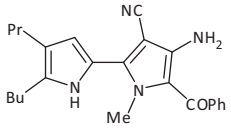
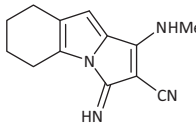
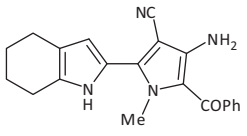
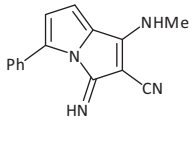
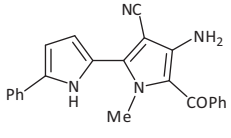
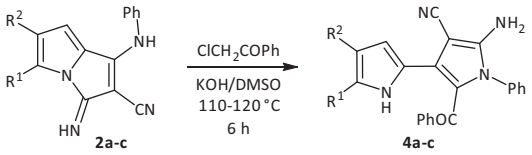
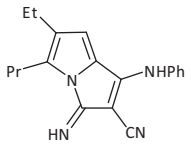
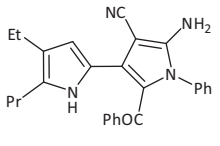
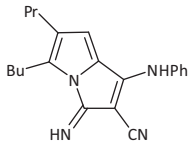
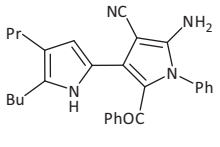
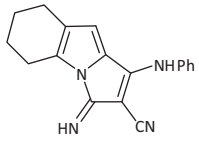
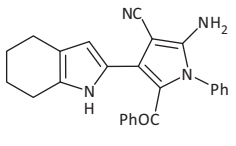
Entry	Pyrrolizine	2,2′-Bipyrrole	Yield (%)
1	 **1a**	 **3a**	54
2	 **1b**	 **3b**	48
3	 **1c**	 **3c**	40
4	 **1d**	 **3d**	20

Table 2
Synthesis of 2,3′-bipyrroles **4a–c** from pyrrolizines **2a–c** and 1-chloroacetophenone



Entry	Pyrrolizine	2,3-Bipyrrole	Yield (%)
1	 **2a**	 **4a**	10
2	 **2b**	 **4b**	7
3	 **2c**	 **4c**	5

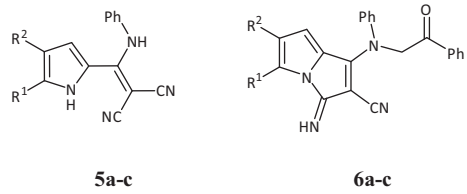
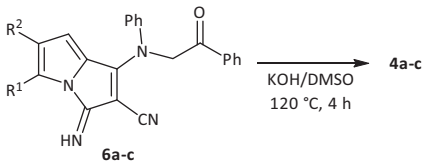
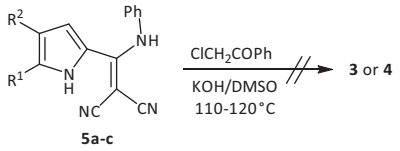


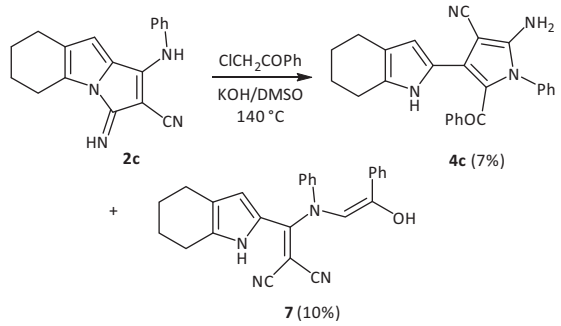
Figure 1. 1-Anilino-2,2-dicyanoethenylpyrroles **5a**–**c** and 3-imino-1-[(2-oxo-2-phenylethyl)anilino]-3*H*-pyrrolizine-2-carbonitriles **6a**–**c**.



Scheme 2. Synthesis of 2,3′-bipyrroles **4a**–**c** from ketones **6a**–**c**.



Scheme 3. Reaction of 1-anilino-2,2-dicyanoethenylpyrroles **5a-c** with 1-chloroacetophenone.



Scheme 4. Reaction of 1-anilino-3-imino-3*H*-pyrrolizine **2c** with 1-chloroacetophenone in KOH/DMSO at 140 °C.

KOH/DMSO for 4 h resulted in the formation of additional amounts of the respective 2,3′-bipyrroles (13–23%). Thus, the overall yield of this two-step procedure ranges from 19% to 33% (Scheme 2).

It is worth noting that 1-anilino-2,2-dicyanoethenylpyrroles **5a**–**c**, when reacted with 1-chloroacetophenone under the above conditions, did not give either 2,2′- or 2,3′-bipyrroles suggesting that they are not intermediates in the bipyrrole synthesis (Scheme 3).

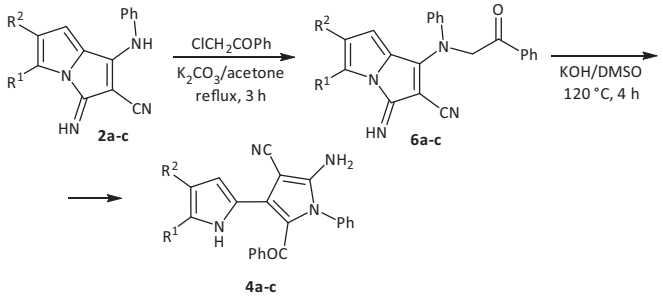
As shown in the example of 1-anilino-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indole-2-carbonitrile (**2c**), a temperature increase (140 °C) did not improve the yield of 2,3′-bipyrrole **4c**. In this case, enol **7**, the tautomer of the expected ketone **6c**, was also isolated in 10% yield (Scheme 4).

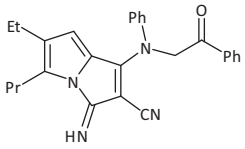
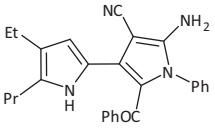
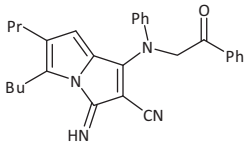
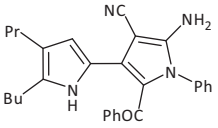
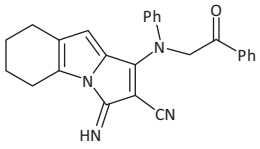
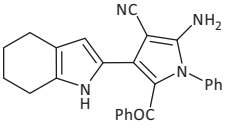
The same reaction using the Cs_2CO_3/DMSO system at 120 °C gave a 13% (22% based on the conversion of **2c**) yield of 2,3′-bipyrrole **4c** and a 13% yield of enol **7**, with the conversion of the starting compound **2c** being 59%.

Furthermore, 2,3′-bipyrroles **4a-c** were obtained in 12–26% yield via the reaction of pyrrolizines **2a**–**c** with 1-chloroacetophenone in the K_2CO_3/acetone system (reflux, 3 h) to deliver ketones **6a**–**c** (37–65% yield), which were converted to the target products **4a**–**c** using the following conditions: KOH/DMSO, 120 °C, 4 h (Table 3).

We also carried out the reaction of intermediate **6a** with *t*-BuOK/DMSO (120 °C, 2 h). Surprisingly, the expected 2,3-bipyrrole **4a** was not formed. Instead, unidentified products were formed in a gum-like reaction mixture (^{1}H NMR data).

Table 3
Synthesis of 2,3′-bipyrroles **4a–c** via ketones **6a–c**



Entry	Ketone **6**	Yield (%)	2,3′-Bipyrrole	Yield (%)
1	 **6a**	65	 **4a**	12
2	 **6b**	37	 **4b**	26
3	 **6c**	54	 **4c**	14

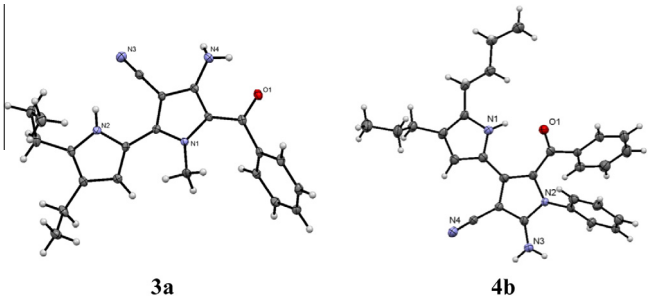
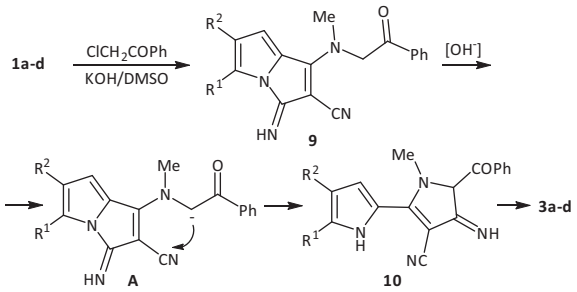
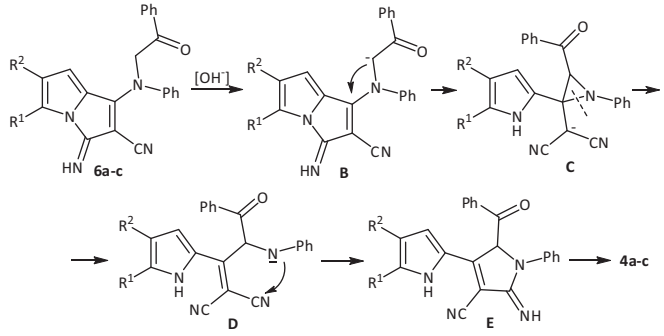


Figure 2. Single crystal X-ray structures of 2,2′-bipyrrole **3a** and 2,3′-bipyrrole **4b**.



Scheme 5. Proposed mechanism for 2,2′-bipyrrole **3a–d** formation.



Scheme 6. Proposed mechanism for 2,3′-bipyrrole **4a–c** formation.

To suppress the formation of side-products **5a–c**, we investigated the reaction of pyrrolizine **2a** with 1-chloroacetophenone using a milder base (K_3PO_4/DMSO, 120 °C, 6 h) and also under standard phase-transfer conditions (TEBA, 50% aqueous NaOH, benzene, 60–70 °C, 6 h). However, in the first case pyrrole **5a** was obtained, and in the second case the starting pyrrolizine **2a** was recovered almost quantitatively.

Single crystal X-ray diffraction images of 2,2′-bipyrrole **3a** and 2,3′-bipyrrole **4b** are shown in Figure 2.

The mechanism for the formation of 2,2′-bipyrroles can be rationalized as depicted in Scheme 5. 1-Methylaminopyrrolizines **1a–d** are alkylated with 1-chloroacetophenone to give ketones **9**. Their carbanions **A** intramolecularly attack the cyano group with simultaneous pyrrolizine ring-opening (due to the relief of steric strain) to give, after re-protonation, pyrrolyliminopyrrolines **10**, which further aromatize to give 2,2′-bipyrroles **3a–d** (Scheme 5).

A plausible mechanism for the extraordinary rearrangement leading to 5′-amino-4′-cyano-2,3′-bipyrroles **4** may involve the following transformations (Scheme 6). Ketones **6a–c** in their carbanionic forms **B** intramolecularly attack the C–C double bond with simultaneous pyrrolizine ring-opening (caused by the relief of steric strain) to give the intermediate carbanionic aziridines **C**. The latter undergo ring-opening from the other side to give aniline-anions **D**, which intramolecularly attack the cyano group to afford pyrrolyliminopyrrolines **E** which are subsequently transformed into 2,3′-bipyrroles **4** (Scheme 6).

A driving force of the alternative recyclization in the case of anilino derivatives **2a–c** is likely to be the formation of *N*-phenyl anionic moieties, more stable than the corresponding *N*-methyl anionic intermediates, which could be formed from *N*-methyl-amino pyrrolizines **1a–d**.

In conclusion, the reaction of 1-amino-3-imino-3*H*-pyrrolizine-2-carbonitriles with 1-chloroacetophenone in a KOH/DMSO or Cs_2CO_3/DMSO system affords 4-amino-3-cyano-2,2′-bipyrroles (in the case of 1-methylamino-3-imino-3*H*-pyrrolizine-2-carbonitriles) or 5′-amino-4′-cyano-2,3′-bipyrroles (in the case of 1-anilino-3-imino-3*H*-pyrrolizine-2-carbonitriles), bearing neighboring amino and cyano functional groups. These previously inaccessible functionalized bipyrroles may serve as precursors for purine analogues with a pyrrole ring.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data, copies of ^1H, ^{13}C NMR spectra and single crystal X-ray data for **3a** and **4b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.006.

References and notes

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