Research Article

Efficient Synthesis of Dispiropyrrolidines Linked to Sugars

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An expedient method for the synthesis of glyco-dispiropyrrolidines is reported through 1,3-dipolar cycloaddition reaction (1,3 DC reaction). The novel glycosyl dipolarophiles derived from D-glucose underwent neat [3+2] cycloaddition reaction with the azomethine ylides generated from 1,2-diketones and sarcosine to give the corresponding glycosidic heterocycles in good yields.

1. Introduction

Carbohydrates and their derivatives which are potential useful substrates in chemical and biological fields [1, 2] are present in natural products [3, 4]. Recent studies on these glycomolecules [5, 6], such as proteoglycans, glycoproteins [7, 8], glycolipids [9, 10], and antibiotics, have shed light on the significance of carbohydrate parts (glycons) in molecular recognition for the transmission of biological information [11, 12]. Therefore, it is now recognized that carbohydrates are at the heart of a multitude of biological events. With this stimulating biological background, 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 [13]. Hence there has been renewed interest in the synthesis of carbohydrate-based heterocycles.

Heterocyclic compounds, particularly five and six membered ring compounds, have occupied a prominent place among the organic compounds in view of their diverse biological activities [14–18]. The spiropyrrolidine ring systems [19, 20] have acquired a prominent place among various heterocyclic compounds owing to their presence in many pharmacologically relevant alkaloids, as typified by rhynchophylline, corynoline, mitraphylline, hortisiline, and spirotryprostatins [21–23]. Synthesis and bioactivities of some of the spiropyrrolidines were reported by us recently [24]. Multicomponent intermolecular 1,3-dipolar cycloaddition reaction is an efficient method for the construction of heterocyclic units in a highly region- and stereoselective manner [25, 26]. 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 [27, 28]. This method is widely used for the synthesis of natural products such as alkaloids and pharmaceuticals [29, 30].

Continuing our interest in the area of 1,3-dipolar cycloaddition reaction [31, 32] and prompted by reports on the structural features and biological activity of carbohydrates and spiropyrrolidines, we contemplated fusing structurally unique spiropyrrolidine 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 ylde that reacts with sugar-derived precursors.

2. Materials and Methods

2.1. General Considerations. 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 spectra were recorded on a Bruker 300 spectrometer at 75 MHz. Mass spectra were recorded using Thermo Finnigan (LCQ) Amax
600 ESI mass spectrometer. Elemental analysis was carried out using Perkin-Elmer CHNS 2400B instrument.

2.1.1. Representative Procedure for the Synthesis of Dipolarophile Glycosylidene N,N-Dimethyl Barbituric Acid 8. To a stirred solution of sugar aldehyde 6 (1 mmol) and N,N-dimethyl barbituric acid (1 mmol) in ethanol (10 mL), triethylamine (1 mmol) was added at room temperature and stirring was continued for 4 h. After completion of the reaction, the reaction mixture was poured into the ice water (5 mL) and 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 Na2SO4. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography using hexane and ethyl acetate (8:2) as eluent to afford the corresponding dipolarophile in good yields.

2.2. General Procedure for Synthesis of Cycloadducts. To a mixture of isatin 9/ninhydrin 12/aceanaphthenequinone 14 (1 mmol) and sarcosine 10 (2 mmol), glycosylidene N,N-dimethyl barbituric acid 8 (1.0 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. Dihydrogen(2'S,3'S)-3'-[(3'aR,5'S,6'S,6'dR)-6'-(benzyl-oxy)-tethydrospiro[cyclohexane-1,2'-furo[2,3-d'][1,3]dioxole-5'-yl]-1',5-trimethyl-1',2''-dihydridospiro[1,5-diazinanene-3,4',pyrrolidine-2',3'-indene]-2,2''-dienitro (II). Colourless powder. Yield: 56%; m.p. 56°C. IR (KBr): 3070, 2926 cm⁻¹. 1H NMR (CDCl3, 300 MHz); δ 1.42–1.64 (m, 10 H), 3.02 (s, 6 H), 3.72–3.82 (m, 2 H), 4.09 (d, J = 12 Hz, 1 H), 4.45–4.54 (m, 2 H), 5.96 (d, J = 3.6 Hz, 1 H), 7.03–7.20 (m, 5 H), 7.32 (s, 1 H). 13C NMR (75 MHz); ppm 22.79, 23.17, 25.30, 28.17, 37.35, 38.51, 36.17, 63.51, 70.41, 72.40, 80.14, 83.34, 105.43, 114.41, 127.40, 128.64, 128.42, 129.92, 137.41, 147.49, 157.42, 160.93, 161.41. MS (ESI); m/z 4572 (M⁺ + 1).

2.4. Dihydrogen(3'S)-3'-[(3'aR,5'S,6'S,6'dR)-6'-(benzyl-oxy)-tetrahydrospiro[cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-5'-yl]-1',5-trimethyl-1',3'-di-hydridospiro[1,5-diazinanene-3,4',pyrrolidine-2',3'-indene]-1,2,3'-4,6-pentenone (I). Colourless powder. Yield: 60%; m.p. 94°C. IR (KBr); 1672, 1719, 1720, 1732, 1732 cm⁻¹. 1H NMR (CDCl3, 300 MHz); δ 1.45–1.62 (m, 10 H), 2.10 (s, 3 H), 2.41 (d, J = 8.4 Hz, 1 H), 2.59 (d, J = 8.4 Hz, 1 H), 3.19 (s, 6 H), 3.32 (d, J = 7.2 Hz, 1 H), 3.81 (dd, J = 3.6, 7.2 Hz, 1 H), 4.12 (d, J = 12 Hz, 1 H), 4.61–4.65 (m, 3 H), 6.02 (d, J = 3.6 Hz, 1 H), 6.79–7.84 (m, 9 H). 13C NMR (75 MHz); ppm 22.59, 22.91, 24.22, 28.87, 28.96, 35.47, 36.12, 37.48, 42.37, 44.22, 56.34, 68.39, 71.09, 77.49, 80.79, 80.83, 104.87, 113.52, 117.39, 118.07, 122.19, 122.79, 125.79, 126.49, 127.30, 127.82, 129.56, 131.23, 135.92, 139.18, 160.27, 164.21, 164.54, 196.32, 196.91. MS (ESI); m/z 644 (M⁺ + 1). Anal. Calcd for: C34H32N2O6; C, 65.31; H, 5.79; N, 6.53%. Found: C, 65.37; H, 5.84; N, 6.48%.

2.5. Dihydrogen(15'S,3'S)-3'-[(3'aR,5'R,6'S,6'dR)-6'-(benzyl-oxy)-tetrahydrospiro[cyclohexane-1,2'-furo[2,3-d][1,3]dioxole-5'-yl]-1',5-trimethyl-2'-H- dihydropyridazinylene-1,2'-pyrrolidine-3',4'-indene]-2,2''',4',6'-tetraene (I5). Colourless powder. Yield: 59%; m.p. 58°C. IR (KBr); 1674, 1720, 1722, 1728 cm⁻¹. 1H NMR (CDCl3, 300 MHz); δ 1.49–1.62 (m, 10 H), 2.08 (s, 3 H), 2.32 (d, J = 8.7 Hz, 1 H), 2.58 (d, J = 8.7 Hz, 1 H), 3.11 (s, 6 H), 3.43 (d, J = 6.9 Hz, 1 H), 3.88 (dd, J = 3.6, 6.9 Hz, 1 H), 4.09 (d, J = 11.7 Hz, 1 H), 4.58–4.64 (m, 3 H), 5.98 (d, J = 3.6 Hz, 1 H), 6.67–8.04 (m, 11 H). 13C NMR (75 MHz); ppm 23.12, 23.79, 23.54, 28.72, 28.84, 35.52, 36.49, 37.84, 40.29, 42.52, 56.13, 67.97, 70.98, 78.03, 81.64, 82.44, 105.47, 114.02, 118.39, 119.42, 121.31, 122.48, 122.79, 125.54, 126.17, 126.54, 127.41, 129.41, 130.32, 131.42, 135.42, 139.39, 140.42, 159.97, 163.54, 163.88, 192.39. MS (ESI); m/z 666 (M⁺ + 1). Anal. Calcd for: C35H39N2O6; C, 68.56; H, 5.90; N, 6.31%. Found: C, 68.63; H, 5.94; N, 6.25%.

3. Results and Discussion

As shown in Scheme 1, the construction of a sugar-fused diisopropylpyrroline ring system in 3 was envisaged from a [3+2] cycloaddition reaction involving an azomethine ylide with an olefin, while templates for such cycloaddition could be conveniently realized from dicyclohexylidene glycol 1.

Accordingly, O-alkylation of 1 with benzyl bromide in the presence of NaH gave 4 in 84% yield. Acid hydrolysis (60% aq. AcOH) of 4 at room temperature, followed by oxidative cleavage of resultant 5 with NaOCl, furnished aldehyde 6 [33]. The reaction of 6 with 1,3-indanedione 7a in the presence of triethyl amine yielded the required dipolarophile glycosylidene N,N-dimethyl barbituric acid 8 in good yield and the product was confirmed by the 1H NMR spectrum. In the 1H NMR spectrum of compound 8, the presence of singlet at Δ 3.02 for two N–CH3 groups of barbituric acid and the presence of singlet at Δ 7.32 for alkene proton confirmed the formation of the product (Scheme 2).

Having synthesized carbohydrate derived dipolarophile 8, we carried out the cycloaddition reaction of azomethine ylide generated in situ by the decarboxylative condensation
of isatin 9 and sarcosine 10 with dipolarophile 8 in refluxing toluene, which led to the formation of glyco-
dispiropyrrolidine 11 as a single product, as evidenced by TLC and spectral analysis. The cycloaddition was found to be highly regioselective (Schemes 3 and 4). The structure and the stereochemistry of all the products were determined by analysis of their \(^1\)H, \(^{13}\)C, DEPT-135, \(^1\)H-\(^1\)H-, \(^1\)H-\(^{13}\)C-COSY, and NOESY experiments in the NMR spectrum. The absolute configurations of these compounds were assigned by establishing the relative stereochemistry of the newly formed stereocenters with those already present in the starting material 1 [34, 35].

The product was characterized on the basis of its elemental analysis as well as by \(^1\)H, \(^{13}\)C, DEPT-135, 2D NMR, and mass spectral analysis. For instance, the IR spectrum of the product 11 exhibited a peak at 1716 cm\(^{-1}\) characteristic
The absorption bands at 1670, 1722 cm\(^{-1}\), and 1726 cm\(^{-1}\) are attributed to the presence of barbituric acid carbonyl groups.

The \(^1\)H NMR spectrum of compound II showed a sharp singlet at \(\delta\) 2.03 which confirms the presence of N–CH\(_3\) protons. The N–CH\(_3\) protons of the pyrrolidine ring appeared as two doublets at \(\delta\) 2.38 (\(J = 8.7\) Hz) and \(\delta\) 2.54 (\(J = 8.7\) Hz). The two N–CH\(_3\) protons of the barbituric acid appeared as a singlet at \(\delta\) 3.12. The N–CH proton (H\(_5\)) of the pyrrolidine ring appeared as a doublet at \(\delta\) 3.29 (\(J = 7.2\) Hz), which clearly shows the regioselectivity of the cycloadduct. If other isomers 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 \(\delta\) 3.77 (\(J = 3.6, 7.2\) Hz). The H\(_4\) proton of the furanose ring appeared as a doublet at \(\delta\) 5.99 (\(J = 3.6\) Hz). The aromatic protons exhibited multiplets in the region \(\delta\) 6.85–7.55. The –NH proton of the oxindole moiety appeared as a singlet at \(\delta\) 7.98.

The intermolecular cycloaddition has occurred with complete facial selectivity providing the pyrrolidine derivatives with high diastereoselectivity. The stereochemistry observed can be explained by considering that the dipolarophile approaches the 1,3-dipole in an endo mode (TS I) with respect to the dipole. The stereochemistry observed is also consistent with this observation. Although two different transition states are possible (Figure 1), transition state TS II would be less favorable due to steric repulsion between the sugar moiety and imide carbonyl and products are not formed in this orientation.

The relative stereochemistry of the cycloadduct II (endo isomer I) was elucidated on the basis of NOE experiment (Figure 2). In 1-D NOE measurements selective irradiation of
After the successful completion of cycloaddition reaction glycosylidene N,N-dimethyl barbituric acid 8 with isatin and sarcosine, we have carried out the cycloaddition reaction of glycosylidene N,N-dimethyl barbituric acid 8 with the azomethine ylide generated from the sarcosine 10 and ninhydrin 12/acenaphthenequinone 14. The reaction had occurred around the exocyclic double bond of the glycosylidene derivative and resulted in the formation of dispiropyrrolidines as a single product 13 and 15 in both cases. The structure of these products was also established by spectral data (Schemes 5 and 6).

4. Conclusion

In conclusion we have synthesized a series of novel glycosidispiropyrrolidine derivatives through 1,3-dipolar cycloaddition reaction of azomethine ylide generated from sarcosine and isatin/ninhydrin/acenaphthenequinone with sugar-derived dipolarophile glycosylidene N,N-dimethyl barbituric

H₄ affected enhancement of the signal of H₃ (15.7%) and H₅ (5.1%). From the coupling constants and 1D NOE data, the proton H₄ was found to be cis to H₃ and trans to H₅ (Figure 2).

The off-resonance decoupled ¹³C NMR spectrum of the product 11 showed a peak at 38.70 ppm due to N–CH₃ carbon of pyrrolidine ring. The two spiro-carbons appeared at 78.43 ppm and 45.95 ppm. The N=CH₂ and –CH carbons of the pyrrolidine ring exhibited peaks at 54.23 ppm and 41.45 ppm which were confirmed by DEPT-135 and ¹H-¹³C correlation spectrum. The O–CH₂ carbon appeared at 71.52 ppm. The furanose ring carbons appeared at 67.85, 81.53, 82.51, and 105.23 ppm. The oxindole carbonyl carbon appeared at 174.05 ppm and the barbituric acid carbonyl groups appeared at 159.65, 163.67, and 163.99 ppm.

The mass spectrum of compound 11 showed the molecular ion peak at m/z 631.2 (M⁺ + 1) which when coupled with the above spectral features confirms the structure of the cycloadduct. Also the product exhibited satisfactory elemental analysis.
acid. The addition is highly regioselective and gave single regioisomer in all the cases studied.

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References


