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An efficient one-pot synthesis of C_2-symmetric pyrrolidines and dispiro pyrrolidines/pyrrolizidines through 1,3-dipolar cycloaddition reaction

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ABSTRACT

A facile and efficient one-pot synthesis of pyrrolidines and dispiro pyrrolidines/pyrrolizidines has been accomplished by the 1,3-dipolar cycloaddtion reaction of azomethine ylides generated insitu from paraformaldehyde/ninhydrin and secondary amino acids with electron-deficient dipolarophiles in good yield. The reaction proceeded with high regio and stereoselectivity. The products have been characterized by elemental analyses and spectroscopic techniques, namely IR, ^1H NMR and ^{13}C NMR spectroscopies as well as mass spectrometry.

Key words: Intermolecular cycloaddition, azomethine ylide, Pyrrolidines, pyrrolizidines, spiro compounds.

INTRODUCTION

In recent years multicomponent reactions [1] leading to interesting heterocyclic scaffolds have emerged as powerful tools for delivering the molecular diversity needed in combinatorial approaches for the synthesis of bioactive compounds [2]. 1,3-Dipolar cycloaddition reactions are efficient methods for the construction of heterocyclic units in a highly regio- and stereoselective manner [3]. In particular, the chemistry of azomethine ylides has gained significance in recent years as it serves as an expedient route for the construction of nitrogen-containing five-membered heterocycles which constitute the central skeleton of numerous natural products [4]. Among various aza heterocycles, functionalised pyrrolidines are a class of heterocycles with significant biological activity [5]. The pyrrolidine alkaloids mimicking the structures DMDP and DRB of pentose with nitrogen in the ring are known to be inhibitors of glycosidases (Figure-1) [6]. Spiro compounds are elegant targets in organic synthesis because of their significant biological activities [7]. In particular, spiro oxindolopyrrolidine and their derivatives have served as potential synthetic intermediates [8] and also act as antiviral, antitumoral, antibiotic agents, local aneasthetics, and inhibitors of human NK-1 receptor etc [9]. Strychnofoline, rhychophylline, elacomine, and pteropodine are some of the alkaloids containing spiropyrrolidinyloxindole-ring system [10].

Natural and synthetic chalcones are of great significance because of their broad spectrum of pharmacological activity [11]. Depending on the substitution pattern on the two aromatic rings, a wide range of pharmacological activities have been identified for various chalcones [12].

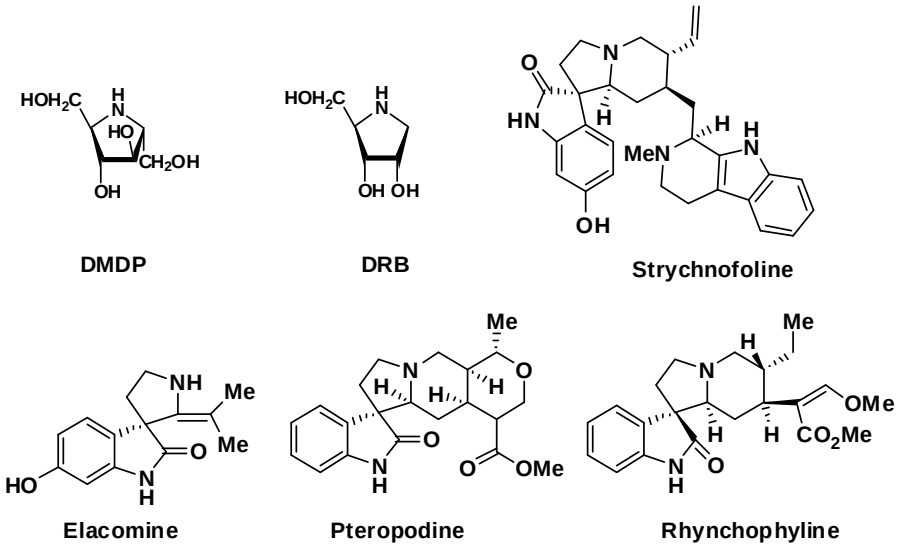


Figure-1

EXPERIMENTAL SECTION

General procedure for synthesis of cycloadducts 7a-c, 8a-c and 10a-c

To a solution of ninhydrin (2 eq), cyclic/acyclic amino acid (3 eq) in dry toluene (15 mL) bischalcones (1eq) was added. The solution was refluxed until the completion of the reaction as evidenced by TLC analysis. The solvent was removed in vacuo and the crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether/ethyl acetate (9:1) as eluent.

1'-methyl-4'-(4-((3'S,4'S)-1'-methyl-3'-(benzoyl)-1,3-dioxo-1,3-dihydrospiro[indene-2,2'-pyrrolidine]-4'-yl)phenyl)-3'-(4-methylbenzoyl)spiro[indene-2,2'-pyrrolidine]-1,3-dione (7a). Yellow solid; yield: 67%; m.p: 98°C; IR (KBr): 1739, 1732, 1643 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 6H), 3.50 (t, 2H), 3.76 (t, 2H), 4.40 (d, 2H *J* = 9.0 Hz), 4.56 (m, 2H), 6.70-8.05 (m, 22H). ^{13}C NMR (75 MHz); δ 36.40, 45.79, 62.33, 64.50, 76.34, 122.67, 122.88, 127.86, 127.97, 128.29, 128.49, 128.76, 133.00, 133.40, 135.53, 136.25, 136.52, 140.80, 181.52, 188.01, 201.23 ppm. MS (EI); m/z = 713.2 (M^+). Anal.Calcd for : $C_{46}H_{36}N_2O_6$: C, 77.51; H, 5.09; N, 3.93; Found; C, 77.60; H, 5.03; N,3.97.

1'-methyl-4'-(4-((3'S,4'S)-1'-methyl-3'-(4-methylbenzoyl)-1,3-dioxo-1,3dihydrospiro [indene-2,2'-pyrrolidine]-4'-yl)phenyl)-3'-(4-methylbenzoyl)spiro[indene-2,2'-pyrrolidine]-1,3-dione (7b). Yellow solid; yield: 71%; m.p: 108°C; IR (KBr): 1742, 1730, 1632 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 6H), 2.32 (s, 6H), 3.39 (m, 2H), 3.68 (m, 2H), 4.20 (d, 2H *J* = 9.0 Hz), 4.46 (m, 2H), 6.55-7.84 (m, 20H). ^{13}C NMR (75 MHz); δ 21.63, 29.69, 36.42, 62.41, 64.54, 98.32, 122.22, 127.82, 128.28, 128.37, 128.51, 128.65, 129.41, 135.36, 135.92, 136.44, 140.71, 140.97, 141.74, 143.93, 179.91, 187.72, 201.18 ppm. MS (EI); m/z = 741.3 (M^+). Anal.Calcd for : $C_{48}H_{40}N_2O_6$: C, 77.82; H, 5.44; N, 3.78; Found; C, 77.92; H, 5.38; N, 3.85.

1'-methyl-4'-(4-((3'S,4'S)-1'-methyl-3'-(2-hydroxybenzoyl)-1,3-dioxo-1,3 dihydrospiro [indene-2,2'-pyrrolidine]-4'-yl)phenyl)-3'-(4-methylbenzoyl)spiro[indene-2,2'-pyrrolidine-1,3-dione (7c). Yellow solid; yield: 68%; m.p: 121°C; IR (KBr): 3038, 1736, 1732, 1647 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 6H), 3.54 (t, 2H), 3.77 (t, 2H), 4.40 (d, 2H *J* = 9.0 Hz), 4.50 (m, 2H), 6.28-7.53 (m, 20H), 11.49 (s, 2H). ^{13}C NMR (75 MHz); δ 35.45, 45.97, 58.55, 63.13, 72.19, 119.72, 120.49, 121.23, 122.19, 122.86, 123.45, 123.77, 129.94, 130.17, 130.79, 131.32, 135.87, 136.37, 136.68, 141.63, 174.19, 183.89, 201.50 ppm. MS (EI); m/z = 745.2 (M^+). Anal.Calcd for : $C_{46}H_{36}N_2O_8$: C, 74.18; H, 4.87; N, 3.76; Found; C, 74.27; H, 4.81; N, 3.81.

(1'R,2'R,7a'S)-2'-benzoyl-1'-(4-((1'S,2'S,7a'R)-2'-benzoyl-1,3-dioxo-1,1',2',3,5',6',7',7a'-octahydrospiro [indene-2,3'-pyrrolizine]-1'-yl)phenyl)-1',2',5',6',7',7a'-hexahydrospiro[indene-2,3'-pyrrolizine]-1,3-dione(8a). Yellow solid; yield: 65%; m.p:114º C; IR (KBr): 1736, 1731, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.76-1.90 (m, 4H), 1.94-1.96 (m, 2H), 2.32 (m, 2H), 2.49 (m, 2H), 2.71 (m, 2H), 3.96 (m, 2H), 4.66 (d, 2H *J* = 11.10 Hz), 4.87 (m, 2H), 6.73-7.79 (m, 22H). ^{13}C NMR (75 MHz); 26.43, 30.01, 45.91, 49.92, 57.17, 68.12, 73.54, 117.03, 119.94,

121.02, 122.38, 125.63, 127.14, 128.10, 128.89, 133.67, 134.20, 135.45, 136.02, 179.43, 184.32, 204.47. MS (EI); m/z = 765.3 (M^+). Anal.Calcd for : $C_{50}H_{40}N_2O_6$: C, 78.52; H, 5.27; N, 3.66; Found; C, 78.61; H, 5.30; N, 3.52.

(1'R,2'R,7a'S)-2'-(4-methylbenzoyl)-1'-(4-((1'S,2'S,7a'R)-2'-(4-methylbenzoyl)-1,3-dioxo-1,1',2',3,5',6',7',7a'-octahydrospiro[indene-2,3'-pyrrolizine]-1'-yl)phenyl)-1',2',5',6',7',7a'-hexahydrospiro[indene-2,3'-pyrroliz -ine]-1,3-dione(8b). Yellow solid; yield: 65%; m.p:148º C; IR (KBr): 1747, 1734, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.73-1.80 (m, 4H), 1.88-1.95 (m, 2H), 1.99 (s, 6H), 2.27 (m, 2H), 2.43 (m, 2H), 2.66 (m, 2H), 4.01 (m, 2H), 4.52 (d, 2H *J* = 11.40 Hz), 4.69 (m, 2H), 6.67-7.61 (m, 20H). ^{13}C NMR (75 MHz); 24.50, 28.67, 30.32, 46.69, 50.62, 58.35, 69.05, 76.25, 117.55, 118.29, 120.59, 121.16, 121.65, 122.18, 126.41, 126.53, 128.21, 128.96, 134.64, 135.16, 136.15, 180.37, 186.37, 204.12. MS (EI); m/z = 793.4 (M^+). Anal.Calcd for : $C_{52}H_{44}N_2O_6$: C, 78.77; H, 5.59; N, 3.53; Found; C, 78.81; H, 5.51; N, 3.47.

(1'R,2'R,7a'S)-2'-(2-hydroxybenzoyl)-1'-(4-((1'S,2'S,7a'R)-2'-(2-hydroxybenzoyl)-1,3-dioxo-1, 1', 2', 3, 5', 6', 7',7a'-octahydrospiro[indene-2,3'-pyrrolizine]-1'-yl)phenyl)-1',2', 5',6',7',7a'-hexahydrospiro[indene-2,3'-pyrrolizine]-1,3-dione(8c). Yellow solid; yield: 73%; m.p:158º C; IR (KBr): 3046, 1741, 1732, 1646 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.75-1.91 (m, 4H), 1.97 (m, 2H), 2.49 (m, 2H), 2.70 (m, 2H), 3.02 (m, 2H), 3.85 (m, 2H), 4.29 (d, 2H *J* = 11.4 Hz), 4.62 (m, 2H), 6.87-7.84 (m, 20H). 12.16 (s, 2H). ^{13}C NMR (75 MHz); 27.76, 30.73, 46.69, 50.65, 58.36, 69.17, 78.76, 117.76, 118.29, 120.59, 121.56, 124.45, 126.54, 128.96, 131.90, 135.02, 138.90, 139.91, 177.24, 186.91, 202.82. MS (EI); m/z = 797.6 (M^+). Anal.Calcd for : $C_{50}H_{40}N_2O_8$: C, 75.36; H, 5.06; N, 3.52; Found; C, 75.42; H, 5.13; N, 3.41.

(1'R,2'R,8a'S)-2'-benzoyl-1'-(4-((1'S,2'S,8a'R)-2'-benzoyl-1,3-dioxo-1,2',3,5',6', 7',8',8ª -octahydro-1'H-spiro[indene-2,3'-indolizine]-1'-yl)phenyl)-2',5',6',7',8',8a'-hexahydro-1'H-spiro[indene-2,3'-indolizine]-1,3-dione(10a). Yellow solid; yield: 67%; m.p:104º C; IR (KBr): 1739, 1734, 1642cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34-1.40 (m, 4H), 1.57(m, 2H), 1.89 (m, 4H), 2.38 (m, 2H), 3.30 (m, 2H), 3.39 (m, 2H), 3.93 (m, 2H), 4.14 (d, 2H *J* = 9.3 Hz), 4.29 (m, 2H), 6.85-7.97 (m, 22H). ^{13}C NMR (75 MHz); 23.27, 27.69, 28.07, 45.35, 49.43, 58.22, 65.08, 74.62, 119.75, 120.74, 121.03, 125.99, 126.61, 126.79, 127.36, 130.81, 130.98, 134.08, 134.27, 136.02, 138.41, 141.07, 141.57, 142.64, 182.63, 188.28, 203.12. MS (EI); m/z = 793.2 (M^+). Anal.Calcd for : $C_{52}H_{44}N_2O_6$: C, 78.77; H, 5.59; N, 3.53; Found; C, 78.85; H, 5.64; N, 3.42.

(1'R,2'R,8a'S)-2'-(4-methylbenzoyl)-1'-(4-((1'S,2'S,8a'R)-2'-(4-methylbenzoyl)-1,3-dioxo-1,2',3,5',6',7',8',8a'-octahydro-1'H-spiro[indene-2,3'-indolizine]-1'-yl)phenyl)-2',5',6',7',8',8a'-hexahydro-1'H-spiro[indene-2,3'-indolizine]-1,3-dione(10b). Yellow solid; yield: 70%; m.p:148ºC; IR (KBr): 1741, 1730, 1639cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26-1.57 (m, 5H), 1.72 (m, 3H), 1.91 (m, 2H), 2.01 (s, 6H), 2.22 (m, 2H), 2.71 (m, 2H), 3.84 (m, 2H), 4.01 (m, 2H), 4.45 (d, 2H *J* = 9.3 Hz), 4.71 (m, 2H), 6.49-7.84 (m, 20H). ^{13}C NMR (75 MHz); 21.36, 25.59, 29.17, 47.35, 51.18, 58.32, 61.27, 66.63, 72.53, 120.45, 121.48, 123.79, 125.47, 126.53, 126.70, 126.98, 127.89, 129.97, 131.69, 133.81, 134.87, 136.25,140.08, 141.57, 178.35, 188.64, 203.37. MS (EI); m/z = 821.4 (M^+). Anal.Calcd for : $C_{54}H_{48}N_2O_6$: C, 79.00; H, 5.89; N, 3.41; Found; C, 79.14; H, 5.81; N, 3.36.

(1'R,2'R,8a'S)-2'-(2-hydroxybenzoyl)-1'-(4-((1'S,2'S,8a'R)-2'-(2-hydroxybenzoyl)-1,3-dioxo-1, 2', 3, 5', 6', 7', 8', 8a'-octahydro-1'H-spiro[indene-2,3'-indolizine]-1'-yl)phenyl)-2',5',6',7',8',8a'-hexahydro-1'H-spiro[indene-2,3'-indolizine]-1,3-dione(10c). Yellow solid, yield: 70%. m.p:138º C. IR (KBr): 3043, 1744, 1734, 1654cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.24-1.51 (m, 6H), 1.74 (m, 3H), 1.89 (m, 2H), 2.18 (m, 2H), 2.59 (m, 2H), 3.76 (m, 2H), 3.99 (m, 2H), 4.34 (d, 2H *J* = 9.0 Hz), 4.61 (m, 2H), 6.69-7.85 (m, 20H), 11.77 (s, 2H). ^{13}C NMR (75 MHz); 24.47, 28.38, 37.34, 48.14, 56.67, 60.02, 68.37, 71.83, 119.37, 120.15, 120.67, 121.39, 123.34, 124.48, 124.94, 126.15, 127.35, 128.55, 129.08, 129.85, 130.78, 131.37, 133.78, 136.79, 139.38, 141.17, 176.39, 186.38, 202.39. MS (EI); m/z = 825.7 (M^+). Anal.Calcd for : $C_{52}H_{44}N_2O_8$: C, 75.71; H, 5.38; N, 3.40; Found; C, 75.79; H, 5.41; N, 3.31.

General procedure for synthesis of cycloadducts 12a-c

To a solution of paraformaldehyde (4 eq), sarcosin (3 eq) in dry toluene (15 mL) bischalcones (1eq) was added. The solution was refluxed until the completion of the reaction as evidenced by TLC analysis. The solvent was removed in vacuo and the crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether/ethyl acetate (8:2) as eluent.

(3R,3'S)-4,4'-(1,4-phenylene)bis(1-methylpyrrolidine-4,3-diyl)bis(phenylmethanone) (12a). Light yellow solid;. Yield: 65%; m.p:108°C; IR (KBr): 1637 cm-1; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 6H), 2.71 (m, 2H), 3.07(d, 2H), 3.35(t, 2H), 4.01 (m, 2H), 4.22 (m, 2H), 4.46 (m, 2H), 6.68-7.79 (m, 14H). ^{13}C NMR (75 MHz); δ 30.07, 42.35, 49.36, 54.18, 56.39, 125.59, 126.36, 127.18, 127.83, 128.94, 131.84, 141.29, 143.37, 190.15 ppm. MS (EI); m/z = 453.6 (M+1). Anal.Calcd for : $C_{30}H_{32}N_2O_2$: C, 79.61; H, 7.13; N, 6.19; O, 7.07; Found; C, 79.72; H, 7.09; N, 6.12.

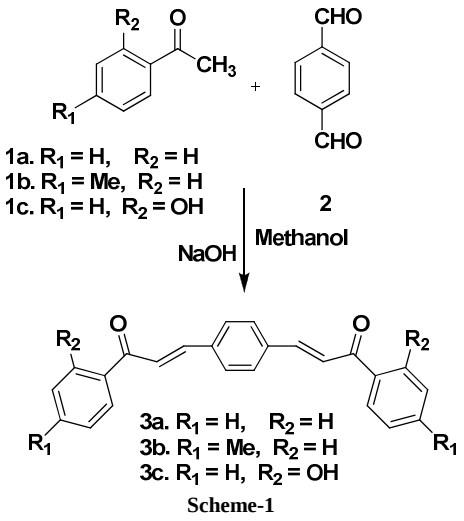
4,4'-(1,4-phenylene)bis(1-methylpyrrolidine-4,3-diyl)bis(p-tolylmethanone)(12b). Light yellow solid; Yield: 69%; m.p:130°C; IR (KBr): 1632 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 6H), 2.36 (s, 6H), 2.89 (m, 2H), 3.11 (d, 2H),3.40(t, 2H), 3.92 (m, 2H), 4.13 (m, 2H), 4.38 (m, 2H), 6.79-7.86 (m, 12H). ^{13}C NMR (75 MHz); δ 20.65, 28.67, 40.75, 45.51, 53.48, 61.44, 127.27, 127.63, 127.77, 127.83, 128.33, 132.71, 142.63, 142.92, 189.01 ppm. MS (EI); m/z = 481.4 (M+1). Anal.Calcd for : $C_{32}H_{36}N_2O_2$: C, 79.96; H, 7.55; N, 5.83; Found; C, 79.89; H, 7.62; N, 5.79.

(3R,3'S)-4,4'-(1,4-phenylene)bis(1-methylpyrrolidine-4,3-diyl)bis((2-hydroxyphenyl)methanone) (12c).
Yellow solid; Yield: 71%.; m.p:102°C; IR (KBr): 3032 and 1642 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 6H), 2.24 (t, 2H), 2.71 (t, 3H), 2.83 (t, 2H),3.05 (t, 2H), 3.50 (m, 2H), 3.99 (m, 2H), 6.61-7.44 (m, 12H), 11.54 (s, 2H). ^{13}C NMR (75 MHz); δ 34.33, 40.88, 53.70, 59.27, 69.54, 117.51, 117.74, 122.95, 123.34, 123.44, 126.36, 126.97, 127.36, 129.20, 135.42, 204.34 ppm. MS (EI); m/z = 485.5 (M+1). Anal.Calcd for : $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78; Found; C, 74.47; H, 6.57; N, 5.63.

RESULTS AND DISCUSSION

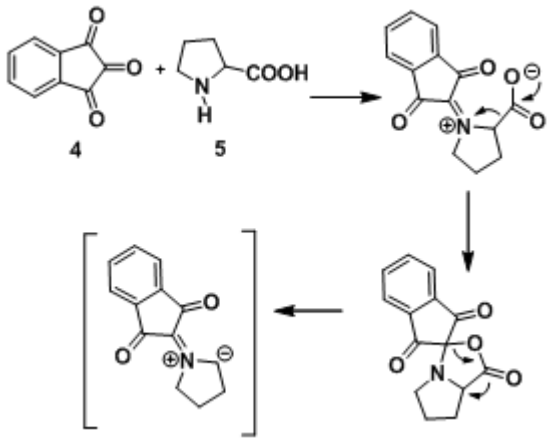
In view of these observations and in continuation of our work in the area of cycloaddition reactions [13], we herein report for the first time, the reaction of bischalcone derivatives **1a–c** as 2π components in 1,3-dipolar cycloaddition reactions with various azomethine ylides for the facile synthesis of hitherto unknown dispiro pyrrolidines/pyrrolizidines.

The required dipolarophiles **3a-c** for the present study, were prepared by the Claisen-Schmidt reaction, by reacting various substituted acetophenones with terephthalaldehyde (Schemes-1). The products were assigned the (*E*)-configuration based on the chemical shift value of olefinic protons in accordance with the literature data [14].

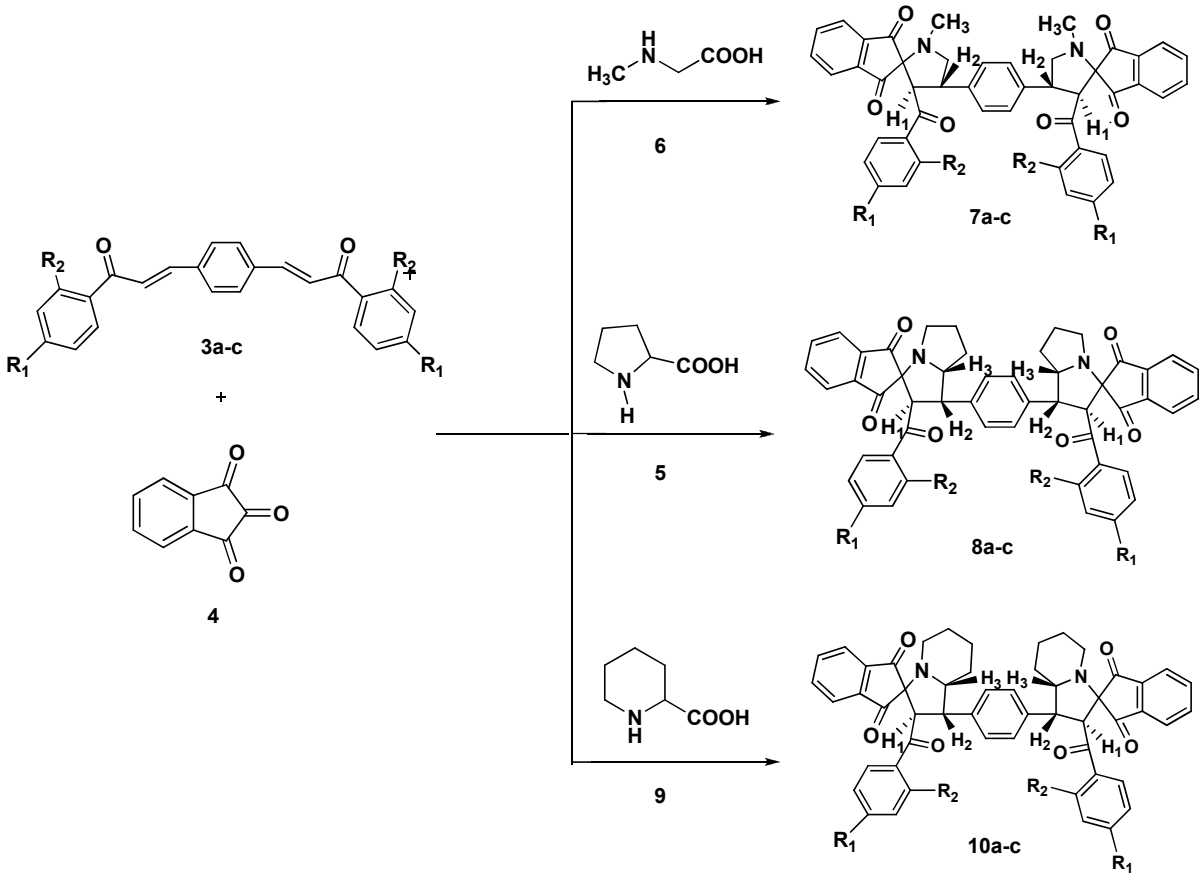


Scheme-1

Thus the dipoles generated from ninhydrin **4** and various amino acids namely sarcosine **6**, proline **5** and pipecolinic acid **9** were reacted with the bischalcone dipolarophiles **3a–c** in refluxing toluene under Dean-Stark reaction condition to afford a series of novel dispiro pyrrolidines/pyrrolizidines **7a–c, 8a–c and 10a–c**. (Table-1) The structures of the cycloadducts were confirmed through spectral and elemental analysis. (Scheme-3)



Scheme-2: Mechanism for the generation of azomethine ylide



a. R_1 = H,R_2 = H b. R_1 = Me,R_2 = H c. R_1 = H,R_2 = OH

Scheme-3: Synthesis of dispiro pyrrolidines/pyrrolizidines

Double cycloaddition with the azomethine ylides generated from ninhydrin and various amino acids gave a good yield of the bis-adduct. The complete regio and stereoselectivity occurred, ^{1}H NMR indicated a single isomer in the very well resolved spectra of this molecule and the global symmetry of this molecule is C_2.

The products were characterized on the basis of their elemental analysis as well as ^{1}H, ^{13}C, DEPT 135, 2D NMR and mass spectral analysis. For instance, the IR spectrum of the compound **8a** exhibited peak at 1643 cm^{-1} for the benzoyl carbonyl and the indane-1,3-dione carbonyls showed a peaks at 1731 and 1736 cm^{-1}.

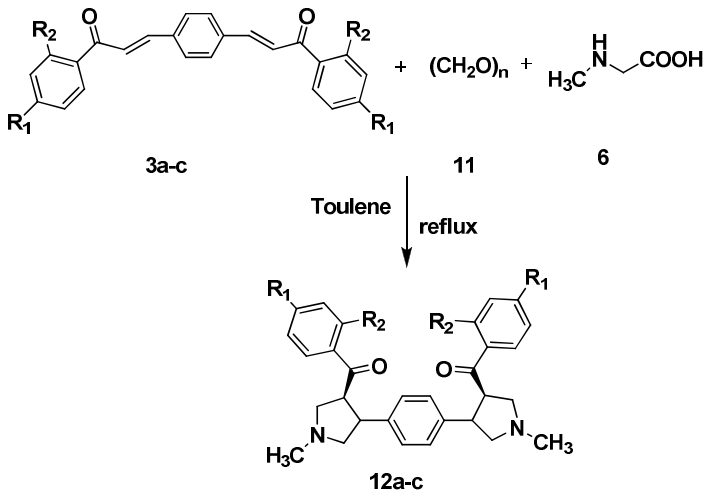
The ^{1}H NMR spectrum of the compound **8a** showed a multiplets in the region δ 1.76-1.90, 1.94-1.96, 2.32, 2.49 and 2.71 for the pyrrolizidine ring protons. The –CH protons of the pyrrolizidine ring H_3 resonated as a multiplet at δ 3.96. The benzylic H_2 proton showed a multiplet at δ 4.87 and the benzoyl proton H_1 appeared as a doublet at δ 3.42 (J = 11.10 Hz), which clearly shows the regioselectivity of the cycloadduct. If other isomer had formed benzoyl proton H_1 would have shown a multiplet instead of a doublet.

The configuration of the newly formed asymmetric centres on the cycloadduct **8a** was proposed based on 2D NMR experiments. In Scheme 2, the useful information taken from the COSY and NOESY spectra of adduct **8a** is summarized. The COSY experiment allowed the complete assignment of the hydrogens. The strong NOESY between H_2 and Hc shows *cis* stereochemistry and there is no NOESY between H_2 and H_1 of **8a** shows *trans* stereochemistry. Furthermore, interaction between the *cis* H_3 and H_2 protons confirmed the assignment made on the basis of the COSY experiment. The multiplets appeared in the region δ 6.73-7.79 were due to aromatic protons.

The ^{13}C NMR spectrum of **8a** showed carbon signals at 26.43, 30.01, 45.91, 49.92, 57.17, and 68.12 ppm for the pyrrolizidine ring carbons. The spiro carbon exhibited signal at 73.54 ppm. The aromatic carbons appeared at 117.03, 119.94, 121.02, 122.38, 125.63, 127.14, 128.10, 128.89, 133.67, 134.20, 135.45, and 136.02 ppm. The benzoyl carbonyl carbon appeared at 204.47 ppm, and the indane-1,3-dione ring carbonyl carbons at 184.32 and 179.43 ppm.

In addition, the mass spectrum of the compound **8a** showed the molecular ion peak at m/z 765.3(M^+) and the compound gave satisfactory elemental analysis.

The protocol was extended for the synthesis of bis-pyrrolidines **12a-c** by reacting sarcosin **6** and paraformaldehyde **11** with bisdipolarophiles **3a-c**.(Table-1) The dipolarophiles **1a-c** the double bonds of the bischalcone to give bis-pyrrolidines **12a-c** in good yield. (Scheme-4)



Scheme-4: synthesis of bis-pyrrolidines

The formation of the cycloadducts **12a-c** was confirmed by mass spectral studies and the structures of the products were deduced by NMR spectroscopic techniques. For instance, the IR spectrum of the cycloadduct **12a** showed characteristic bands at 1637cm^{-1} which correspond to the benzoyl carbonyl group.

The ^{1}H NMR spectrum of the cycloadduct **12a** exhibited a singlet at δ 2.31 which corresponds to N-CH_3 protons of the pyrrolidine ring. Multiplets were observed at δ 4.22 and 4.46 for benzylic and benzoyl protons. The aromatic protons exhibited multiplet in the region δ 6.68-7.79. In the ^{13}C NMR the -NCH_3 carbon of the pyrrolidine ring showed a peak at 30.07 ppm and two –NCH_2 carbons appeared at 42.35, 49.36 ppm respectively. Peaks at 190.15 ppm correspond to the benzoyl carbonyl group. The mass spectrum of the compound **12a** showed a peak at 453.6 (M^+) which corresponds to the molecular weight of the compound.

Table-1: synthesis of dispiro pyrrolidines/pyrrolizidines and bis-pyrrolidines

S.No	Product	R_1	R_2	Time (h)	Yield (%)
1	4a	H	H	6	67
2	4b	Me	H	5.5	71
3	4c	H	OH	6	68
4	6a	H	H	5	65
5	6b	Me	H	5.5	65
6	6c	H	OH	6.5	73
7	8a	H	H	6	67
8	8b	Me	H	5	70
9	8c	H	OH	5.5	70
10	10a	H	H	8.5	65
11	10b	Me	H	9	69
12	10c	H	OH	8	71

In summary, we have successfully synthesized C_2-symmetrical dispiro pyrrolidines /pyrrolizidines and bis-pyrrolidine derivatives by 1,3-dipolar cycloaddition reaction of azomethine ylide generated from ninhydrin with sarcosine /proline/ pipecolinic acid and paraformaldehyde with sarcosin for the efficient three-component one-pot synthesis.

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