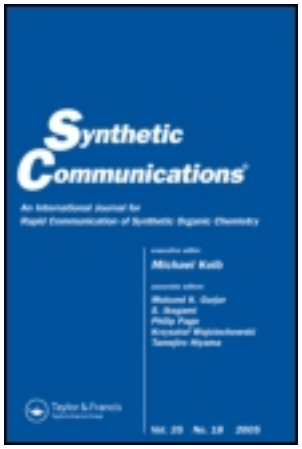

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Synthesis of Pyrrolo[2,3-a]pyrrolizidino Derivatives Through Intramolecular 1,3-Dipolar Cycloaddition in Ionic Liquid Medium

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SYNTHESIS OF PYRROLO[2,3-*a*]PYRROLIZIDINO DERIVATIVES THROUGH INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION IN IONIC LIQUID MEDIUM

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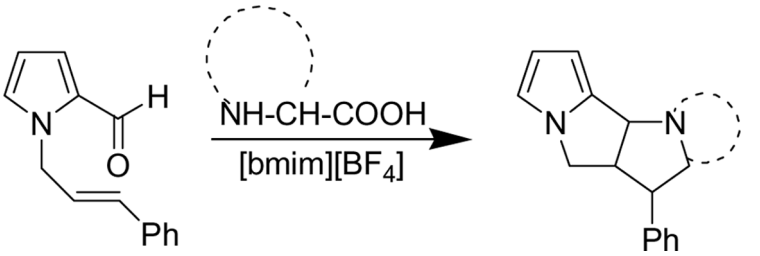
GRAPHICAL ABSTRACT



Abstract *An ecofriently method for the synthesis of pyrrole-fused polycyclic heterocycles through intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylides derived from pyrrole-2-carbaldehyde and secondary amino acids in ionic liquid [bmim][BF_4] as green solvent is reported.*

Keywords Azomethine ylide; cycloaddition; heterocycles; ionic liquid; green solvents

INTRODUCTION

In recent years, ionic liquids as alternative reaction media have been frequently reported in the literature.[1–3] Molten salts at ambient temperature that contain only ions and no solvent are referred to as ''ionic liquids.'' They have been successfully used in a variety of catalytic reactions as environmentally benign solvents and catalysts because of their relatively low viscosities, low vapor pressure, and high thermal and chemical stability.[4,5] Their nonvolatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction solvents. They are used as green solvents for the immobilization of transition-metal-based catalysts, Lewis acids, and enzymes.[6–8] Much attention has been focused on the organic reactions with ionic liquids as catalysts or solvents.[9–12] Many reactions such as Friedel–Crafts reactions,[13] arene

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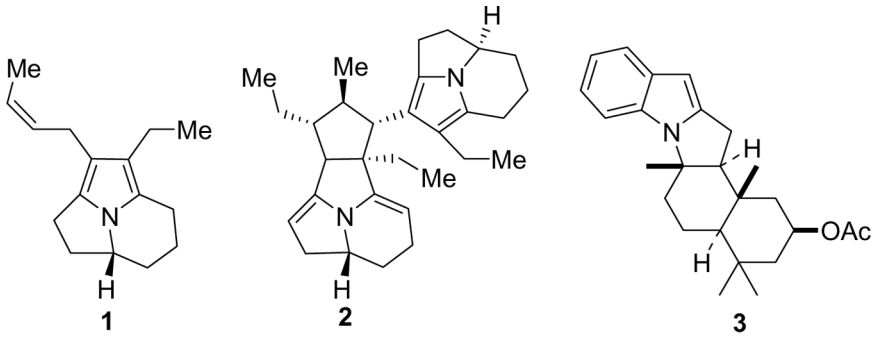


Figure 1. Biologically active pyrrole alkaloids.

hydrogenation,[14] dimerizations of alkenes,[15] allylations of aldehydes,[16] Heck reactions,[17] and Diels–Alder reactions[18] have been reported with good results, indicating that use of ionic liquids as catalysts may be possible for those traditionally important reactions. To our knowledge, there is no report in the literature on the intramolecular 1,3-dipolar azomethine ylide cycloaddition reaction in ionic liquid medium for the synthesis of pyrrolo[2,3-*a*]-pyrrolidines, pyrrolizidines, indolizidines and isoquinolines. Herein, we report a simple and efficient protocol for the synthesis of pyrrolo[2,3-*a*]pyrrolizidino derivatives using [bmim][BF_4] as ionic liquid.

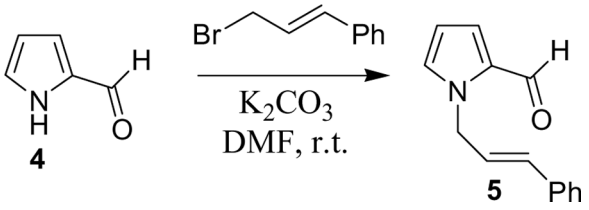
Nitrogen-containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active compounds.[19] The syntheses of polysubstituted and fused pyrrolidines, pyrrolizidines, indazolidines, and isoquinoline ring systems have received attention over the because since these heterocycles form the structural subunits of biologically important alkaloids[20] and pharmaceutically important compounds.[21]

1,3-Dipolar cycloaddition reaction is one of the most useful methods for the preparation of five-membered heterocycles, and consequently, it has been extensively studied.[22] In particular, the reaction of azomethine ylides[23] with alkenes provides pyrrolidine ring systems that are the central skeleton of numerous alkaloids[24] and physiologically active compounds.[25] The intramolecular version of this reaction results in the formation of fused or bridged nitrogen-containing bicyclic systems and generally occurs with high regio- and stereocontrol.[26–28]

In continuation of our research in cycloaddition chemistry,[29] we have developed a simple method for the synthesis of pyrrolo[2,3-a]pyrrolidines, pyrrolizidines, indolizidines, and isoquinolines using [bmim][BF_4] as green solvent through intramolecular 1,3-dipolar cycloaddition reactions from N-alkenyl pyrrole-2-carbaldehyde. These systems are of interest because they are related to alkaloids such as mirmicarin (**1** and **2**) and polyavolensin (**3**)[30] (Fig. 1)

RESULTS AND DISCUSSION

N-Alkenyl carboxaldehyde **5** was prepared from pyrrole-2-carbaldehyde by the reported procedure as outlined in Scheme 1.[31]



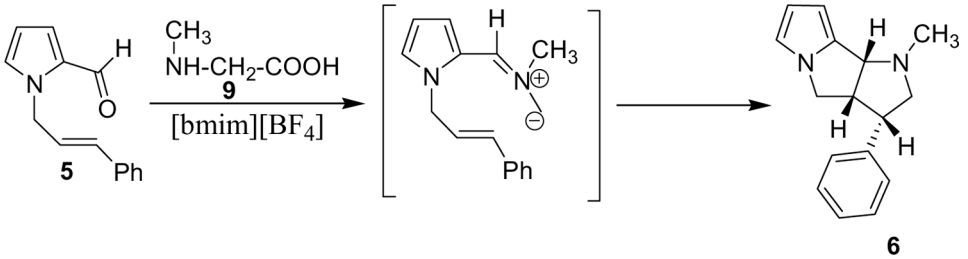
Scheme 1. Synthesis of *N*-cinnamyl pyrrole-2-carbaldehyde.

N-Alkenyl pyrrole-2-carbaldehyde (**5**), when treated with sarcosine (**9**) in [Bmim][BF_4] medium at 85–95 °C for about 3 h, forms pyrrolopyrrolidines in good yield (Scheme 2).

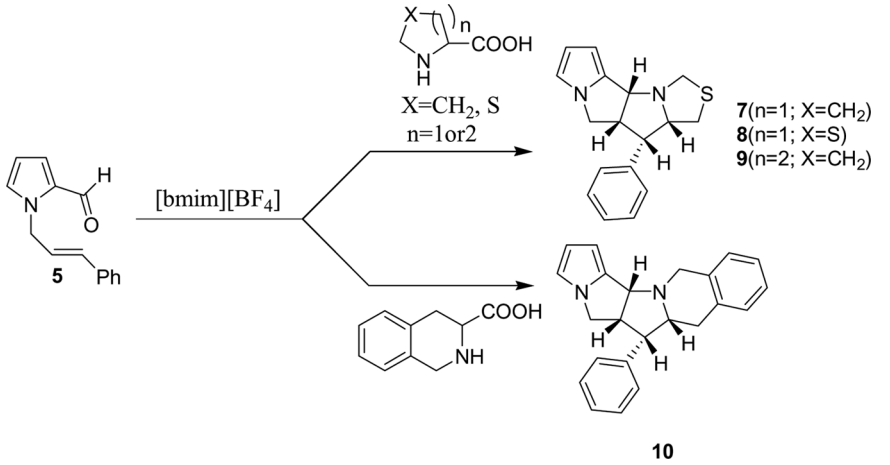
The formation of the product was established by spectroscopic data. The ^{1}H NMR spectrum of **6** exhibited a singlet at δ 2.46 corresponding to N-methyl group. The two –NCH_2 protons appeared as multiplets in the ranges δ 3.25–3.40 and δ 3.42–3.51. The benzylic proton appeared as a triplet at δ 4.11 with the coupling constant value 9.6 Hz. A peak at δ 3.92 was observed as a doublet with the coupling constant value 4.8 Hz for the *N*-CH proton. The small value of the coupling constant suggested a *cis* fusion at the ring junction. The pyrrole and aromatic ring protons appeared in the regions δ 5.92–6.49 and δ 7.15–7.29 respectively. The ^{13}C NMR spectrum of **6** showed carbon signals at 50.45, 51.40, and 53.93 ppm for methylene carbons. The pyrrole and aromatic carbons appeared at 98.94, 111.40, 112.08, 113.04, and 127.66, 128.16, 128.69 ppm respectively. To demonstrate the generality of this reaction, we carried out the reaction of pyrrole-2-carbaldehyde with cyclic secondary amino acids such as proline, pipecolinic acid, and isoquinolinic acid to give the corresponding linearly fused pyrrolizidine, indolizidine, and isoquinoline derivatives (Scheme 3).

The structures of all the products were determined by spectroscopic techniques and confirmed by x-ray crystal analysis of one of the products (**10**).[32] The results are tabulated in Table 1.

To compare the efficiency of this method, we carried out the reaction in various organic solvents such as toluene, methanol, and acetonitrile. The reaction was slow in organic solvents and afforded lesser yields of the desired products.



Scheme 2. Synthesis of *N*-methyl pyrrolo[2,3-*a*]pyrrolizidine.



Scheme 3. Synthesis of pyrrolo[2,3-*a*]pyrrolizidine, indolizidine, thiapyrrolizidine, and isoquinoline.

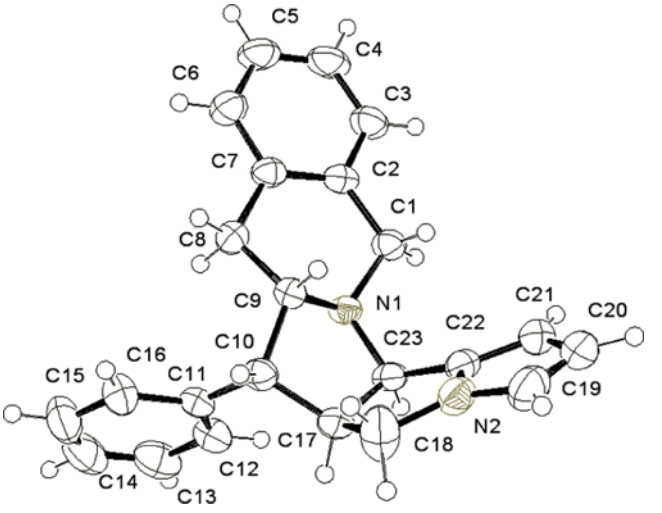
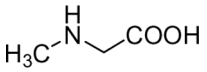
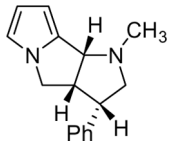
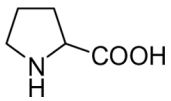
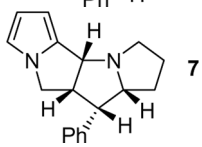
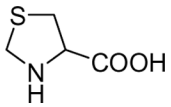
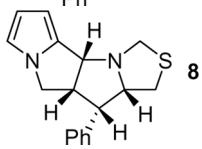
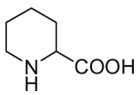
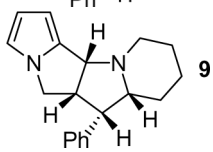
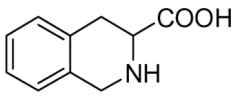
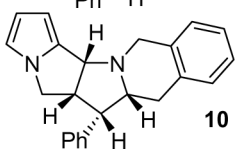


Figure 2. X-ray crystal structure of compound **10**. (Figure is provided in color online.)

In conclusion, we have demonstrated that it is possible to carry out intramolecular 1,3-dipolar cycloaddition in ionic liquid [bmim][BF_4] as green and reusable reaction medium. Separation of the final products could be done by simple extraction with organic solvents. In addition, the work described here has furnished a number of products of biological interest and offers a promising step for a synthetic approach to natural products.

Table 1. Synthesis of pyrrolo-[2,3-*a*]pyrrolizidino derivatives

Entry	*N*-Cinnamyl pyrrole-2-carbaldehyde	Amino acid	Cycloadducts[a]	Time (h)	Yield[b] (%)
1	5			3.0	92
2	5		 **7**	3.0	88
3	5		 **8**	3.5	85
4	5		 **9**	3.0	90
5	5		 **10**	4.0	80

[a]Isolated products were characterized by ^{1}H NMR, ^{13}C NMR, mass spectra, and x-ray analysis.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fourier transform (FT)–IR 8300 instrument. Mass spectra were recorded on a Jeol DX 303 HF spectrometer with Maspec System (msw/9629). ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ using tetramethylsilane (TMS) as internal standard on a Bruker spectrometer at 300 and 75 MHz, respectively. Elemental analyses were carried out on a Perkin-Elmer 2400 B instrument.

Representative Experimental Procedure for the Synthesis of Cycloadducts 6–10

A mixture of *N*-cinnamyl pyrrole-2-carbaldehyde (0.2 g, 1 mmol) and the secondary amino acid (0.08 g, 1.1 mmol) in [bmim][BF_4] (0.5 g) was placed in a round-bottom flask (50 mL). The flask was then dipped in a oil bath preheated at 85–95 °C. The homogenous mixture was stirred for about 3 h. After completion of the reaction as evidenced by thin-layer chromatographic (TLC) analysis, the mixture

was cooled to rt and extracted with Et_2O (2 × 10 mL). The ether layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was subjected to column chromatography using hexane and ethyl acetate as eluent.

Cycloadduct 6

R*f* = 0.6 (hexane–ethylacetate 95:5), light yellow liquid, yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3H), 2.56–2.64 (m, 1H), 3.25–3.40 (m, 2H), 3.42, 3.51 (m, 1H), 3.85–3.90 (m, 1H), 3.92 (d, *J* = 4.8 Hz, 1H), 4.11(t, *J* = 9.6 Hz, 1H), 5.92 (d, *J* = 3.6 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 6.48 (t, *J* = 1.2 Hz, 1H), 7.15–7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.23, 50.45, 51.40, 53.93, 64.25, 67.06, 98.94, 112.08, 113.04, 125.74, 126.38, 127.66, 135.61, 141.30; *m/z* 237.5(M^+). Elemental anal. calcd. for $C_{16}H_{18}N_2$: C, 80.67; H, 7.56; N, 11.76. Found: C, 80.53; H, 7.51; N, 11.82.

Cycloadduct 7

R*f* = 0.6 (hexane–ethylacetate 95:5), light yellow liquid, yield 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68–1.85 (m, 2H), 2.03–2.08 (m, 1H), 2.44 (s, 1H), 2.96–3.04 (m, 1H), 3.27–3.35 (m, 1H), 3.56–3.73(m, 2H), 3.81–3.84 (m, 2H), 4.04–4.07 (m, 1H), 4.09 (d, *J* = 4.8 Hz, 1H), 6.04 (s, 1H), 6.27 (d, *J* = 2.7 Hz, 1H), 6.50 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.63, 27.37, 48.01, 49.38, 52.17, 56.54, 69.16, 72.18, 99.78, 113.19, 113.61, 126.70, 127.99, 128.54, 139.14, 139.57; *m/z* 215.4 (M^+). Elemental anal. calcd. for $C_{18}H_{20}N_2$: C, 81.81; H, 7.57; N, 11.76. Found: C, 81.76; H, 7.50; N, 11.80.

Cycloadduct 8

R*f* = 0.6, (hexane–ethylacetate 95:5), light yellow solid, mp 95 °C, yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.42–2.47 (m, 2H), 3.81–3.96 (m, 4H), 4.09–4.15 (m, 2H), 4.28–4.38 (m, 2H), 5.91 (s, 1H), 6.21 (s, 1H), 6.45 (s, 1H), 7.15–7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.82, 47.78, 50.99, 52.99, 60.08, 64.08, 99.28, 109.93, 113.92, 114.08, 117.16, 127.24, 127.66, 128.62, 137.75, 138.57; *m/z* 281.3 (M^+). Elemental anal. calcd. for $C_{17}H_{18}N_2S$: C, 72.34; H, 8.38; N, 11.76. Found: C, 72.21; H, 8.31; N, 11.79.

Cycloadduct 9

R*f* = 0.6 (hexane–ethylacetate 95:5), light yellow crystal, mp 110 °C, yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.45–0.49 (m, 1H), 1.14–1.27 (m, 1H), 0.92–0.97 (m, 1H), 1.43–1.46 (m, 1H), 2.35–2.468 (m, 2H), 2.92–2.65 (m, 2H), 3.07–3.11 (m, 1H), 3.37–3.43 (m, 1H), 3.79 (d, *J* = 3.0 Hz, 1H), 3.82 (d, *J* = 3.0 Hz, 1H), 4.11 (q, *J* = 8.5 Hz, 1H), 4.74 (d, *J* = 7.5 Hz, 1H), 5.85 (d, *J* = 3.3 Hz, 1H), 6.19 (t, *J* = 1.9 Hz, Hz, 1H), 6.49 (q, *J* = 1.2 Hz, 1H), 7.11–7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.97, 25.30, 28.07, 48.88, 52.07, 53.40, 57.12, 62.63, 64.97, 102.22, 112.93, 114.06, 126.33, 128.04, 128.95, 134.34, 143.36; *m/z* 277.6 (M^+). Elemental anal. calcd. for $C_{19}H_{22}N_2$: C, 82.01; H, 7.91; N, 11.76. Found: C, 81.91; H, 7.82; N, 11.84.

Cycloadduct 10

R*f* = 0.6 (hexane–ethylacetate 95:5), light yellow crystal, mp 116 °C, yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 1H), 1.61 (s, 1H), 2.60 (d, *J* = 4.2 Hz, 1H), 2.31 (d, *J* = 4.2 Hz, 1H), 3.03–3.08 (m, 1H), 3.22–3.25 (m, 1H), 3.57–3.62 (m, 1H), 3.86–4.23 (m, 1H), 4.91 (d, *J* = 7.2 Hz, 1H), 5.02 (d, *J* = 5.7 Hz, 1H), 6.00 (s, 1H), 6.34 (s, 1H), 6.55 (s, 1H), 7.00–7.25 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.33, 49.63, 51.39, 51.99, 54.88, 58.48, 63.33, 101.80, 108.97, 111.98, 113.36, 125.62, 126.88, 127.34, 129.84, 131.77, 132.85, 132.91, 133.52, 135.21, 141.02. *m/z* 335.8 (M^+). Elemental anal. calcd. for $C_{23}H_{22}N_2$: C, 85.11; H, 6.54; N, 11.76. Found: C, 85.02; H, 6.50; N, 11.83.

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