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Bicyclization of Isocyanides: A Synthetic Strategy for Fused Pyrroles

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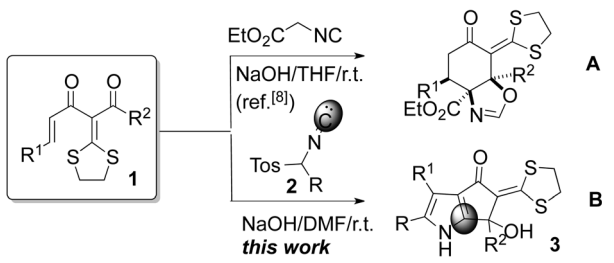
Abstract: On the isocyanide carbon atom, two C–C sigma bonds are formed in the bicyclization reaction of the readily available acyclic substrates with tosylmethyl isocyanides. The reaction can proceed under extremely mild and metal-free conditions to give the products in high to excellent yields. The powerful potential of this strategy deserves attention because it is a new paradigm for trapping of the incipient imidoyl anion, by a carbon electrophile instead of a proton.

Keywords: bicyclization; fused pyrroles; imidoyl anion trapping; isocyanides; tandem reactions

Although the reaction of methyl isocyanides with acceptor-substituted alkenes to furnish pyrrole and dihydropyrrole derivatives *via* [3+2]cycloaddition has found ample application,[1–3] the utility of isocyanides in such reactions remains to be explored because the highly reactive imidoyl anion intermediate has been exploited only for trapping a proton.[1–4] In our research to develop new domino reactions using ethyl isocyanoacetate as the Michael donor,[5,6] a synthesis of fused oxazolines, from the base-promoted reaction of alkenoyl ketene dithioacetals (**1**)[7] with ethyl isocyanoacetate, was described [Scheme 1 (**A**)].[8] During the course of these studies, surprisingly, it was found that the reaction of **1** with tosylmethyl isocyanides (TosMICs) **2** could lead to the formation of cyclopenta[*b*]pyrroles **3** [Scheme 1 (**B**)]. We report here on the new bicyclization methodology, which represents an important extension of the classical pyrrole synthesis, by the formation of two C–C sigma bonds on the isocyanide carbon atom.



Scheme 1.

Cyclopenta[*b*]pyrroles can be constructed starting from pyrroles[9] and five-membered carbon rings,[10] respectively. On the other hand, several procedures have been reported for their synthesis from acyclic precursors, such as the $W(CO)_5$(L)-catalyzed reaction of dienol silyl ethers,[11a] the Rh(l)-catalyzed hydroformylation of 1,4-diolefins in the presence of primary amines (in 11–40% isolated yield),[11b] the pyrrolidine-mediated reaction of 3,5-disubstituted 1,2,4-triazines with cyclobutanone (in 38–50% isolated yield),[11c] and the methods used in the synthesis of the antibiotic roseophilin (Figure 1).[12] Clearly, a convenient general method for the preparation of cyclopenta[*b*]pyrrole derivatives is highly desired.

It was found that, under identical conditions as described for the synthesis of fused oxazolines [Scheme 1 (**A**)],[8] the reaction of alkenoyl ketene dithioacetal **1a** (1.0 mmol) with TosMIC **2a** (1.1 equiv.) promoted by NaOH (1.1 equiv.) in THF (10 mL) at room temperature gave cyclopenta[*b*]pyrrole **3a** and pyrrole **4a**, respectively (Scheme 2). This reaction showed the significantly different performances between TosMIC **2a** and ethyl isocyanoacetate.

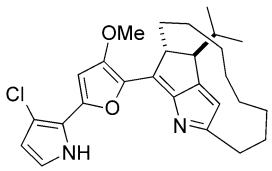
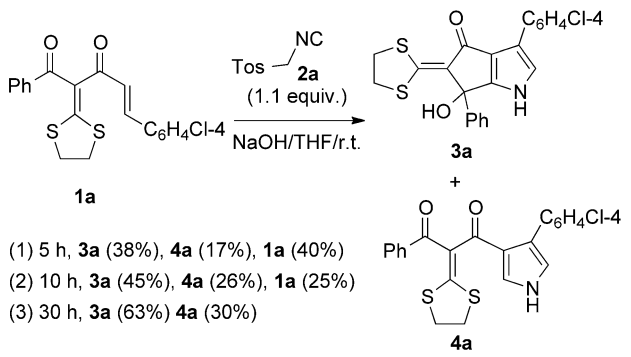


Figure 1. Structure of roseophilin.



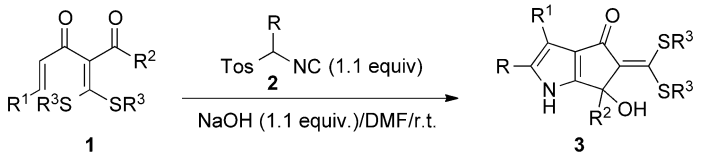
Scheme 2.

In view of the novelty of the above bicyclization reaction based on methyl isocyanides and the simplicity of the synthesis of cyclopenta[*b*]pyrroles **3**, the generality of the method was investigated (Table 1). To our delight, after optimization of the reaction conditions, cyclopenta[*b*]pyrrole **3a** was prepared in 91% yield by performing the reaction of **1a** (1.0 mmol) with TosMIC **2a** (1.1 equiv.) promoted by NaOH (1.1 equiv.) in DMF (10 mL) for only 1.8 h (Table 1, entry 1). From the experimental results, it is clear that the reactions of TosMIC **2a** (R = H) with alkenoyl ketene dithioacetals **1a–f** [R^2 = Ph, R^3,R^3 = $(CH_2)_2$] having alkyl (entry 6), phenyl (entry 2), electron-rich (entry 3), electron-deficient (entry 1) aryl, or heteroaryl groups (entries 4 and 5) at the β-position of the enone moiety can give the corresponding cyclopenta[*b*]pyrroles **3a–f** in high to excellent yields.[13] In addition, the reactions of **2a** with alkenoyl ketene dithioacetals **1** bearing a phenylvinyl (**1g**, entry 7), or alkyl (**1j**, entry 10) R^2 group can also lead to the desired cyclopenta[*b*]pyrroles **3g** and **3j** in 93 and 82% yields, respectively. As illustrated in entries 8, 9 (R^2 = 4-$CH_3C_6H_4$) and 10, 11 [R^3,R^3 = $(CH_2)_3$], the compatibility of the reaction to various functional groups in the alkenoyl ketene dithioacetals **1** and high product yields further demonstrate the usefulness of this bicyclization reaction.

It was noted that, although the alkenoyl ketene dithioacetal substrates **1l** and **1m** (R^3 = Me), are prone to undergo a [5+1] annulation reaction when reacted with active methylene compounds,[7,14] in the current research, the reactions of **1l** and **1m** with **2a** proceed regiospecifically to give cyclopenta[*b*]pyrroles **3l** and **3m**, respectively, in high yields (entries 12 and 13). Moreover, cyclopenta[*b*]pyrroles **3n–p** were prepared from the reactions of **1a** with TosMICs **2b** (R = Me), **2c** (R = Bn) and **2d** (R = allyl), respectively, under identical conditions in excellent yields (Table 1, entries 14–16).

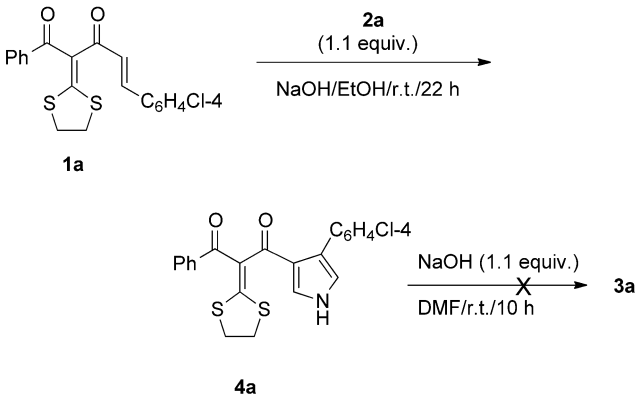
To understand the reaction mechanism, the reaction of **1a** with **2a** was performed in a protic solvent. As a result, 3,4-disubstituted pyrrole **4a** was obtained in 40% yield from the reaction of **1a** (1.0 mmol) with **2a**

Table 1. Synthesis of cyclopenta[*b*]pyrroles **3**.



Entry[a]	R^1	R^2	R^3, R^3	R	Time [h]	**3**	Yield [%][b]
1	4-Cl-C_6H_4	Ph	$(CH_2)_2$ (**1a**)	H (**2a**)	1.8	**3a**	91
2	Ph	Ph	$(CH_2)_2$ (**1b**)	H (**2a**)	2.0	**3b**	92
3	4-Me-C_6H_4	Ph	$(CH_2)_2$ (**1e**)	H (**2a**)	3.0	**3c**	91
4	2-furyl	Ph	$(CH_2)_2$ (**1c**)	H (**2a**)	5.5	**3d**	91
5	2-thienyl	Ph	$(CH_2)_2$ (**1d**)	H (**2a**)	6.0	**3e**	89
6	*t*-Bu	Ph	$(CH_2)_2$ (**1f**)	H (**2a**)	40	**3f**	87
7	Ph	PhCH=CH	$(CH_2)_2$ (**1g**)	H (**2a**)	2.3	**3g**	93
8	4-Cl-C_6H_4	4-Me-C_6H_4	$(CH_2)_2$ (**1h**)	H (**2a**)	2.5	**3h**	88
9	Ph	4-Me-C_6H_4	$(CH_2)_2$ (**1i**)	H (**2a**)	3.0	**3i**	90
10	4-Me-C_6H_4	Me	$(CH_2)_3$ (**1j**)	H (**2a**)	2.5	**3j**	82
11	4-Cl-C_6H_4	Ph	$(CH_2)_3$ (**1k**)	H (**2a**)	1.0	**3k**	89
12	4-Cl-C_6H_4	Ph	Me, Me (**1l**)	H (**2a**)	2.0	**3l**	87
13	4-Cl-C_6H_4	4-Me-C_6H_4	Me, Me (**1m**)	H (**2a**)	2.2	**3m**	87
14	4-Cl-C_6H_4	Ph	$(CH_2)_2$(**1a**)	Me (**2b**)	5.5	**3n**	91
15	4-Cl-C_6H_4	Ph	$(CH_2)_2$ (**1a**)	Bn (**2c**)	7.0	**3o**	92
16	4-Cl-C_6H_4	Ph	$(CH_2)_2$ (**1a**)	allyl (**2d**)	7.0	**3p**	87

[a] Substrate **1** (1.0 mmol) in DMF (10 mL).
[b] Yield of isolated products.



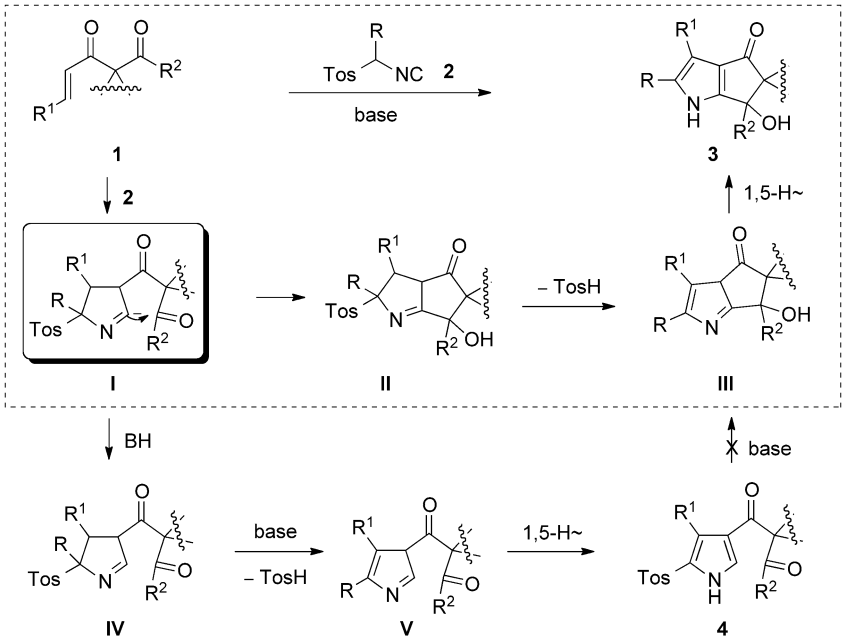
Scheme 3. Preparation of 3,4-disubstituted pyrrole **4a**.

(1.1 mmol) in the presence of NaOH (1.1 equiv.) in ethanol (10 mL) for 22 h, along with the recovery of **1a** in 55% yield (Scheme 3). This result is in accordance with the van Leusen pyrrole synthesis (for reaction mechanism, see Scheme 4).[1]

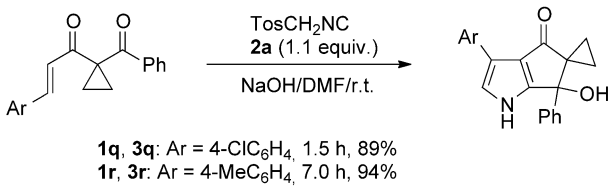
Further experiment showed that no cyclopenta[*b*]pyrrole **3a** could be detected by treatment of **4a** under identical conditions as in Table 1, indicating that cyclopenta[*b*]pyrroles **3** could not be formed *via* cyclization of pyrroles **4** (Scheme 3). Taken together, the present results (Table 1, Scheme 2 and Scheme 3) and related reports,[1–3,15,16] a plausible mechanism for the formation of cyclopenta[*b*]pyrroles **3** and pyrrole **4** is proposed in Scheme 4.

The overall process may involve (i) a formal [3+2]cycloaddition of TosMIC **2** with Michael acceptor **1** under basic conditions to provide the imidoyl anion intermediate **I**;[1,2] (ii) intramolecular trapping of the resulting anion **I** by the tethered carbonyl group (intermediate **I**→**II**) followed by elimination of tosylic acid (intermediate **II**→**III**); and finally (iii) 1,5-sigmatropic hydrogen shift to furnish cyclopenta[*b*]pyrroles **3**. Therefore, the whole process can be considered as a tandem [3+2]cycloaddition/cyclization sequence and the key feature of the reaction is the intramolecular trapping of the incipient imidoyl anion species **I** by the electrophilic terminal carbonyl carbon. On the other hand, protonation of anion **I** seems to be a dominant process in a protic solvent (Scheme 4, intermediate **I**→**IV**). In such a case, pyrrole **4** is formed (Scheme 4, **IV**→**V**→**4**). The latter case is common not only in the van Leusen pyrrole synthesis,[1] but also in almost all [3+2]cycloaddition reactions based on methyl isocyanides,[1–4,6,7] including α-metalated isocyanides.[15]

Very recently, a copper-catalyzed tandem reaction of methyl isocyanides with 1-(2-haloaryl)-ynones involving intramolecular trapping of the relevant organocopper intermediate was reported by Cai and coworkers [reaction conditions: CuI (0.1 equiv.), Cs_2CO_3 (2.0 equiv.) at 90 °C].[16] Therefore, our results (Table 1) represent the first direct evidence that the imidoyl anion species generated in the pyrrole synthesis can be trapped by a carbon electrophile.[1–4,6–8,15–17] To test the generality of this new approach, the reactions of TosMIC **2a** with selected substrates **1**, pent-4-ene-1,3-diones **1q** and **1r** bearing a cyclopropane ring, were examined under identical conditions as in Table 1. Fortunately, cyclopenta[*b*]pyrroles **3q** and **3r**



Scheme 4. Proposed mechanism for formation of **3** and **4**.



Scheme 5. Synthesis of cyclopenta[*b*]pyrroles **3q** and **3r**.

were prepared in excellent yields, respectively (Scheme 5).

Finally, it should be emphasized that a comparison of the present work (Table 1, Scheme 2 and Scheme 5) with previous results shows the significantly different performance between TosMIC and ethyl isocyanoacetate. The reaction of alkenoyl ketene dithioacetals **1** with ethyl isocyanoacetate gave fused oxazolines *via* a base-catalyzed tandem Michael addition/intramolecular isocyanide [3+2] cycloaddition, in which the cycloaddition involves the terminal carbonyl group behaving as the dipolarophile [Scheme 1, (**A**)].[8] In contrast, the terminal carbonyl carbon of **1** is acting as an electrophilic center to trap the initially formed imidoyl anion species in the present work (Scheme 4).

In conclusion, a variety of cyclopenta[*b*]pyrroles was synthesized in high to excellent yields under extremely mild and metal-free conditions from simple acyclic precursors in a single step. This tandem bicyclization reaction exhibits not only a highly efficient use of the reactive sites in the substrates, but also a new application of methyl isocyanides through intramolecular trapping of the incipient imidoyl anion species. The powerful potential of this strategy deserves more attention, because two C–C sigma bonds are formed on the isocyanide carbon atom in a single step. In addition, the significantly different performances between TosMIC and ethyl isocyanoacetate were also observed. Further studies are in progress.

Experimental Section

General Procedure for the Synthesis of 3 (3a as Example)

To the solution of **1a** (386 mg, 1.0 mmol) and tosylmethyl isocyanide **2** (215 mg, 1.1 mmol) in DMF (10 mL) was added NaOH (4.4 mg, 1.1 mmol) in one portion. The reaction mixture was stirred at room temperature until **1a** was consumed as indicated by TLC. The resulting mixture was then poured into brine (30 mL) under stirring. The solid was collected by filtration, washed with water (3×10 mL), and dried under vacuum to afford the crude product, which was purified by flash chromatography on silica gel (petroleum ether/EtOAc=6:1) to give **3a** as a yellowish solid; yield: 387 mg (91%); mp 193–195 °C. ^{1}H NMR (DMSO-d_6, 500 Hz): δ= 2.98–3.03 (m, 1H), 3.15–3.20 (m, 1H), 3.23–3.28 (m, 1H), 3.30–3.34 (m, 1H), 6.37 (s, 1H, OH), 7.19 (t, J=7.5 Hz, 1H), 7.27 (t, J=7.5 Hz, 2H), 7.32 (d, J=7.5 Hz, 2H), 7.36 (s, 1H), 7.39 (d, J=8.0 Hz, 2H), 8.10 (d, J=8.0 Hz, 2H) 11.7 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 Hz): δ=36.4, 37.0, 74.8, 118.8, 123.2, 124.3, 126.0, 126.9, 127.8, 127.9, 128.5, 130.3, 133.1, 135.3, 141.9, 150.9, 159.4, 181.9; HR-MS (ESI-TOF): m/z=426.0388, calcd for $C_{22}H_{17}ClNO_2S_2^+$ ([M+H]$^+$): 426.0384.

Acknowledgements

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