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Synthesis of highly functionalised linear pentacyclic compounds from Baylis-Hillman adduct of heteroaldehydes with azomethine ylides *via* [3+2] cycloaddition

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Montmorillonite K10 clay promoted one-pot synthesis of penta- and tetracyclic systems from Baylis-Hillman adduct of heteroaldehydes with azomethine ylides generated from ninhydrin and proline or sarcosine *via* [3+2] cycloaddition is reported.

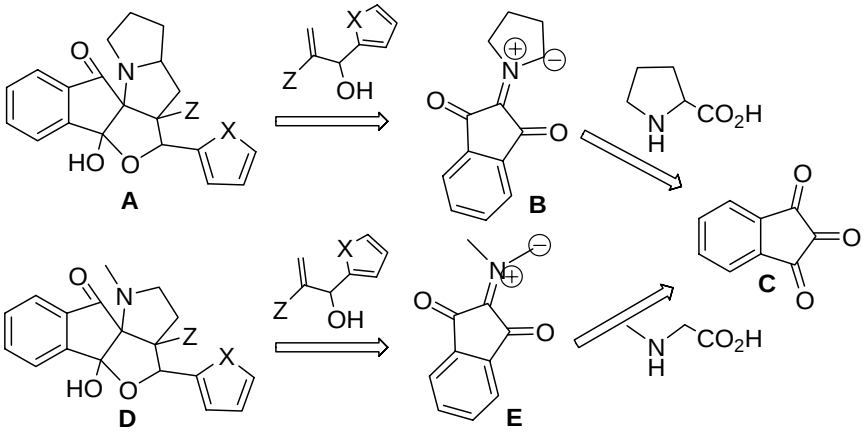
Keywords: Azomethine ylide, cycloaddition, proline, sarcosine, Baylis-Hillman adduct, ninhydrin

Azomethine ylides are class of powerful reagents to utilise in the [1,3]-dipolar cycloaddition reactions which generally afford a range of pharmacologically important heterocyclic compounds[1]. Amongst various carbon-carbon bond forming reactions, the Baylis-Hillman reaction is an important reaction giving rise to densely functionalized molecules and is considered atom economic. Highly functionalized Baylis-Hillman adducts have been used as starting materials for various stereoselective preparations of functionalized intermediates and in natural product synthesis[2]. The clay catalysts are known as eco-friendly acid catalysts which have potential for replacing the conventional mineral acids and are non-pollutant. The advantages of the clay-catalyzed reactions are that they are generally mild, solvent free and easy work-up[3]. As part of our research in the area of novel synthetic applications of Baylis-Hillman adducts[4], particularly with 1,3-dipolar cycloaddition reaction of Baylis-Hillman adducts with azomethine ylides[5], we continued to explore the [3+2]-cycloaddition reaction of Baylis-Hillman adducts of heteroaldehydes with azomethine ylides generated from ninhydrin and proline or sarcosine. The reaction afforded novel penta- and tetracyclic systems. The preliminary results of the study are the content of this letter.

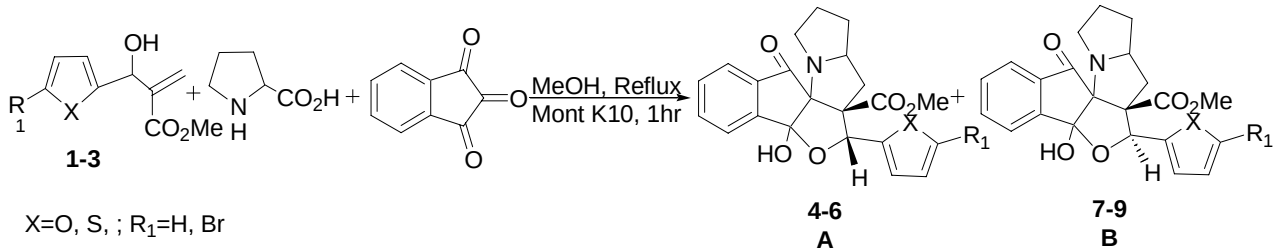
In contemporary, the synthesis of the polycyclic compound, it was envisaged that the core pyrrolizidine or pyrrolidine ring could be formed by the 1,3-dipolar cycloaddition (**Scheme I**). The azomethine ylide **B** or **E**, formed from ninhydrin **C** and proline or sarcosine, add to the activated alkene of the Baylis-Hillman adduct and followed by cyclisation leading to the pentacyclic or tetracyclic furan derivative **A** or **D**.

In a pilot experiment, the reaction of azomethine ylide generated from ninhydrin and proline with Baylis-Hillman adduct of furanaldehyde, catalyzed by Mont K10 clay, in refluxing methanol for 1 hr yielded one isomer of the pentacyclic furan compound **4** in 50% and the other isomer **7** in 20% yield (**Scheme II, Table I,** Entry 1). In the proton NMR spectrum of the compound **4**, a multiplet centered at δ 3.7 corresponds to methine proton of the pyrrolizidine ring and the two doublets of doublets centered at δ 2.37 (J = 5.6 Hz, J = 13.9 Hz) and δ 2.11 (J = 8 Hz, J = 13.9 Hz) show the two mutually coupled protons which are coupled to the methine proton of the pyrrolizidine ring. Methine proton of the furan moiety appears as a well separated singlet at δ 4.98, the ^{13}C NMR spectrum of **4** showed peaks at δ 198.6 for benzylic carbonyl and δ 171.5 for ester carbonyl groups. In the other isomer **7**, the methine proton of the pyrrolizidine ring appeared as multiplets centered at δ 4.13 and the methine proton of the furan moiety resonated at δ 5.3. All the compounds were characterized by NMR, IR and mass spectral analysis.

Adducts derived form thiophene and bromofuran aldehyde gave very good yield of the desired product (**Table I,** Entries 2 and 3). Under optimised conditions, efforts toward cycloaddition reaction of the corresponding Baylis-Hillman adduct of pyridine



Scheme I — Retrosynthetic analysis



Scheme II — Synthesis of pentacyclic compounds

Table I — Synthesis of pentacyclic compounds

Entry	X	R_1	Yield (%) A	Yield (%) B
1	O	H	50	20
2	O	Br	70	11
3	S	H	98	2

Table II — Synthesis of tetracyclic compounds

Entry	X	R_1	Yield (%) A	Yield (%) B
1	O	H	45	12
2	O	Br	40	16
3	S	H	60	10

and oxindole moieties with azomethine ylides **B** or **E** were unsuccessful.

Looking at the mechanism of the reaction, the back side attack of the azomethine ylide to the alkene of the Baylis-Hillman adduct and the secondary interaction[1f] of the hetero aryl ring with the aryl ring of the azomethine ylide rules out the possibility of the formation of the intermediate **I** by path b **(Scheme III)**, only the intermediate **II** will form and followed by cyclization to give the pentacyclic furan moiety with hetero aryl substituent.

Encouraged by the preliminary results, we then switched over our attention to the tetracyclic compound from Baylis-Hillman adducts of hetero aldehydes and azomethine ylide generated from sarcosine and ninhydrin in refluxing methanol using Mont K10 clay as catalyst. The results were summarized in **Scheme IV, Table II**.

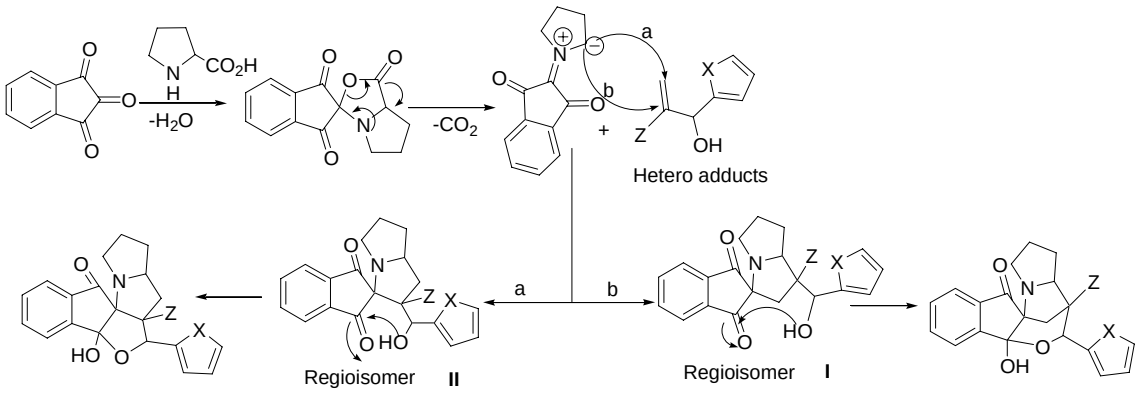
In conclusion, we have demonstrated a facile and efficient synthesis of highly functionalised linear tetra and pentacyclic compounds from Baylis-Hillman adducts of heteroaldehydes with azomethine ylides generated from ninhydrin and proline/sarcosine *via* [3+2] cycloaddition. Further work on novel synthetic applications of Baylis-Hillman adducts are in progress.

Typical Experimental Procedure

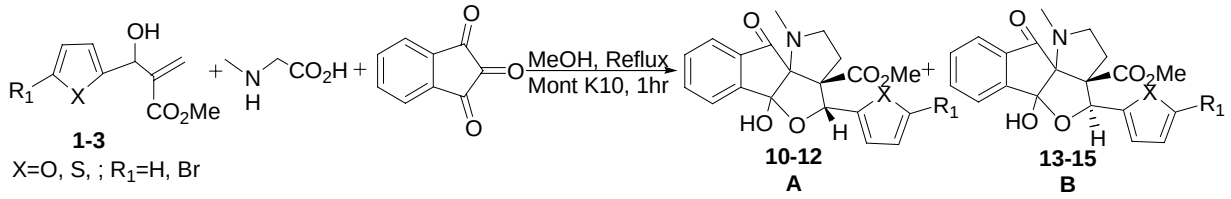
A mixture of Baylis-Hillman adducts (100 mg,), L-(-) proline or sarcosine (1.2eq), ninhydrin (1.2eq.) and montmorillonite K-10 Clay (100% w/w) in methanol (1 mL) was refluxed for 1 hr. After the reaction (TLC), the crude mixture was filtered through a pad of celite and then purified by a silica gel column chromatography to afford products in good yields.

Spectral data for selected compounds

Compound 4: IR (CH_2Cl_2): 1087, 1714, 1738, 3417 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 1.73-1.87



Scheme III — Mechanism of the reaction



Scheme IV — Synthesis of tetracyclic compounds

(m, 2H), 1.96-2.07 (m, 2H), 2.09-2.16 (dd, *J* = 8 MHz, *J* = 13.9 MHz, 2H), 2.34-2.40 (dd, *J* = 5.6 MHz, *J* = 13.9 MHz, 1H), 2.87-2.94 (m, 1H), 3.33-3.42 (m, 1H), 3.64 (s, 3H), 3.72-3.81 (m, 1H), 4.98 (s, 1H), 6.30-6.39 (m, 2H), 7.26-7.93 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.65, 30.76, 34.16, 48.75, 52.66, 56.35, 67.80, 69.80, 76.10, 104.09, 108.06, 110.11, 115.11, 122.85, 125.05, 130.55, 136.88, 142.38, 149.36, 149.83, 171.75, 198.68; LRMS: Calcd. for $C_{22}H_{21}NO_6$: 395.41; Found: 396.03 (M^++1).

Compound 5: IR (CH_2Cl_2): 693, 1014, 1717, 1732, 3464 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz): 1.80-1.86 (m, 2H), 1.92-2.00 (m, 2H), 2.13-2.21 (dd, *J* = 6 MHz, *J* = 15 MHz, 1H), 2.37-2.43 (dd, *J* = 6 MHz, *J* = 12MHz, 1H), 2.89-2.91 (m, 1H) , 3.35-3.39 (m, 1H), 3.64 (s, 3H), 3.75-3.79 (m, 2H), 4.89 (s, 1H), 6.21-6.33 (m, 2H), 7.56-7.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.73, 30.87, 34.09, 48.84, 52.70, 67.91, 69.51, 75.65, 86.78, 96.15, 104.10, 109.80, 111.90, 122.88, 125.17, 127.18, 130.55, 136.86, 136.88, 149.29, 151.73 171.32, 197.68; LRMS: Calcd. for $C_{22}H_{20}NO_6Br$: 474.30. Found: 473.98 (M^+).

Compound 6: IR (CH_2Cl_2): 1087, 1713, 1737, 3489 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz): 1.75-1.86 (m, 2H), 1.97-2.09 (m, 2H), 2.10-2.16 (dd, *J* = 6 MHz, *J* = 12 MHz, 1H), 2.22-2.28 (dd, *J* = 5.6 MHz, *J* = 13.8 MHz, 1H), 2.86-2.93 (m, 1H), 3.38-3.47 (m, 1H), 3.75 (s, 3H), 3.76-3.83 (m, 1H), 5.20 (s, 1H), 6.85-6.94 (m, 2H), 7.19-7.93 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.64, 30.76, 34.12, 48.65, 52.62, 67.64, 70.86, 76.57, 86.90, 103.78, 122.83, 124.22, 124.64, 125.05, 126.053, 130.50, 136.76, 136.89, 138.73, 149.50, 171.93, 197.86; LRMS: Calcd. for $C_{22}H_{21}NO_5S$: 411.47; Found: 411.91 (M^+).

Compound 7: IR (CH_2Cl_2): 1082, 1717, 1736, 3447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz): 1.75-1.89 (m, 2H), 2.06-2.28 (m, 3H), 2.34-2.41 (dd, *J* = 6 MHz, *J* = 13.6 MHz, 1H), 2.59-2.64 (dd, *J* = 6 MHz, *J* = 9 MHz, 1H), 3.07-3.15 (m, 1H) , 3.27 (s, 3H), 4.06-4.15 (m, 1H), 5.3 (s, 1H), 6.26-6.30 (m, 2H), 7.31-7.90 (m, 5H); LRMS: Calcd. for $C_{22}H_{21}NO_6$: 395.41; Found: 394.88 (M^+).

Compound 8: IR (CH_2Cl_2): 695, 1013, 1717, 1737, 3450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz): 1.75-1.89 (m, 2H), 2.03-2.29 (m, 3H), 2.32-2.38 (dd, *J* = 6 MHz, *J* = 15 MHz, 1H), 2.58-2.63 (dd, *J* = 6 MHz, *J* = 9 MHz, 1H), 3.07-3.14 (m, 1H) , 3.32 (s, 3H), 4.05-4.11 (m, 1H), 5.30 (s, 1H), 6.19-6.27 (m, 2H), 7.51-7.88 (m, 4H); LRMS: Calcd. for $C_{22}H_{20}NO_6Br$: 474.30; Found: 473.94 (M^+).

Compound 9: IR (CH_2Cl_2): 1068, 1715, 1735, 3465 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz): 1.77-1.90 (m, 2H), 2.04-2.18 (m, 3H), 2.29-2.38 (dd, *J* = 6 MHz, *J* = 12 MHz, 1H), 2.59-2.63 (dd, *J* = 6 MHz, *J* = 9 MHz, 1H), 3.08-3.15 (m, 1H) , 3.16 (s, 3H),

4.10-4.17 (m, 1H), 5.62 (s, 1H), 6.90-6.96 (m, 2H), 7.18-7.92 (m, 5H); LRMS: Calcd. for $C_{22}H_{21}NO_5S$: 411.47; Found: 411.91 (M^+).

Compound 10: IR (CH_2Cl_2): 1088, 1713, 1736, 3411 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 2.11-2.17 (m, 2H), 2.46 (s, 3H), 3.33-3.38 (m, 2H), 3.68 (s, 3H), 4.9 (s, 1H), 5.95-6.39 (m, 2H), 7.26-7.95 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): 29.4, 37.7, 52.5, 58.0, 67.4, 69.1, 73.9, 85.3, 96.1, 102.9, 108.1, 110.0, 122.7, 125.5, 130.6, 136.9, 142.4, 149.4, 170.8, 198.7; LRMS: Calcd. for $C_{20}H_{19}NO_6$: 369.37. Found: 369.79 (M^+).

Compound 11: IR (CH_2Cl_2): 686, 1018, 1712, 1747, 3425 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 2.15-2.19 (m, 2H), 2.46 (s, 3H), 3.33-3.40 (m, 2H), 3.68 (s, 3H), 4.82 (s, 1H), 6.20-6.28 (m, 2H), 7.55-7.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.53, 37.82, 52.66, 58.05, 68.92, 73.57, 85.31, 96.18, 102.96, 111.30, 111.89, 122.06, 122.75, 125.61, 130.70, 136.76, 149.38, 151.30, 170.53, 198.44; LRMS: Calcd. for $C_{20}H_{18}NO_6Br$: 448.26; Found: 447.88 (M^+).

Compound 12: IR (CH_2Cl_2): 1015, 1714, 1741, 3454 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 1.92-2.07 (m, 2H), 2.47 (s, 3H), 3.32-3.39 (m, 2H), 3.71 (s, 3H), 5.14 (s, 1H), 6.83-6.94 (m, 2H), 7.17-7.97 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.4, 37.8, 52.6, 57.9, 70.1, 85.6, 96.1, 102.8, 122.7, 124.3, 124.7, 125.6, 126.6, 130.6, 136.7, 171.1, 196.7; LRMS: Calcd. for $C_{20}H_{19}NO_5S$: 385.43; Found: 385.79 (M^+).

Compound 13 : IR (CH_2Cl_2): 1143, 1713, 1737, 3445 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 2.09-2.20 (m, 1H), 2.24 (s, 3H), 2.77-2.84 (m, 1H), 3.33 (s, 3H), 3.52-3.57 (m, 2H), 5.45 (s, 1H), 6.26-6.28 (m, 2H), 7.26-7.88 (m, 5H); LRMS: Calcd. for $C_{20}H_{19}NO_6$: 369.37; Found: 369.91 (M^+).

Compound 14: IR (CH_2Cl_2): 738, 1017, 1717, 1735, 3464 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 2.17-2.28 (m, 1H), 2.85 (s, 3H), 3.56 (s, 3H), 3.71-3.76 (m, 2H), 4.22 (s, 3H), 6.12-6.16 (m, 2H), 7.85-8.00 (m, 5H); LRMS: Calcd. for $C_{20}H_{18}NO_6Br$: 448.26; Found: 447.31 (M^+).

Compound 15: IR (CH_2Cl_2): 1012, 1717, 1747, 3454 cm^{-1}; ^1H NMR ($CDCl_3$, 300.1 MHz): 2.15-2.19 (m, 1H), 2.24 (s, 3H), 2.84-2.85 (m, 1H), 3.22 (s, 3H), 3.53-3.56 (m, 2H), 5.71 (s, 1H), 6.88-7.90 (m, 7H); LRMS: Calcd. for $C_{20}H_{19}NO_6$: 385.79; Found: 385.85 (M^+).

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