Research Paper www.ijcps.com

International Journal of
Chemical and Pharmaceutical Sciences
2013, June., Vol. 4 (2)

ISSN: 0976-9390
IJCPS

Synthesis of sugar-annulated dispiro pyrrolizidines through intermolecular 1,3-dipolar cycloaddition reaction

Sirisha Nallamala and Raghavachary Raghunathan*

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India.

*Corresponding Author: E-Mail: ragharaghunathan@yahoo.com

ABSTRACT

An expedient method for the synthesis of glyco dispiro pyrrolizidines is reported through 1,3-dipolar cycloaddition reaction (1,3 DC reaction). The novel glycosyl dipolarophile derived from dicyclohexylidine glucose underwent neat [3+2] cycloaddition reaction with the azomethine ylide generated from 1,2-diketones and cyclic amino acid to give the corresponding glycosidic heterocycles in good yields.

Keywords: Carbohydrates, 1,3-dipolar cycloaddition, azomethine ylide, dispiroheterocyclics, pyrrolizidines, glycosides.

1. INTRODUCTION

Carbohydrates are one of the most important classes of organic compounds in nature. In recent years, much attention has been focused on the synthesis and development of glycosidase inhibitors [1] because of an increasing awareness of the vital role played by carbohydrates in biological process. A variety of carbohydrate-derived heterocyclic compounds have been synthesized and found to act as potent inhibitor of various glycosidases. Therefore, it is now recognized that carbohydrates are at the heart of a multitude of biological events. With this stimulating biological background, the efficient synthesis of not only carbohydrates themselves, but also carbohydrate-containing heterocycles is becoming more and more important in the field of organic chemistry and chemical biology [2]. Hence there has been renewed interest in the synthesis of carbohydrate based heterocycles.

1,3-Dipolar cycloaddition reactions are efficient methods for the construction of heterocyclic units in a highly regio- and stereoselective manner [3-5]. 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 fivemembered heterocycles, which constitute the central skeleton of numerous natural products [6]. Amongst various aza heterocycles, functionalized pyrrolizidines are a class of alkaloids with significant biological activity [7,8] Spiro compounds represent an important class of naturally occurring substances characterized by their pronounced biological properties [9–15], including potent aldose reductase inhibitions and polio and rhinovirus 3C-proteinase inhibitions.

Continuing our interest in the area of 1,3-dipolar cycloaddition reaction [16,17] and prompted by reports on the structural features and biological activity of carbohydrates and spiropyrrolidines, we contemplated fusing structurally unique spiro-pyrrolidine motifs with properly functionalized glycoside derivatives, on the assumption that fusion might lead to a new class of carbohydrate- based heterocycles with potential biological activities. Towards this end, we report, for the first time, a simple and short approach to a new series of sugar-fused dispiropyrrolidines by using sarcosine and 1,2-di/tri ketones (isatin/ ninhydrin/ acenaphthoquinone) to generate azomethine ylide that react with a sugar-derived precursors derived from dicyclohexylidine glucose.

2. MATERIALS AND METHODS

IR spectra were recorded on a SHIMADZU 8300 series FT-IR instrument. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Bruker 300 spectrometer at 300 MHz. ^{13}C NMR was recorded on a Bruker 300 spectrometer at 75 MHz. Mass spectra were recorded Thermo Finnigan (LCQ) Amax 6000 ESI mass spectrometer. Elemental analysis was carried out using Perkin-Elmer CHNS 2400B instrument.

2.1. Representative procedure for the synthesis of dipolarophile **3**

To a stirred solution of sugar aldehyde 1 (1mmol) and dimedone 2 (1mmol) in ethanol (10 mL), triethylamine (1 mmol) was added at room temperatue and stirring was continued for 4 h. After completion of the reaction, the reaction mixture was poured in to the ice water (5 mL) sticky solid was formed which was extracted with ethyl acetate (3×20 mL). The organic phase was successively washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography using hexane and ethyl acetate and (9:1) as eluent to afford the corresponding dipolarophile in good yields.

2.1.1. 2-[(3'aR,5'R,6'S,6'aR)-6'-(benzyloxy)-tetrahydrospiro[cyclohexane-1,2'-furo[2,3d] [1,3]dioxole]-5'-ylmethylidene]-5,5-dimethylcyclohexane-1,3-dione (3)

Colourless powder. Yield 70%. m.p; 152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz); δ 0.85 (s, 3H), 0.92 (s, 3H), 1.41-1.64 (m, 10H), 2.02 (d, J = 8.7 Hz, 2H), 2.27 (d, J = 8.7 Hz, 2H), 2.57 (d, J = 3.9 Hz, 1H), 4.21 (d, J = 12 Hz, 1H),4.37-4.47 (m, 3H),5.67 (d, J = 3.6 Hz, 1H), 7.2-7.24 (m, 5H), 7.49 (s, 1H).^{13}C NMR (75 MHz); ppm 22.49, 23.12, 24.94, 25.90, 26.02, 30.74, 33.29, 34.41, 70.27, 71.42, 72.41, 84.49, 85.42, 106.49, 114.42, 127.49, 128.52, 128.59, 130.49, 136.72, 147.44, 194.37, 194.88. MS (ESI); *m/z* 441.2 (M^++1).

2.2. General procedure for synthesis of cycloadducts (6,8,10)

To a mixture of ninhydrin 5/ isatin 7/ acenaphthequinone 9 (1 mmol) and proline 4 (2 mmol), glycosylidene dimedone **3** (1 mmol) was added and heated under reflux in methanol (20 mL) until the disappearance of the starting materials as evidenced by TLC. The solvent was removed under vacuo. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate as eluent.

2.2.1. Spectral data of compound 6

Colourless powder. Yield; 61%. m.p: 66 °C. IR (KBr); 1722, 1726, 1732, 1734 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz); δ 0.92 (s, 3H), 0.95 (s, 3H), 1.25-1.39 (m, 8H), 1.42-1.60 (m, 6H), 1.91- 1.94 (m, 1H), 2.13- 2.16 (m, 1H), 2.22 (d, J = 9.3 Hz, 2H), 2.32(d, J = 9.3 Hz, 2H), 2.90-2.97 (m, 1H), 3.43 (d, J = 6.9 Hz, 1H), 3.54 (dd, J = 6.9, 3.6 Hz, 1H), 4.07-4.12 (m, 2H), 4.46 (d, J = 12.3 Hz, 1H), 4.74 (d, J = 3.6 Hz, 1H), 6.03 (d, J = 3.6 Hz, 1H), 6.73- 6.82 (m, 5H), 7.95- 8.03 (m, 4H). ^{13}C NMR (75 MHz); ppm 20.52, 21.54, 22.47, 23.24, 24.17, 25.67, 26.54, 27.12, 29.06, 32.19, 33.08, 50.08, 50.49, 53.15, 57.89, 66.18, 67.42, 69.51, 75.79, 80.15, 81.23, 103.87, 113.67, 119.87, 120.78, 121.08, 122.21, 122.25, 123.37, 127.54, 128.99, 130.02, 131.15, 132.61, 134.49, 195.78, 196.08, 201.19, 201.68. MS (ESI); *m/z* 654.5 (M^++1). Anal.Calcd for $C_{39}H_{43}NO_8$; C, 71.65; H, 6.63; N, 2.14%. Found; C, 71.68; H, 6.67; N, 2.09%.

2.2.2. Spectral data of compound **8**

Colourless powder. Yield; 59%. m.p; 64 °C. IR (KBr); IR (KBr); 1697, 1730, 1733 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz); δ .92 (s, 3H), 0.96 (s, 3H), 1.28-1.47 (m, 10H), 1.53-1.59 (m, 4H), 1.82- 1.90 (m, 1H), 2.03- 2.11 (m, 1H), 2.18(d, J = 9 Hz, 2H), 2.28 (d, J = 9 Hz, 2H), 2.89-2.91 (m, 1H), 3.32 (d, J = 6.6 Hz, 1H), 3.54 (dd, J = 6.6, 3.6 Hz, 1H), 3.96- 4.07 (m, 2H), 4.42(d, J = 12.3 Hz, 1H), 4.63 (d, J = 3.6 Hz, 1H), 5.99 (d, J = 3.6 Hz, 1H), 6.82- 7.21 (m, 6H), 7.55- 7.82 (m, 3H), 8.37 (s, 1H). ^{13}C NMR (75 MHz); ppm 20.52, 21.54, 22.47, 23.24, 24.17, 25.67, 26.54, 27.12, 29.06, 32.19, 33.08, 50.08, 50.49, 53.15, 57.89, 66.18, 67.42, 69.51, 75.79, 80.15, 81.23, 103.87, 113.67, 119.81, 120.44, 121.29, 124.45, 125.06, 125.95, 126.26, 127.16, 128.26, 128.46, 132.37, 133.27, 174.12, 201.38, 201.75. MS (ESI); *m/z* 641.4 (M^++1). Anal.Calcd for $C_{38}H_{44}N_2O_7$; C, 71.23; H, 6.92; N, 4.37%. Found; C, 71.31; H, 6.98; N, 4.26%.

2.2.3. Spectral data of compound 10

Colourless powder. Yield; 63%. m.p; 52 °C. IR (KBr); 1720, 1734, 1736 cm^{-1}.^{1}HNMR ($CDCl_3$, 300 MHz); δ 0.92 (s, 3H), 0.95 (s, 3H), 1.22-1.46 (m, 8H), 1.52-1.61 (m, 6H), 1.86- 1.91 (m, 1H), 2.14- 2.23(m, 1H), 2.18 (d, J = 9 Hz, 2H), 2.28 (d, J = 9 Hz, 2H), 2.91-2.95 (m, 1H), 3.31 (d, J = 6.9 Hz, 1H), 3.64 (dd, J = 6.9, 3.6 Hz, 1H), 4.06- 4.12 (m, 2H), 4.36 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 3.6 Hz, 1H), 5.98 (d, J = 3.6 Hz, 1H), 6.72- 7.48 (m, 11H). ^{13}C NMR (75 MHz); ppm 21.13, 22.45, 23.17, 24.14, 25.28, 25.78, 26.26, 27.12, 29.42, 32.15, 33.16, 51.56, 52.05, 54.27, 58.18, 66.14, 67.25, 69.12, 77.03, 80.14, 81.14 104.01, 113.90, 119.34, 120.42, 121.29, 122.15, 123.13, 124.42, 126.63, 127.62, 128.52, 130.62, 131.92, 132.61, 135.16, 136.18, 139.53, 140.09, 195.42, 200.68, 201.08. MS (ESI); *m/z* 676.6 (M^++1). Anal.Calcd for $C_{42}H_{45}NO_7$; C, 74.64; H, 6.71; N, 2.04%. Found; C, 74.72; H, 6.69; N, 2.01%.

2.3. General procedure for synthesis of cycloadducts (12, 13, 14)

To a mixture of ninhydrin 5/ isatin 7/ acenaphthequinone 9 (1 mmol) and pipecolinic acid 11 (2 mmol), glycosylidene dimedone 3 (1 mmol) was added and heated under reflux in methanol (20 mL) until the disappearance of the starting materials as evidenced by TLC. The solvent was removed under vacuo. The crude product was subjected to column chromatography using petroleum ether-ethyl acetate as eluent.

2.3.1. Spectral data of compound 12

Colourless powder. Yield; 661%. m.p: 54 °C. IR (KBr); 1722, 1726, 1731, 1735 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz); δ 0.93 (s, 3H), 0.97 (s, 3H), 1.15-1.34 (m, 6H), 1.46-1.55 (m, 5H), 1.59-1.65 (m, 5H), 1.88- 1.92 (m, 1H), 2.04- 2.14 (m, 1H), 2.19 (d, J = 9 Hz, 2H), 2.27 (d, J = 9 Hz, 2H), 2.84-2.92(m, 1H), 3.45 (d, J = 6.9 Hz, 1H), 3.57 (dd, J = 6.9, 3.6 Hz, 1H), 3.95- 4.08 (m, 2H), 4.32 (d, J = 12.3 Hz, 1H), 4.71 (d, J = 3.6 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 6.71- 6.83 (m, 5H), 7.92- 8.01 (m, 4H). ^{13}C NMR (75 MHz); ppm 20.12, 21.43, 22.13, 22.52, 26.34, 27.42, 28.95, 29.42, 30.16, 31.16, 33.17, 34.03, 48.34, 53.05, 54.16, 57.52, 66.82, 68.25, 70.21, 78.39, 80.64, 81.51, 103.74, 114.86, 119.42, 120.93, 121.32, 122.82, 122.81, 123.25, 127.63, 128.93, 130.05, 131.52, 132.62 134.53, 194.53, 195.34, 201.52, 201.86. MS (ESI); *m/z* 666.3 (M^++1). Anal.Calcd for $C_{41}H_{47}NO_7$; C, 73.96; H, 7.12; N, 2.10%. Found; C, 73.99; H, 7.21; N, 2.01%.

2.3.2. Spectral data of compound 13

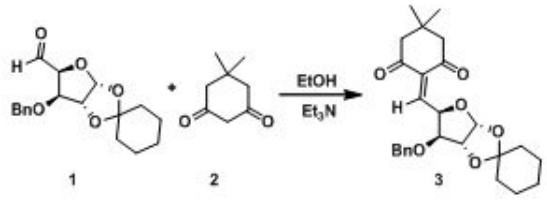
Colourless powder. Yield; 58%. m.p; 62 °C. IR (KBr); 1712, 1728, 17332 cm^{-1}.^{1}HNMR ($CDCl_3$, 300 MHz); δ 0.94 (s, 3H), 0.97 (s, 3H), 1.18-1.34 (m, 5H), 1.38-1.57 (m, 6H), 1.65-1.71 (m, 5H), 1.78- 1.85 (m, 1H), 1.96- 2.05 (m, 1H), 2.23 (d, J = 9.3 Hz, 2H), 2.32 (d, J = 9.3 Hz, 2H), 2.93-3.03 (m, 1H), 3.25 (d, J = 6.6 Hz, 1H), 3.54 (dd, J = 6.6, 3.6 Hz, 1H), 4.04- 4.08 (m, 2H), 4.35 (d, J = 12.3 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 5.99 (d, J = 3.6 Hz, 1H), 6.72- 7.15 (m, 6H), 7.54- 7.85 (m, 3H), 8.25 (s, 1H). ^{13}C NMR (75 MHz); ppm 21.07, 22.18, 23.05, 23.64, 25.51, 26.22, 28.42, 28.95, 30.16, 32.24, 32.75, 46.65, 54.72, 55.25, 57.62, 67.41, 68.65, 70.86, 78.95, 80.67, 81.38, 103.53, 114.23, 119.93, 120.61, 121.41, 124.63, 125.13, 125.62, 126.66, 127.15, 127.96, 128.16, 132.05, 133.50, 174.76, 201.82, 202.15. MS (ESI); *m/z* 655.4 (M^++1). Anal.Calcd for $C_{39}H_{46}N_2O_7$; C, 71.54; H, 7.08; N, 4.28%. Found; C, 71.61; H, 7.12; N, 4.15%.

2.3.3. Spectral data of compound 14

Colourless powder. yield; 63%. m.p; 56 °C. IR (KBr); 1719, 1732, 1738 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz); δ 0.91 (s, 3H), 0.95 (s, 3H), 1.21-1.48 (m, 9H), 1.53-1.72 (m, 7H), 1.89- 1.96 (m, 1H), 2.03- 2.12 (m, 1H), 2.27 (d, J = 9 Hz, 2H), 2.56 (d, J = 8.1 Hz, 1H), 2.87-2.93(m, 1H), 3.34 (d, J = 6.9 Hz, 1H), 3.62 (dd, J = 6.9, 3.6 Hz, 1H), 3.95- 4.05 (m, 2H), 4.37 (d, J = 12.3 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 5.97 (d, J = 3.6 Hz, 1H), 6.56- 7.41 (m, 11H). ^{13}C NMR (75 MHz); ppm 20.18, 21.52, 22.28, 23.91, 24.18, 25.92, 26.39, 27.49, 28.07, 30.61, 32.13, 32.72, 47.65, 53.83, 56.25, 58.62, 67.15, 68.34, 69.72, 78.05, 80.52, 81.52, 103.41, 114.63, 119.84, 120.95, 122.09, 122.82, 123.94, 124.96, 126.25, 127.91, 128.26, 130.16, 131.82, 132.56, 135.53, 136.63, 139.72, 140.15, 194.62, 200.89, 201.13. MS (ESI); *m/z* 670.4 (M^++1). Anal.Calcd for $C_{43}H_{47}NO_7$; C, 74.87; H, 6.87; N, 2.03%. Found; C, 74.94; H, 6.91; N, 1.96%.

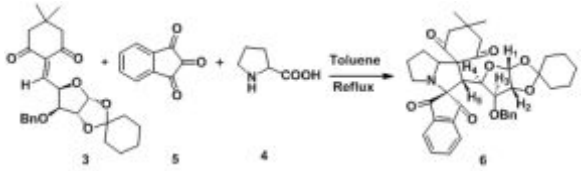
3. RESULTS AND DISCUSSION

Our strategy commenced with the synthesis of glycosylidene dimedone 3 by the base catalysed condensation of dimedone 2 with O-benzyl tethered sugar aldehyde [18] 1 (Scheme-1). The structure of the glycoside 3 was deduced on the basis of ^{1}H NMR spectral data where the presence of singlet at δ 7.49 for alkene proton and two singlets at δ 0.85, 0.92 for two –CH_3 groups of dimedone group confirmed the formation of the product.



Scheme-1

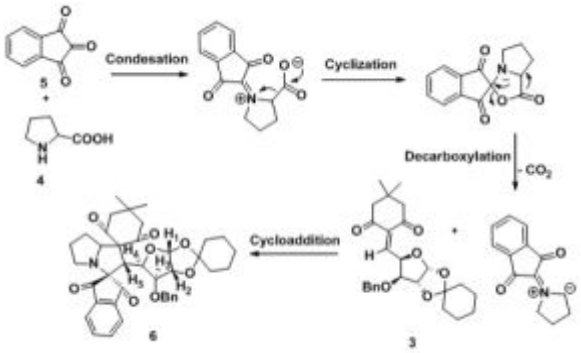
Having synthesized carbohydrate derived dipolarophile 3, we carried out the cycloaddition reaction of azomethine ylide generated in situ by the decarboxylative condensation of ninhydrin 5 and proline 4 with dipolarophile 3 in refluxing toluene, which led to the formation of glyco-dispiropyrrolizidine 6 as a single product, as evidenced by TLC and spectral analysis. The cycloaddition was found to be highly regioselective. (Schemes-2&3) The structure and the stereochemistry determined by analysis of their ^{1}H, ^{13}C, DEPT-135, ^{1}H-^{1}H-, ^{1}H-^{13}C-COSY, sNOESY experiments in the NMR spectrum. The absolute configurations of these compounds were assigned by establishing the relative stereochemistry of the newly formed stereocentres with those already present in the starting material 1 [19,20].



Scheme-2

In the ^{1}H NMR spectrum of the compound 6 the *N*-CH proton (H_5) of the pyrrolizidine ring appeared as a doublet at δ 3.43 (J = 6.9 Hz) which clearly shows the regioselectivity of the cycloadduct. If other isomer had formed H_5 proton would have shown a multiplet instead of a doublet. The H_4 proton of the furanose moiety appeared as a doublet of doublet at δ 3.54 (J = 3.6, 6.9 Hz). The H_1 and H_2 protons of the furanose ring

appeared as two doublets at δ 6.03 (J = 3.6 Hz), and δ 4.74 (J = 3.6 Hz) respectively. One of the benzyl proton and the H_3 proton appeared as a multiplet in the region δ 4.07- 4.12 and the other benzyl proton appeared as a doublet at δ 4.46 (J = 12.3 Hz). The H_6 proton of the pyrrolizidine moiety appeared as a multiplet in the region δ 2.90-2.97 and the *N*-CH_2 protons showed two separate multiplets in the region δ 2.13- 2.16 and δ 1.91- 1.94. From the ^1H–^1H COSY and ^1H–^{13}C COSY spectra of 6 we have assigned the signals at δ 6.03 to H_1 proton, δ 4.74 to H_2 proton, δ 3.54 to H_4 proton and δ 3.43 to H_5 proton.

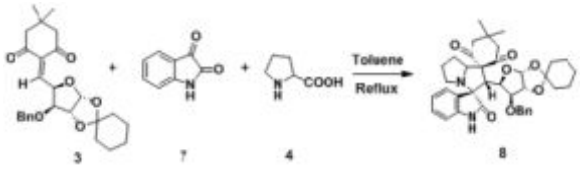


Scheme-3

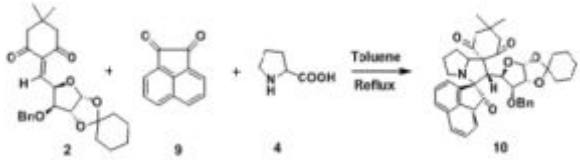
The off resonance decoupled ^{13}C NMR spectrum of the product 6 showed a peak at 57.89 ppm due to *N*-CH carbon of pyrrolizidine ring. The two spiro carbons appeared at 75.79 and 66.18ppm. The *N*-CH_2 carbon of the pyrrolizidine ring exhibited peak at 53.15 ppm and was confirmed by DEPT-135 & ^1H-^{13}C correlation spectrum. The DEPT -135 spectrum showed a peak at 67.42 ppm in negative region confirmed the presence of *O*-CH_2 carbon. The furanose ring carbons appeared at 69.51, 80.15, 81.23, 103.87ppm. The indane-1,3-dione ring carbonyl carbons exhibited at 195.78, 196.08 ppm and the dimedone carbonyl groups appeared at 201.19, 201.68 ppm.

The mass spectrum of the compound 6 showed a molecular ion peak at m/z 654.5 (M^++1) which when coupled with the above spectral features confirms the structure of the cycloadduct. Also the product exhibited satisfactory elemental analysis.

After the successful completion of cycloaddition reaction glycosylidene dimedone 3 with ninhydrin 5 and proline 4, we have carried out the cycloaddition reaction of glycosylidene dimedone 3 with the azomethine ylide generated from the proline 4 and isatin 7/ acenaphthequinone 9. The reaction had occurred around the exocyclic double bond of the glycosylidene derivative and resulting in the formation of dispiro pyrrolizidines as a single product 8 and 10 in both cases. The structure of these products was also established by spectral data. (Schemes-4&5)

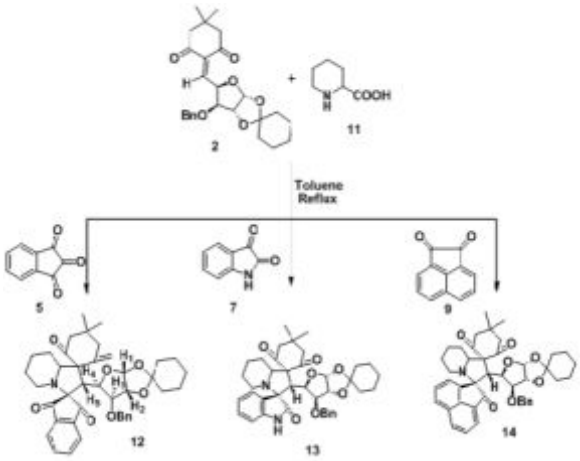


Scheme-4



Scheme-5

In order to extend the scope of the reaction, the same reaction was extended with pipecolinic acid 11. We have studied the reaction of glycosylidene dimedone 3 with azomethine ylide generated *in situ* by the decarboxylative condensation of pipecolinic acid 11 and ninhydrin 5/ isatin 7/ acenaphthequinone 9. The reaction proceeded smoothly resulting in the formation of dispiro pyrrolizidines 12, 13 and 14 as a single product in all cases. The structure of the products was established by spectral data. (Scheme 6)



Scheme-6

For instance, the IR spectrum of the product 13 exhibited a peak at 1712cm^{-1}characteristic of oxindole carbonyl carbon. The absorption bands at 1728 and 17332 cm^{-1} are attributed to the presence of dimedone carbonyl peaks.

The ^1H NMR spectrum of 13 exhibited a doublet at δ 3.25 (J = 6.6 Hz) for the *N*-CH proton (H_5) of the pyrrolizidine ring which clearly shows the regioselectivity of the cycloadduct. The H_4 proton of the furanose moiety appeared as a doublet of doublet at δ 3.54 (J = 3.6, 6.6 Hz). The H_6 proton of the pyrrolizidine moiety appeared as

a multiplet in the region δ 2.93-3.03 and the *N*-CH_2 protons showed two separate multiplets in the region δ 1.78- 1.85, 1.96- 2.05. The oxindole –*N*H proton appeared as a singlet at δ 8.25. The signals in the ^{13}C NMR spectrum of 13 at 67.41, and 78.95, ppm correspond to the two spiro carbons. The oxindole carbonyl carbon appeared at 174.76 ppm and the dimedone carbonyl peaks appeared at 201.82, 202.15 ppm.

Moreover, the presence of a molecular ion peak at m/z 655.4 (M^++1) in the mass spectrum of 13 confirming the structure of the cycloadduct.

4. CONCLUSIONS

In conclusion we have synthesized a series of novel sugar fused dispiro pyrrolizidine derivatives through 1,3-dipolar cycloaddition reaction of azomethine ylide generated from proline/ pipecolinic acid and isatin/ ninhydrin/ acenaphthequinone with sugar derived dipolarophile. The addition is highly regioselective and gave single regioisomer in all the cases studied.

Acknowledgments

One of the authors, N.S. thanks the Council of Scientific and Industrial Research, New Delhi, India, for the research fellowship.

5. REFERENCES

1. McGuire JL. Pharmaceuticals, Ed.; Wiley-VCH; Weinheim. 2000; 1-4
2. Hanessian S. Preparative CarbohydrateChemistry. Ed.; Marcel Dekker: New York, 1997.
3. Padwa A. 1,3-Dipolar Cycloaddition Chemistry, vols. 1-2,Wiley, NewYork, 1984.
4. Tsuge O and Kanemasa, S. In Advances in Heterocyclic Chemistry; Katritzky, A. R., Ed.; Academic Press: San Diego, 1989, Vol. 45, pp 231–252.
5. Grigg R. Sridharan V and Curran DP. Advances in Cycloaddition, Eds.; Jai Press: London, 1993; 3:161–180.
6. Liddel JR. Pyrrolizidine alkaloids, Natural Product Reports. 1996; 13: 187–193.
7. Hartmann T. and Witte L. Chemistry, Biology and Chemoecology of Pyrrolizidine Alkaloids. In Alkaloids: Chemical and Biological Perspectives, Pelletier, S. W., Ed.; Pergamon Press, 1995; 9.
8. Molineux, RJ. In Alkaloids: Chemical and Biological Perspective, Pelletier, S. W., Ed, Wiley, New York, 1987; Chapter 1.
9. Del A. William BH. Morris HR. Smith GA. Feeney J. and Robert, GCK. Structure revision of the antibiotic echinomycin, Journal of the American Chemical Society. 1975; 97: 2497–2502.
10. Kumar RS. Rajesh SM. Perumal S. Banerjee D. Yogeeswari P. and Sriram, D. Novel three-component domino reactions of ketones, isatin and amino acids: Synthesis and discovery of antimycobacterial activity of highly functionalised novel dispiropyrrolidines, European Journal of Medicinal Chemistry. 2010; 45: 411-422.
11. Howe RK. and Shelton BR. Spiroheterocycles from the reaction of nitrile oxides with 3-methylenephthalimidines, The Journal of Organic Chemistry. 1990; 55: 4603–4607.
12. Periyasami G. Raghunathan R. Surendiran G. and Mathivanan N. Synthesis of novel spiropyrrolizidines as potent antimicrobial agents for human and plant pathogens, Bioorganic **&** Medicinal Chemistry Letters. 2008; 18: 2342-23425.
13. Karthikeyan K. Sivakumar PM. Doble M. and Perumal, PT. Synthesis, antibacterial activity evaluation and QSARstudies of noveldispiropyrrolidines, European Journal of Medicinal Chemistry. 2010; 45: 3446-3452.
14. Kumar RR. Perumal S. Senthilkumar P. Yogeeswari P. and Sriram, D. A facile synthesis and antimycobacterial evaluation of novel spiro-pyrido-pyrrolizines and pyrrolidines, European Journal of Medicinal Chemistry. 2009; 44: 3821–3829.
15. Suresh Babua AR. Raghunathan R. Kumaresan K. and Raaman N. Synthesis, Characterisation and Anti-Microbial Activity Studies of Novel Dispiro-Oxindolopyrrolizidines, Current Chemical Biology. 2009; 3: 432-443.
16. Rao JNS. and Raghunathan, R. An expedient diastereoselective synthesis of pyrrolidinyl spirooxindoles fused to sugar lactone via [3+2] cyclo addition of azomethine ylides, Tetrahedron Letters. 2012; 53: 854-858.
17. Rajesh R. and Raghunathan R. Regio- and stereoselective synthesis of novel tetraspiro-bispyrrolidine and bisoxindolopyrrolidine derivatives through 1,3-dipolar cycloaddition reaction, Tetrahedron Letters. 2010; 51: 5845–5848.
18. Xavier NM. and Rauter AP. Sugars containing α,β-unsaturated carbonyl systems: synthesis and their usefulness as scaffolds in

carbohydrate chemistry. Carbohydrate Research. 2008; 343: 1523-1539.

19. Yadav JS. Subbareddy BV. Hara Gopal, AV. Nageshwar Rao R. Somaiah R. Purushottam Reddy P. and Kunwar. AC. Domino Knoevenagel–hetero-Diels–Alder reactions: a stereoselective synthesis of sugar-annulated furo[3,2-b] pyrano[4,3-d]pyran derivatives, Tetrahedron Letters. 2010**;** 51: 2305-2308.
20. Sirisha N. and Raghunathan R. Stereoselective synthesis of novel glyco-pyrano pyrrolidines/pyrrolizidines/ indolizidines through intramolecular [3+2] cycloaddition approach, Tetrahedron Letters. 2010; 51: 2515-2518.