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A multicomponent bicyclization reaction of isocyanide, allenate, imine and water to synthesize pyrrolidine-fused rings†

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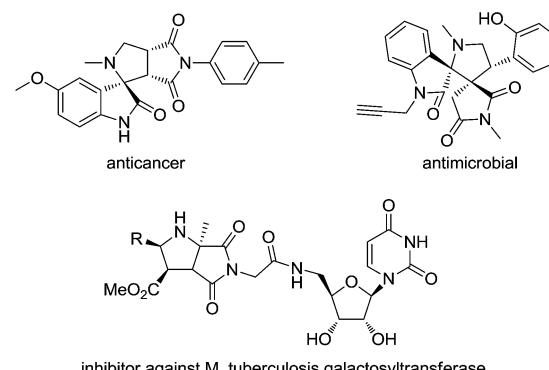
A multicomponent bicyclization of isocyanide, allenate, imine, and water has been disclosed. This protocol involves the formation of five chemical bonds (two C–C, two C–N, and one C–O), thus providing a new pathway to structurally unusual fused rings.

Isocyanide is a fascinating one-carbon synthon that is widely used in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions.^{1,2} In particular, the reactivity of isocyanide to undergo an α -addition with both an electrophile and a nucleophile has made isocyanide a particularly significant reaction partner in multicomponent reactions (IMCRs)³ ever since the classical Ugi and Passerini reactions. To date, the isocyanide-based multicomponent reaction has become a powerful synthetic tool in organic synthesis.^{4,5} Recently, the multicomponent bicyclization reactions (MBRs) have enjoyed considerable attention from the organic chemistry community.⁶ Notably, the isocyanide-based bicyclization reactions (IMBRs) as multiple-bond forming processes allow the rapid synthesis of structurally complex drug-like molecules, which make them superior to traditional methods.⁷

Pyrrolidines are important heterocycles that are frequently found in numerous natural products,⁸ bioactive molecules,⁹ as well as organocatalysts¹⁰ in organic synthesis. In this regard, much effort has been devoted to the synthesis of such scaffolds. Among these structures, bicyclic pyrrolidine frameworks bearing pyrrolidine-2,5-dione are found to show significant biological activities, including anticancer and antimicrobial activities.¹¹ A structurally unique pyrrolidine containing diester linkage to the 5'-position of uridine was proven to be inhibitor against *M. tuberculosis* galactosyltransferase enzyme (Scheme 1).¹² Traditionally, these compounds were prepared using [3 + 2] 1,3-dipolar cycloadditions of azomethine ylides with a variety of alkenes or alkynes, thus offering a good tool for the

construction of chiral pyrrolidine scaffolds.¹³ Recently, Zhao and co-workers has reported that organocatalytic [3 + 2] cycloaddition of isatin-derived azomethine ylides with alkenes or alkynes to the enantioselective synthesis of structurally complex, and potentially bioactive pyrrolidine-fused spirooxindoles.¹⁴ Although much progress has been made in the past decades, most of the methods seemed to suffer from insufficient synthetic efficiency since only one ring can be formed in these reactions. As a consequence, there is continues demand to development new strategies to synthesize such scaffolds in an efficient manner.

In the past several years, we have spent much time in the synthesis of heterocycles using isocyanides as versatile building blocks.^{7a–7d,15} As such, many interesting and valuable results were developed. Of late, we have established that the multiple and double isocyanide insertion reaction could serve as efficient tool for the construction of spirooxindole and indole-fused polycyclic rings, respectively.^{15a,15b} Before that, we have initiated a very interesting research program aimed at exploiting the application of isocyanide-based multicomponent reactions involving isocyanide since our first example was developed in 2011.^{15c–15e} In particular, we have also proven that this protocol



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Scheme 1 Representative reactivity mode of isocyanide-based multicomponent reactions involving allenate.



provided a new opportunity for the generation of structurally complex bicyclic derivatives with high synthetic efficiency when substituted allenoates were used.^{7a–7d} The experimental outcome revealed that carbon carbon double bond and carbon oxygen double bond could both compatible in the above-mentioned cycloaddition. However, no successful example using carbon nitrogen double bond as electron-deficient system was ever reported. As a continuation of our previous work, we report the four-component reaction of isocyanide, allenoate, imine, and water to synthesize structurally complex pyrrolidine-fused rings. This strategy also represents the first example using carbon nitrogen double bond electron-deficient system in isocyanide-based multicomponent reaction involving allenoate.

Initially, we began the experiment investigation by selecting *n*-butyl isocyanide **1a**, allenoate **2a**, and imine **3a** as model substrate. In the presence of water, heating the mixture in toluene solution under reflux essentially led to the formation of cycloadduct **4a** in 65% yield (Table 1, entry 1). Furthermore, the structure of compound **4a** was unambiguously confirmed by single-crystal X-ray analysis (Fig. 1).¹⁶ The replacement of toluene with other solvents such as CH₃CN, THF, and DMF only led to decreased yield. The experimental outcome revealed that 50% yield of product **4a** was generated when one equivalent water was added. Poor performance was also observed when the reaction was conducted under lower temperature. The optimization experiment also showed that a slightly excessive amount of allenoate **2a** (1.2 equiv.) could facilitate the formation of product **4a** (65%), while the employment of excessive isocyanide **1a** only led to lower yield (57%). With the optimized conditions in hand, we then focused our attention to investigate the substrate scope with regard to different imine **3**. As shown in

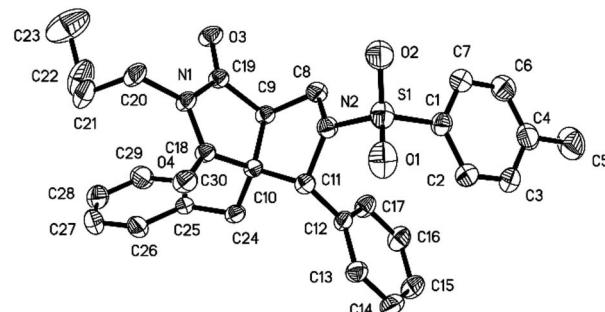
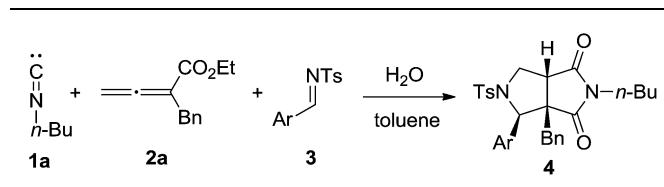


Fig. 1 X-Ray structure of compound **4a**.

Table 1, various substituted imines **3** with electron-withdrawing groups (entries 2–6) and electron-donating substituents (entries 7–10) on the aromatic ring were firstly used to react under optimized conditions and all new compounds **4** were characterized by ¹H NMR, ¹³C NMR, and HRMS spectra.¹⁷ Our experimental findings showed that halide and methoxy group substitution on the aromatic ring was well tolerated, which was potentially useful for further functionalization. Furthermore, the present reaction was not limited to simple substrates bearing mono-substituent on the aromatic ring, dimethyl-substituted imines **3k** and **3l** were also proven to be good reaction components in the present transformation to produce **4k** and **4l** (entries 11–12).

After a broad imine scope was established, changing substituent on the aromatic ring at α -position of substrate **2** was subsequently carried out. As shown in Table 2, a series of substituted allenoates **2** were employed to react with isocyanide **1a**, imine **3a**, and water under the optimized conditions. Gratifyingly, all reactions proceeded smoothly to give the desired

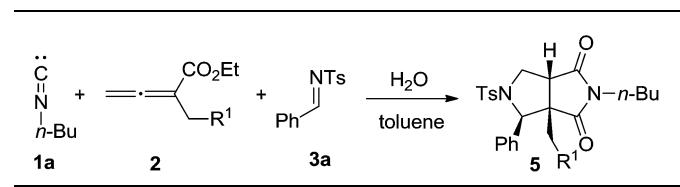
Table 1 Scope of the MCR reaction with respect to the imine substrate **3**^a



Entry	Ar	Product	Yield ^b (%)
1	C ₆ H ₅	4a	65
2	2-ClC ₆ H ₄	4b	81
3	4-ClC ₆ H ₄	4c	79
4	2-BrC ₆ H ₄	4d	82
5	3-BrC ₆ H ₄	4e	71
6	4-BrC ₆ H ₄	4f	85
7	2-MeC ₆ H ₄	4g	73
8	3-MeC ₆ H ₄	4h	75
9	4-MeC ₆ H ₄	4i	76
10	4-MeOC ₆ H ₄	4j	61
11	2,3-Me, MeC ₆ H ₄	4k	78
12	2,4-Me, MeC ₆ H ₄	4l	79

^a Reaction conditions: 0.5 mmol isocyanide **1a**, 0.6 mmol allenoate **2a**, 0.5 mmol imine **3** in 5 mL solvent (toluene/H₂O (v/v) = 6 : 1), reflux, 12 hours. ^b Yields of product after silica gel chromatography.

Table 2 Scope of the MCR reaction with respect to the allenoate substrate **2**^a



Entry	R ¹	Product	Yield ^b (%)
1	3-ClC ₆ H ₄	5a	70
2	4-ClC ₆ H ₄	5b	82
3	3-BrC ₆ H ₄	5c	74
4	4-BrC ₆ H ₄	5d	78
5	4-FC ₆ H ₄	5e	85
6	2-MeC ₆ H ₄	5f	66
7	3-MeC ₆ H ₄	5g	68
8	4-MeOC ₆ H ₄	5h	60
9		5i	80

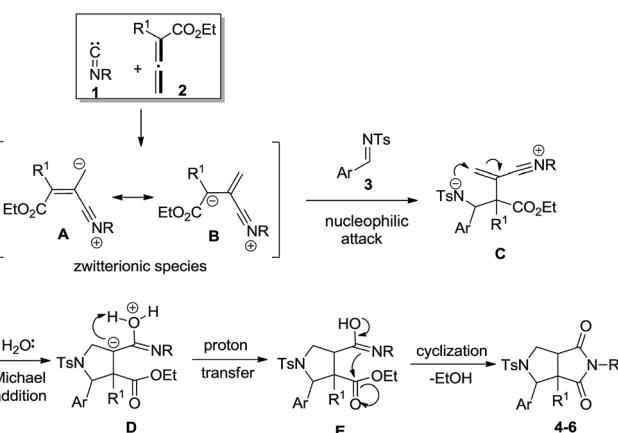
^a Reaction conditions: 0.5 mmol isocyanide **1a**, 0.6 mmol allenoate **2**, 0.5 mmol imine **3a** in 5 mL solvent (toluene/H₂O (v/v) = 6 : 1), reflux, 12 hours. ^b Yields of product after silica gel chromatography.



products **5**. It was also worthy to note that many substituents, including halide, methyl, methoxy, and cyano groups at *ortho*, *meta*, and *para* positions of the aromatic ring were well-tolerated (Table 2, entries 1–8) and the representative results were summarized in Table 2. Moreover, experiments with substrate **2j** containing naphthyl group substitution at β -position was also conducted (Table 2, entry 9). In such cases, product **5j** was afforded in good yield, thus further expanded the substrate scope. Furthermore, the present method show high stereoselectivity in all cases and only one isomer was detected during our investigation. Remarkably, the allenolate was also fully incorporated into the final product as a four carbon building block, which was quite rare in previous reports.

To further explore the utility of the present reaction, the possibility of substituted isocyanides **2** were then performed. As shown in Table 3, a series of aliphatic and aromatic isocyanides **1** were subjected to the optimal conditions. To our delight, all the reactions proceeded smoothly to produce the desired products **6a–6e** in good performance. Notably, the present reaction seemed to be not sensitive to sterical hindrance since *tert*-butyl and admantyl groups were all proven to be compatible. In addition, reactions with the less-reactive *para*-bromo-phenyl isocyanide **1e** also worked well to yield the desired product **6e**, which was quite interesting.

The mechanism of the aforementioned multicomponent cycloaddition reaction has not been unequivocally established, but one reasonable mechanistic proposal is outlined to explain the formation of products **4–6**. As shown in Scheme 2, the present reaction starts from the nucleophilic attack between isocyanide **1** and allenolate **2**, thus leading to the formation of zwitterionic species, which exist as a resonance-stabilized form **A** \leftrightarrow **B**.¹⁵ The *in situ* generated species are then trapped by imine substrate **3** to produce intermediate **C**. After that, the resultant



Scheme 2 Mechanistic proposal.

nitrene cation **C** reacts with water to yield intermediate **D**. Further proton transfer and cyclization gave rise to the final products **4–6**.

Conclusions

In conclusion, we have described a novel multicomponent reaction of isocyanide, allenolate, imine, and water to generate pyrrolidine-fused heterocycles in an efficient manner. Furthermore, two rings and five chemical bonds (two C–C, two C–N, and one C–O) were formed in one operation, which represents high synthetic efficiency. And the resultant structurally unusual compounds are difficult to be synthesized by other methods. Four carbon atoms in allenolate were incorporated into the ring formation, which is quite rare. As a consequence, the above-mentioned advantages and the excellent stereoselectivity make the present strategy be further applied.

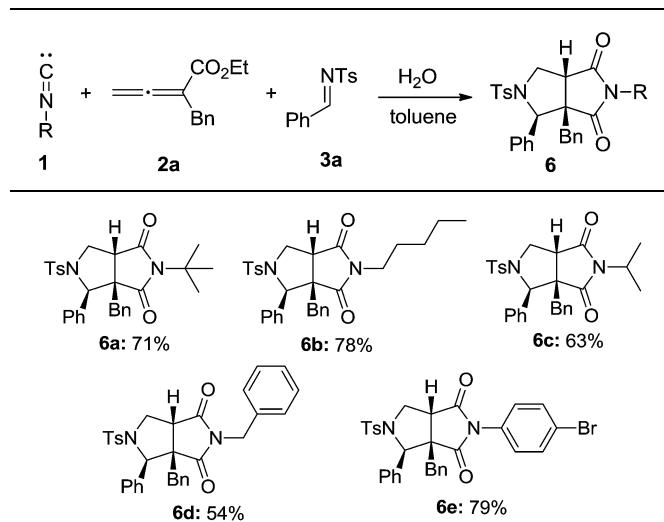
Acknowledgements

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Table 3 Scope of the MCR reaction with respect to the isocyanide substrate **1a–b**



^a Reaction conditions: 0.5 mmol isocyanide **1**, 0.6 mmol allenolate **2a**, 0.5 mmol imine **3a** in 5 mL solvent (toluene/H₂O (v/v) = 6 : 1), reflux, 12 hours. ^b Yields of product after silica gel chromatography.



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16 CCDC 1544098 for compound **4a** contains the supplementary crystallographic data for this paper.†

17 See ESI.†

