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Synthesis of novel spiropyrrolidines through [3+2] cycloaddition reactions with Baylis–Hillman adducts as dipolarophiles

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Abstract—The synthesis of a series of novel spiropyrrolidines and polycyclic heterocycles has been accomplished by 1,3-dipolar cycloaddition reactions with Baylis–Hillman adducts. The reaction also yielded novel furo[3,4-*b*]pyrrole in some cases by an unusual cyclization.
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1,3-Dipolar-cycloaddition reactions are one of the most useful methods for the preparation of five-membered heterocycles[1] because of their high regioselectivity and stereoselectivity.[2] These reactions have been intensively investigated by Grigg and co-workers[3] and Kanemasa and co-workers.[4] The reaction of azomethine ylides with alkenes provides pyrrolidines which are present in numerous alkaloids[5] and physiologically active compounds.[6]

Spiropyrrolidines have received considerable attention as a result of their biological activity.[7–12] They display interesting antimicrobial, antitumor and antibiotic properties. In addition, they also act as inhibitors of human NK-I receptor activity.[13]

The Baylis–Hillman (BH) reaction is an attractive method for forming carbon–carbon single bonds and yields highly functionalized products with a new stereocentre.[14] The Baylis–Hillman reaction has been the subject of several reviews[15,16] and continues to elicit attention.[17,18]

So far, the alkene unit of Baylis–Hillman adducts has not been fully exploited as a dipolarophile in 1,3-dipolar cycloaddition reactions. There is only one report on the synthesis of spirooxazolines through 1,3-dipolar cycloaddition of mesitonitrile to Baylis–Hillman adducts, which proceeded regioselectively by Mg(II) catalysis.[19]

Azomethine ylides generated by the decarboxylative route offer a convenient method for the synthesis of substituted pyrrolidines.[20] As a part of our endeavours[21] in the synthesis of novel spiropyrrolidines, we herein report for the first time the cycloaddition reaction of azomethine ylides with the olefinic bond of Baylis–Hillman adducts **1a–c**. In some cases the reaction yielded novel furo[3,4-*b*]pyrrole derivatives by an unusual cyclization reaction.

Various substituted Baylis–Hillman adducts **1a–c** were synthesized in accordance with the literature procedure. The azomethine ylides generated by the reaction of sarcosine **2** with isatin **3**, ninhydrin **6** or acenaphthequinone **9** in boiling toluene for 48–78 h reacted with the double bond of **1a–c** to give the corresponding cycloadducts as single regioisomers[22] with overall yields of 40–55% (Scheme 1). The reaction afforded a series of novel spiroheterocycles **4a–c**, **7a–c** and **10a–c** in a regio- and stereocontrolled manner. The structures and the regiochemistry of the cycloadducts were confirmed by spectral analysis.

The IR spectrum of **4a** showed sharp peaks at 1712 cm^{-1} and 1741 cm^{-1} for the amide and ester

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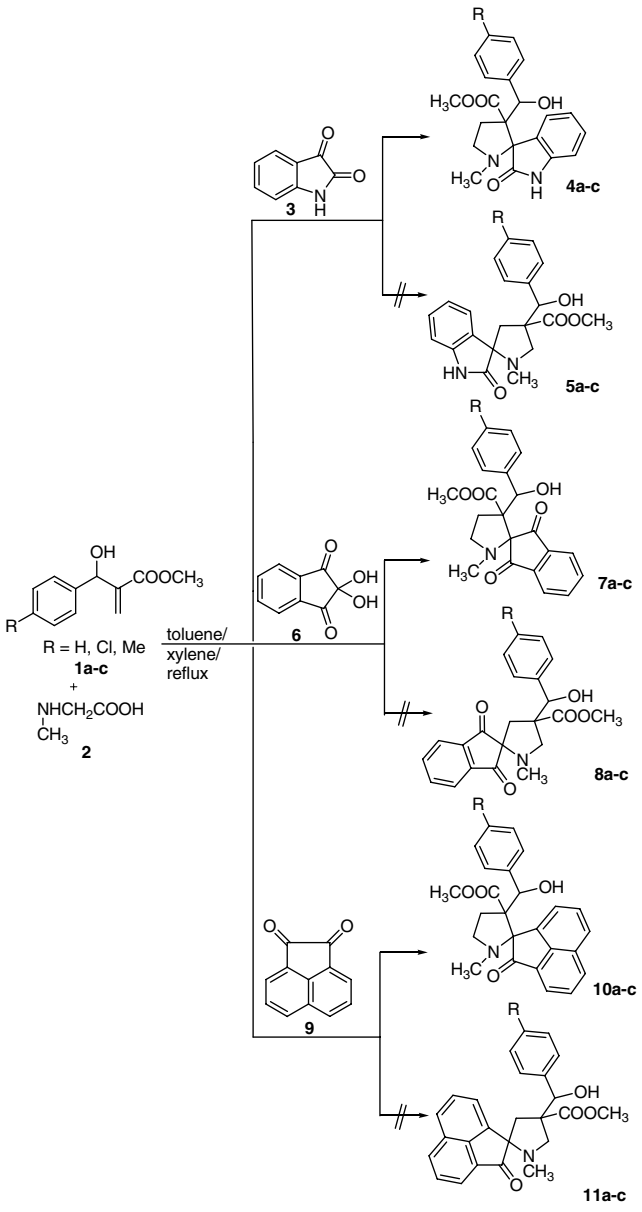


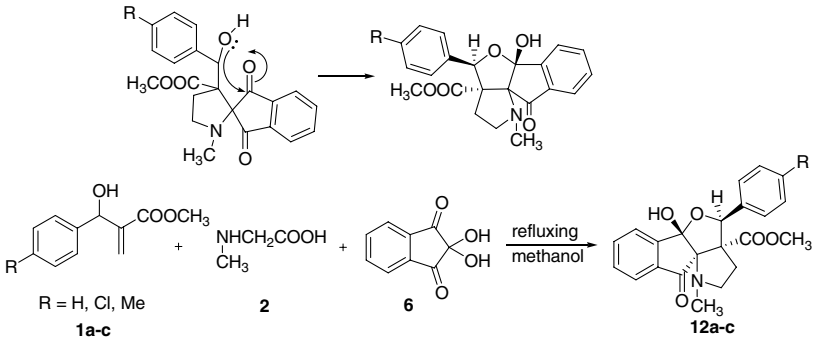
Scheme 1.

carbonyls, respectively. The ^{1}H NMR spectrum of **4a** showed multiplets in the region δ 2.03–2.04 and δ 2.67–2.71 for the CH_2 protons of the pyrrolidine ring system. The NCH_2 protons of the pyrrolidine ring appeared as multiplets in the region δ 2.94–2.98 and δ 3.46–3.49. If the other regioisomer **5a** had been formed, simple doublets for each of the CH_2 protons of the pyrrolidine ring system would have been observed. The ^{13}C NMR of **4a** showed a signal at δ 76.89 for the spiro carbon and the signals at δ 170.98 and δ 177.40 ppm were due to the amide and ester carbonyl carbons, respectively. Finally, the structure of the product **4a** was confirmed by mass spectroscopy, which showed a peak at m/z 365.2.

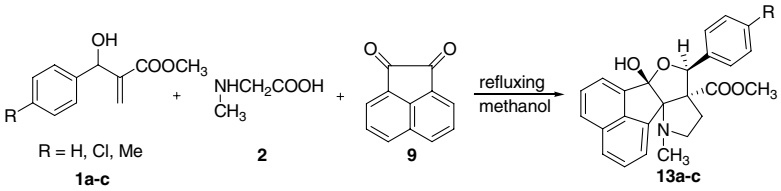
To improve the yields of the product, we carried out the reaction in various solvents. We found that using DMF or xylene did not increase the yield appreciably. However, there was a dramatic increase in the yield along with a decrease in reaction time when the reaction was carried out in methanol. Under the above conditions and to our surprise, we also observed the formation of products **12a–c** and **13a–c**, produced from the initial adducts **7a–c** and **10a–c** by hemiacetal cyclization (Schemes 2 and 3). The cycloadducts **7a–c** and **10a–c** were not obtained in these cases. The structures of products **12a–c** and **13a–c** were confirmed by spectroscopic analysis and X-ray crystallography of **12a**.[23]

The ^{1}H NMR spectrum of **12a** showed multiplets at δ 1.75–1.84 and δ 3.25–3.30 for the pyrrolidine ring protons. The benzylic proton appeared as a singlet at δ 5.01, whilst the OH proton was present as a broad singlet at δ 5.71. In the ^{13}C NMR spectrum of **12a**, a signal at δ 171.85 ppm manifested the presence of an ester carbonyl carbon. The presence of a single ketone carbonyl carbon resonance at δ 199.30 ppm indicated that the ketone carbonyl group of the indane-1,3-dione moiety was not present (cf. **7a**). The stereochemistry of the product **12a** was ascertained by single crystal analysis (Fig. 1).

In conclusion, this letter describes the cycloaddition reactions of nonstabilized azomethine ylides generated by the decarboxylative condensation of di- and triketones with sarcosine with **1a–c** as unusual dipolarophiles to afford novel spiroheterocycles with high regio- and stereoselectivity. In addition, by changing the solvent to methanol, we observed the formation of products obtained by nucleophilic attack of the hydroxyl group on a ketone carbonyl.



Scheme 2.



Scheme 3.

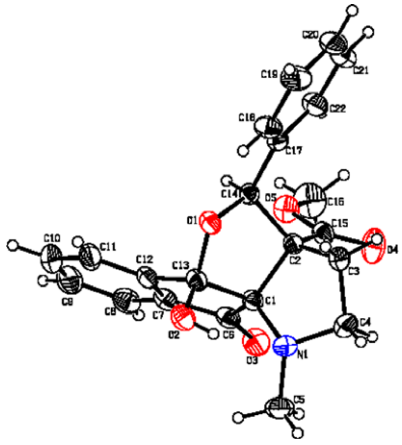


Figure 1. ORTEP diagram of **12a**.

Acknowledgements

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22. *Representative procedure for the preparation of spiropyrrolidine cycloadducts*: A solution of sarcosine **2** (1 mmol), acenaphthaquinone/ninhydrin/isatin (1 mmol) and 2-(hydroxy(aryl)methyl) acrylic acid methyl ester **1a–c** (1 mmol) was refluxed in toluene, xylene, DMF or methanol. Completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuo and the crude product subjected to column chromatography (100–200 mesh) using petroleum ether–ethyl acetate as eluent.

Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.03 (m, 1H, CH_2), 2.06 (s, 3H, NCH_3), 2.65–2.67 (m, 1H, CH_2), 2.91–2.93 (m, 1H, NCH_2), 3.03 (s, 3H, COOCH_3), 3.34–3.36 (m, 1H, NCH_2), 5.55 (br s, 1H, O*H*), 5.74 (s, 1H, C*H*Ph), 6.94–7.42 (m, 8H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 37.6, 49.9, 52.5, 59.9, 66.9, 76.2, 121.4, 124.2, 126.2, 128.4, 128.7, 129.6, 131.5, 137.3, 139.7, 152.7, 172.0, 175.9 ppm; mass *m*/*z*: 400.8 (M^+). Anal. Calcd for $C_{21}H_{21}N_2O_4Cl$: C, 62.92; H, 5.28; N. 6.99. Found: C, 63.15; H, 5.48; N, 6.72.

Compound **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64–1.73 (m, 2H, CH_2), 2.38 (s, 3H, NCH_3), 3.22–3.28 (m, 2H, NCH_2), 3.78 (s, 3H, COOCH_3), 4.90 (s, 1H, C*H*Ph), 5.64 (br s, 1H, O*H*), 6.63–7.03 (m, 9H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 36.5, 37.8, 53.2, 58.1, 71.2, 87.2, 103.5, 121.9, 124.8, 127.6, 132.1, 137.2, 137.8, 138.0, 148.1, 170.2, 198.7 ppm; mass *m*/*z*: 379 (M^+). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N. 3.69. Found: C, 69.94; H, 5.73; N, 3.42.

Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (m, 1H, CH_2), 1.78–1.81 (m, 1H, CH_2), 2.24 (s, 3H, NCH_3), 3.30–3.33 (m, 2H, NCH_2), 3.43 (s, 3H, COOCH_3), 5.12 (s, 1H, C*H*Ph), 5.78 (br s, 1H, O*H*), 6.41–6.95 (m, 11H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.8, 38.0, 50.4, 52.4, 58.1, 67.3, 85.1, 123.8, 125.9, 126.2, 126.7, 127.2, 127.9, 128.1, 128.5, 131.0, 132.0, 133.4, 133.6, 139.1, 143.3, 175.8, 201.9 ppm; mass *m*/*z*: 401 (M^+). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 75.06; H, 5.96; N, 3.26.

Compound **13a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76–1.79 (m, 1H, CH_2), 2.01–2.06 (m, 1H, CH_2), 2.38 (s, 3H, NCH_3), 3.42 (s, 3H, COOCH_3), 3.44–3.58 (m, 2H, NCH_2), 4.99 (s, 1H, C*H*Ph), 6.33 (br s, 1H, O*H*), 7.24–7.82 (m, 11H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 38.9, 39.0, 51.8, 58.2, 69.5, 88.9, 108.2, 120.7, 125.7, 125.8, 126.2, 128.1, 131.0, 135.6, 136.9, 139.8, 172.9 ppm; mass *m*/*z*: 401 (M^+). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 75.05; H, 5.98; N, 3.22.

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