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Synthesis of pyrrolo[2,3-*a*]pyrrolizine and pyrrolizine[2,3-a]pyrrolizine derived from allyl derivatives of Baylis–Hillman adducts through intramolecular 1,3-dipolar cycloaddition

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ABSTRACT

The synthesis of a series of pyrrole-based polycyclic heterocycles has been accomplished through an intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide with the dipolarophile derived from Baylis–Hillman adducts. Improved yields of the products were obtained when the reaction was carried out under microwave conditions.

Intramolecular [3+2] cycloaddition of azomethine ylide has been used widely to construct complex cyclic systems from relatively simple precursors.[1] This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms complex ring systems with regio- and stereocontrol.[2–5] α-Methylene-β-hydroxy esters **1a–c** are easily prepared by the Baylis–Hillman reaction[6,7] and are well utilized as versatile building blocks for the stereoselective construction of natural products, including alkaloids,[8] macrolides,[9] terpenoids,[10–12] and pheromones.[13–15]

Multifunctional allylic compounds such as **1a–c**[16] and derivatives **2a–c**[17] are useful scaffolds for the synthesis of a wide range of complex molecular frameworks.

With the objective of expanding the scope of these allyl halides in synthetic organic chemistry, we have used the allyl bromides derived from Baylis–Hillman adducts as dipolarophiles for intramolecular 1,3-dipolar cycloaddition.

In continuation of our research in the area of 1,3-dipolar cycloaddition,[18–29] we herein report for the first time, the synthesis of pyrrolo[2,3-*a*]pyrrolizine and pyrrolizine[2,3-*a*]pyrrolizine using allyl bromides derived from Baylis–Hillman derivatives in an intramolecular cycloaddition reaction.

The treatment of methyl 3-acetoxy-3-phenyl-2-methylenepropanoate **1a–c**[30] with pyrrole-2-carbaldehyde **3** in the presence of K_2CO_3/dry DMF at 80 °C for 6 h gave moderate yields of the products **4a–c**. However, a synthesis of the same products can be accomplished in good yields by treating Baylis–Hillman bromide derivatives **2a–c**[31] with pyrrole 2-carbaldehyde in the presence of K_2CO_3/dry DMF in 3 h.[32]

The structure of *N*-allyl pyrrole derivatives was confirmed by spectroscopic analysis.

With N-alkenyl aldehyde **4a–c** in hand, the cycloaddition reactions were carried out with the unstabilized azomethine ylide generated by decarboxylative condensation with various secondary amino acids. The condensation of **4a–c** with sarcosine **5** in refluxing toluene under Dean–Stark reaction conditions, generated azomethine ylide that underwent neat intramolecular cycloaddition to yield cis-adducts **6a–c** in moderate yields in all cases.[33,34]

When the same reaction was extended with proline and thiazolidine carboxylic acid, we obtained a series of novel pyrrolizidine and thiopyrrolizidine heterocycles in good yield. The structures of these compounds were also established on the basis of their spectroscopic data (Scheme 1).

To improve the yield, we carried out the reaction under two different conditions. Thus, the reactions of **4a–c** with sarcosine, proline, and thiazolidine carboxylic acid in toluene under reflux afforded cycloadducts **6a–c** in moderate yields in all cases, but required long reaction times and higher temperature.

When the same reactions were carried out under microwave irradiation in a toluene solvent, there was a dramatic increase in the yields of the products with a decrease in reaction time. Under these conditions, cycloadducts were obtained in good yields (79–85%) with high regio- and stereoselectivity.[35] The results are summarized in Table 1.

In conclusion, we have developed a simple method for the synthesis of a variety of polycyclic heterocycles by 1,3-dipolar cycloaddition using Baylis–Hillman adduct derivatives as dipolarophiles. We have observed that the reaction can be carried out more efficiently to give good yields of products in short reaction times under microwave conditions.

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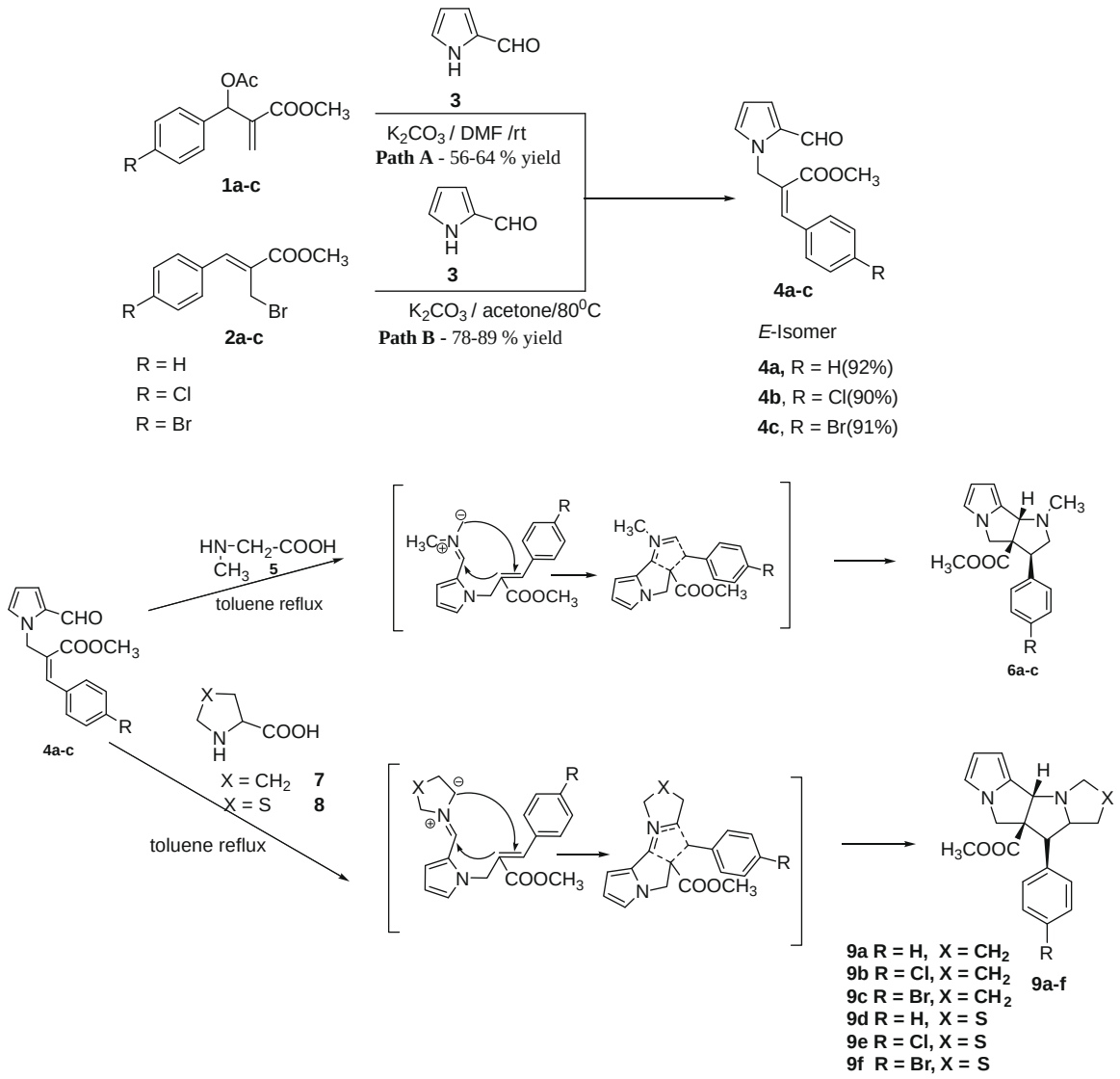

Scheme 1.

Table 1
Synthesis of pyrrole[2,3-a]pyrrolizine/pyrrolizine[2,3-*a*]pyrrolizine derivatives using Method A and Method B

Entry	Pyrrole[2,3-*a*]pyrrolizine/pyrrolizine[2,3-*a*]pyrrolizine	Method A		Method B	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	**6a**	2.0	65	3.5	85
2	**6b**	3.0	56	4.0	75
3	**6c**	3.5	59	4.0	79
4	**9a**	2.0	55	2	87
5	**9b**	2.5	61	2.5	85
6	**9c**	3.0	63	2.5	78
7	**9d**	3.0	51	2	84
8	**9e**	3.5	48	2.5	81
9	**9f**	4.0	48	2.5	78

Method A: toluene reflux.
Method B: toluene under microwave irradiation.

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32. *Synthesis and spectral data for new compounds*: Path A: To a refluxing solution of pyrrole 2-carbaldehyde (20 mmol), K_2CO_3 (25 mmol) in 25 ml of DMF, a Baylis–Hillman derivative (22 mmol) was added. The reaction mixture was stirred for 4–6 h at room temperature, and diluted with water (50 mL). The aqueous layer was extracted with ethyl acetate (4 × 20 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo .The crude product was subjected to column chromatography (100–200 mesh) using a hexane–ethyl acetate mixture (8:2).Path B: To a refluxing solution of pyrrole 2-carbaldehyde (20 mmol), K_2 CO_3 (25 mmol) in 25 ml of acetone, a Baylis–Hillman bromide (22 mmol) was added. The reaction mixture was refluxed at 80 °C for 4–6 h till the completion of the reaction as evidenced by TLC. The reaction mixture was concentrated in vacuo and diluted with water (50 mL) .The aqueous layer was extracted with ethyl acetate (4 × 20 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. The crude product was subjected to column chromatography (100–200 mesh) using a hexane–ethyl acetate mixture (8:2).*(E)-Methyl 2-((2-formyl-1H-pyrrol-1-yl)methyl)-3-phenylacrylate* **4a**: Viscous liquid, Yield: 92%. IR (KBr): 1675, 1715 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): δ 3.77(s, 3H), 6.96 (d, J = 1.5 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 8.07 (s, 1H), 6.20–6.97 (m, 3H), 7.24–7.37 (m, 5H), 9.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.1, 52.3, 126.6, 128.0, 128.4, 128.5, 129.0, 129.1, 129.7, 131.8, 133.9, 145.1, 167.3, 179.5.
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35. *Synthesis of cycloadducts*: Method A: A solution of an *N*-allyl derivative of pyrrole (1 mmol) and cyclic and acyclic amino acids (1 mmol), in anhydrous toluene (10 mL), was refluxed until the completion of the reaction as evidenced by TLC analysis. The solvent was removed under vacuum. The crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate (7:3) as the eluent.
Method B: A mixture of an *N*-allyl derivative of pyrrole (1 mmol), cyclic and acyclic amino acids (1 mmol), in anhydrous toluene (10 mL), was irradiated by microwave irradiations until the disappearance of the starting materials (1–2 min, monitored by TLC). After standing for 1 h, the reaction mixture was concentrated under vacuum and the crude mixture was purified by column chromatography to afford the pure product.
Methyl 1,2,3,3a,4,8b-hexahydro-1-methyl-3-phenylpyrrolo[2,3-a]pyrrolizine-3a-carboxylate **6a**: Yield: 85**%** IR (KBr): 1712 cm^{-1}, Mp: 80 °C, ^1H NMR (300 MHz, $CDCl_3$): δ 2.51 (s, 3H), 2.79 (t, J = 9.6 Hz, 1H), 3.09 (dd, J = 6.6, 3.0 Hz, 1H), 3.55 (d, J = 11.7 Hz, 1H), 3.76 (s, 3H), 4.02 (d, J = 11.7 Hz, 1H), 4.05 (dd, J = 6.9, 4.2 Hz, 1H), 4.67 (s, 1H), 5.88–6.39 (m, 3H), 7.00–7.23 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9, 38.3, 49.8, 50.4, 52.9, 58.3, 67.2, 102.0, 113.0, 114.3, 127.2, 128.5, 128.6, 138.4, 175.0. MS (EI) m/z = 296.15 (M^+) Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.96; H, 6.80; N, 9.45. Found: C, 73.08; H, 6.92; N, 9.37.
Methyl 1,2,3,3a,4,8b-hexahydro-3-phenylthiopyrrolizine[2,3-a]pyrrolizine-3a-carboxylate **9d**:Yield: 84% Viscous liquid, IR (KBr): 1709 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$): 3.77 (s, 3H), 3.9 (d, 3.3 Hz, 1H), 3.9 (m, 1H), 3.02 (dd, J = 4.2, 5.4 Hz, 1H), 3.21 (dd, J = 4.8, 5.3 Hz, 1H), 4.34 (d, J = 9.9 Hz, 1H), 4.28 (d, J = 10.2 Hz, 1H), 4.02 (d, J = 9.9 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 4.61 (s, 1H), 5.97–6.46 (m, 3H), 7.23–7.36 (m, 5H).
^{13}C NMR (75 MHz, $CDCl_3$): 37.1, 50.4, 53.1, 54.1, 58.3, 68.7, 69.8, 75.7, 109.8, 112.7, 114.7, 127.5, 128.8, 129.6, 135.2, 139.0, 174.4. MS (EI) m/z = 340.10 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.17; H, 6.03; N, 8.14.