Densely Functionalized Chiral Pyrroles from Endocyclic, Exocyclic, and Acyclic Vinyl Sulfone-Modified Carbohydrates

Rahul Bhattacharya, Ananta Kumar Atta, Debanjana Dey, and Tanmaya Pathak*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

tpathak@chem.iitkgp.ernet.in

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A wide range of vinyl sulfone-modified carbohydrates have been prepared as starting materials for the synthesis of polysubstituted chiral pyrroles. All these vinyl sulfones reacted efficiently with ethylisocyanoacetate to generate a plethora of new pyrrole derivatives. Furansyl rings opened up during pyrrole synthesis, and pyranosyl rings were opened up by reacting the pyrrole with POCl3/DMF. This paper also reports one of the most efficient and practical routes for the synthesis of \( \beta \)-substituted pyrroles.

Introduction

Pyrrole-containing compounds play crucial roles in nature.\(^1\) Substituted pyrroles are important for research in pharmaceutical and material sciences.\(^2\) Although a variety of synthetic approaches for the synthesis of pyrroles have been developed over the years, a perusal of the literature reveals that even now the synthesis of highly functionalized pyrroles remains a synthetic challenge in terms of regioselectivity and chemoselectivity.\(^3\) Moreover, synthesis of \( \beta \)-substituted pyrroles was reported to be particularly difficult because the direct alkylation or acylation of pyrroles produced the desired products as minor components. Although methods using the directing effects of N-protecting groups or permanent \( \alpha \)-substituents did produce the \( \beta \)-substituted products, designing of a general and practical method for the synthesis of \( \beta \)-substituted pyrroles still remains a difficult challenge.

Conjugate addition of the anion generated from an isocyanoacetate to vinyl sulfones was put forward as a methodology for the synthesis of pyrrole-2-esters.\(^4\) Since the strategy was crucially dependent on the availability of functionalized vinyl sulfones, highly specialized methods were devised in the past decade for the synthesis of the derivatized vinyl sulfones.\(^5\)–\(^6\) Although these vinyl sulfones were reacted with isocyanates for the synthesis of pyrroles, the strategy stagnated over the years for the nonavailability of straightforward and general methods.\(^7\)–\(^8\)
methodologies for the synthesis of polysubstituted vinyl sulfones. A detailed analysis of these synthetic strategies revealed that virtually all vinyl sulfones as starting materials for pyrroles were derived from either symmetrical olefins via the addition of PhSCI across the double bond or methods having no potential for generating regioisomers. The serious shortcomings of currently available methods for the synthesis of polysubstituted pyrroles were compounded by the fact that strategies for the synthesis of pyrroles attached to chiral moieties are virtually nonexistent. The usefulness of such chirally substituted pyrroles in biological and material sciences can be studied only after suitable methodologies are available for their synthesis in relatively large amounts.

Results and Discussion

We opined that the utility of the powerful strategy used in vinyl sulfone-mediated pyrrole synthesis can be immensely increased if the substituted vinyl sulfones are synthesized through regiocontrolled routes. We observed that the C=S bond formation in the synthesis of furanosyl and pyranosyl thiogalactosides is regiocontrolled, and therefore the orientation of the vinyl sulfone group derived from these thiogalactosides is predefined. However, C=S bond formation in exocyclic and acyclic vinyl sulfone can also be made regiocontrolled by suitably incorporating a leaving group or an epoxide ring. We opined that vinyl sulfones derived from carbohydrates would act as excellent and efficient acceptors for the carbanion generated from ethylisocyanoacetate. Moreover, the inbuilt chiral environments of the sugar residue would be automatically transferred to the newly synthesized pyrroles. Therefore, we selected the endocyclic, exocyclic, and acyclic vinyl sulfone-modified carbohydrates 1-8, 9, 10, 11, and 12, respectively, as substrates for the synthesis of pyrroles (Table 1).

For the synthesis of endocyclic vinyl sulfone-modified carbohydrates 1-8, C=S bonds were formed by opening an epoxide in a regioselective fashion or by displacing a suitably designed sulfonate ester. The exocyclic vinyl sulfone-modified carbohydrate 6-C-tolysulfonyl-hex-5-enofuranoside 9 was also obtained by reacting a 5,6-anhydro derivative with tolyl thiol. For the synthesis of 5-C-tolysulfonyl-hex-5-enofuranoside 10, the regioisomer of 9, the fully protected mesylate 11 was treated with tolylthiol/NaOMe followed by aq. acetic acid, afforded the acyclic vinyl sulfone 11, which on treatment with mesyl chloride in DMF, afforded the acyclic bisvinyl sulfone 12. Thus the epoxide ring of an easily available tetrosyl epoxide 13 was regioselectively opened with the sulfur nucleophile to obtain the alcohol 17. Oxidation of the sulfide 17, followed by one-pot mesylation of the sulfone 18 and the elimination of sulfonic acid, afforded the acyclic vinyl sulfone 11 (Scheme 2).

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<th>TABLE 1. Vinyl Sulfone-Modified Carbohydrates as Precursors of Densely Functionalized Chiral Pyrroles</th>
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![SCHEME 1. Synthesis of Exo-Cyclic Vinyl Sulfone](Image)

(7) Even 150 years after its isolation and synthesis, and more than 100 years after the classical pyrrole syntheses were developed, the synthesis of highly substituted pyrroles is anything but straightforward.3c

(8) There are scant reports on the synthesis of sugar linked pyrroles. In these cases the aldehyde group of sugar molecule was directly reacted with pyrrole, see: Yadav, J. S.; Reddy, B. V. Subba; Satheesh, G. Tetrahedron Lett. 2004, 45, 3673. Castraphi, G.; Cornia, M.; Zanardi, F.; Rassa, G.; Raggi, E.; Bortolini, R. J. Org. Chem. 1994, 59, 1801.


Mesylation of the sulfone 21 in pyridine and concomitant elimination of sulfonic acid afforded the acyclic bisvinyl sulfone 12 (Scheme 3).

All vinyl sulfones were treated with ethyl isocyanoacetate in the presence of t-BuOK in dry THF at the reflux temperature for 5 h to afford clean products. The results and the yields are summarized in Table 2. The conversion is usually efficient with the yields varying between 70 and 90%. Interestingly in the case of furanosyl analogues 6–8, the sugar ring opened up in situ to afford three different trisubstituted pyrroles 27–29, respectively.

Although this serendipitous reaction fulfilled our requirement for opening the furanosyl sugar rings to afford polysubstituted pyrroles 27–29, we continued to search for a reaction condition for opening the pyranosyl rings of 22–26. We attempted several reaction conditions for opening the sugar ring, and in almost all cases, either the unreacted starting materials or the breakdown products was obtained. To our surprise, while scanning reaction conditions for the formylation of the pyrrole rings, we observed that the POCl₃·DMF complex smoothly opened the pyranosyl rings of 22 and 23 to afford the trisubstituted pyrroles 34 and 35, respectively, in high yields (Scheme 4). Peaks ranging between δ 9.96–10.87 (1H NMR) and δ 187.0–188.9 (13C NMR) confirmed the presence of a free -CHO group in compounds 27–29, 34, and 35.

In conclusion, we have reported a straightforward and general method for the synthesis of a wide range of polysubstituted pyrroles from vinyl sulfone-modified carbohydrates. Our general and regioselective approach to the synthesis of the vinyl sulfones was pivotal for accessing these crucially important intermediates. In the case of furanosyl compounds, the five-membered ring opened up in situ to afford directly the densely functionalized pyrroles substituted with chiral functional groups, and the pyranosyl compounds underwent ring opening with POCl₃ in DMF. A perusal of the structure of pyrroles in Table 2 also suggests that a myriad of functional groups have been attached to the β-position of pyrrole rings. Some of these groups, such as chiral acyclic chains (27, 28, 29, 32, 33) or sugar residues
Experimental Section

General Methods. 3-0-Benzyl-5-deoxy-(5-C-p-tolylsulfonyl)-1,2-O-isopropylidene-β-L-idopyranose 9. The reaction mixture was poured into satd. aq. NaHCO₃ (70 mL), and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic layers were pooled together, dried over anhyd. Na₂SO₄, and evaporated under reduced pressure. The crude mass was purified over silica gel. To a solution of this compound in EtOH (10 mL) was added aq. HOAc (75%, 25 mL). The reaction mixture was heated at 90 °C for 1.5 h and cooled to room temperature. Volatile matter were evaporated under reduced pressure to near dryness, and the residual acid was coevaporated with toluene (3 mL) and concentrated to dryness under reduced pressure to get the residue. The resulting residue was purified over silica gel to yield 10 (1.1 g, 59%).

3-0-Benzyl-5-deoxy-(5-C-p-tolylsulfonyl)-1,2-O-isopropylidene-β-L-idopyranose 10. To a solution of 14 (0.84 g, 1.94 mmol) in dry MeOH (20 mL) was added MMPP (17.83 g, 36.06 mmol), and the reaction mixture was stirred at room temperature for 6 h under N₂. The reaction mixture was filtered through a celite bed, dried, and concentrated to dryness. The resulting residue was purified over silica gel to yield 10 (1.7 g, 96%).

3-0-Benzyl-5-deoxy-(5-C-p-tolylsulfonyl)-1,2-O-isopropylidene-β-L-idopyranose 11. To a solution of 15 (0.54 g, 1.23 mmol) in dry pyridine (15 mL) was added a solution of methanesulfonyl chloride (0.37 mmol, 5.0 mL) and the aqueous phase was washed with NaOH (70 mL), and the aqueous phase was washed with dichloromethane (3 × 30 mL). Organic extracts were collected together, dried over anhyd. Na₂SO₄, and filtered. The filtrate was evaporated under reduced pressure. The resulting residue was purified over silica gel to yield 11 (1.33 g, 92%).

3-0-Benzyl-5-deoxy-(5-C-p-tolylsulfonyl)-1,2-O-isopropylidene-β-L-idopyranose 12. To a solution of 15 (0.54 g, 1.23 mmol) in dry pyridine (15 mL) was added a solution of methanesulfonyl chloride (0.28 mL, 3.69 mmol) in dry pyridine (5 mL) at 0 °C. The reaction mixture was left overnight at 4 °C. The reaction mixture was poured into satd. aq. NaHCO₃ (70 mL), and the aqueous phase was acidified with HCl to pH 1, and the product was washed with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd. Na₂SO₄, and filtered through a short silica gel column to afford the sulfide 12 (0.625, CHCl₃). 

3-0-Benzyl-5-deoxy-(5-C-p-tolylsulfonyl)-1,2-O-isopropylidene-β-L-idopyranose 13. To a solution of 15 (0.54 g, 1.23 mmol) in dry pyridine (15 mL) was added a solution of methanesulfonyl chloride (0.28 mL, 3.69 mmol) in dry pyridine (5 mL) at 0 °C. The reaction mixture was poured into satd. aq. NaHCO₃ (70 mL), and the aqueous phase was acidified with HCl to pH 1, and the product was washed with EtOAc (3 × 10 mL). The combined organic layer was dried over anhyd. Na₂SO₄, and filtered through a short silica gel column to afford the sulfide 13 (0.625, CHCl₃).
Following the general procedure, compound 2 (0.2 mmol) was converted to yield compound 22 (Yield: 0.15 g, 37 mmol). White crystal. Mp: 117–119 °C. [α]D<sub>28</sub> +15.2° (c 0.625, THF). NHMR (DMSO-<d>): δ 1.27 (t, 3H, J = 7.0 Hz); 3.42 (s, 3H); 3.85–3.95 (m, 2H); 4.15–4.26 (m, 3H); 4.69 (d, 1H, J = 8.4 Hz); 5.62 (s, 1H); 5.80 (s, 1H); 6.89 (d, 1H, J = 2.8 Hz); 7.36–7.47 (m, 5H); 11.99 (bs, 1H). 13C NMR: δ 14.7, 55.9, 60.2 (CH2), 64.6, 68.9 (CH3), 74.6, 96.6, 101.3, 118.0, 118.5, 119.8, 124.2, 126.8, 128.5, 129.3, 138.2, 160.3. HRMS (ES<sup>+</sup>), m/z calcd. for (M + Na)<sup>+</sup> C19H23NO5Na: 368.1249. Found: 368.1248.

General Procedure for the Synthesis of Pyrroles from Vinyl Sulfone-Modified Carbohydrates. To a suspension of 90% BuOK (6 equiv) in dry THF (2 ml/mmol) at 0 °C was added ethyl isocyanoacetate (5 equiv), and the resulting solution was stirred for 15 min under N<sub>2</sub>. A solution of the appropriate vinyl sulfone-modified carbohydrates (1 equiv) in dry THF (1 ml/mmol) was added dropwise to the reaction mixture. The resulting solution was heated under reflux with continuous stirring under N<sub>2</sub> for 5 h. The reaction mixture was cooled to room temperature, and the volatiles were evaporated under reduced pressure. The residue obtained was triturated with EtOAc (30 ml). The organic layer was washed with sat. aq. solution of NH4Cl (3 × 30 ml) and separated. The organic layer was dried over anhyd. Na2SO<sub>4</sub> and filtered, and the filtrate was evaporated under reduced pressure to get a crude mass. The crude residue was purified over silica gel to get the pure product. Eluent:Pet.ether/ EtOAc (3:1).

Ethyl (2R,4aR,6S,9bS)-6-Methoxy-2-phenyl-4a,6,8,9-tetrahydro-4H-[1,3]dioxino[4,5′,5′,6′]pyrano[3,4-c]pyrrole-7-carboxylate 22. Following the general procedure, compound 1 (0.15 g, 0.37 mmol) was converted to yield compound 22 (Yield: 0.99 g, 76%). White crystal. Mp: 117–119 °C. [α]D<sub>28</sub> +15.2° (c 0.625, THF). NHMR (DMSO-<d>): δ 1.27 (t, 3H, J = 7.0 Hz); 3.42 (s, 3H); 3.85–3.95 (m, 2H); 4.15–4.26 (m, 3H); 4.69 (d, 1H, J = 8.4 Hz); 5.62 (s, 1H); 5.80 (s, 1H); 6.89 (d, 1H, J = 2.8 Hz); 7.36–7.47 (m, 5H); 11.99 (bs, 1H). 13C NMR: δ 14.7, 55.9, 60.2 (CH2), 64.6, 68.9 (CH3), 74.6, 96.6, 101.3, 118.0, 118.5, 119.8, 124.2, 126.8, 128.5, 129.3, 138.2, 160.3. HRMS (ES<sup>+</sup>), m/z calcd. for (M + Na)<sup>+</sup> C19H23NO5Na: 368.1249. Found: 368.1248.

Ethyl (2R,4aR,6S,9bS)-6-Methoxy-2-phenyl-4a,6,8,9-tetrahydro-4H-[1,3]dioxino[4,5′,5′,6′]pyrano[3,4-c]pyrrole-9-carboxylate 23. Following the general procedure, compound 1 (0.2 mmol) was converted to yield compound 23. (Yield: 0.135 g, 78%). White solid. Mp: 137–139 °C. [α]D<sub>28</sub> +54.8° (c 0.625, THF). NHMR (DMSO-<d>): δ 1.02 (t, 3H, J = 7.0 Hz); 3.38 (s, 3H); 3.79–3.85 (m, 1H); 3.92–3.98 (m, 1H); 4.06–4.12 (m, 2H); 4.23–4.27 (m, 1H); 4.81 (d, 1H, J = 8.8 Hz); 5.05 (s, 1H); 5.82 (s, 1H); 6.94 (d, 1H, J = 2.8 Hz); 7.34–7.37 (m, 3H); 7.46–7.47 (m, 2H); 11.94 (bs, 1H). 13C NMR: δ 14.4, 55.1, 60.1 (CH3), 64.9, 68.8 (CH3), 75.0, 96.0, 101.2, 118.0, 120.6 (2 x C), 122.8, 126.6, 128.3, 129.1, 138.5. 160.6. HRMS (ES<sup>+</sup>), m/z calcd. for (M + Na)<sup>+</sup> C19H23NO5Na: 368.1247. Found: 368.1247.

Ethyl (4S,6S,7R)-7-(Benzyloxy)-6-methoxy-4-(triphenylmethyl)oxymethyl)-2,4,6,7-tetrahydro[3,4-c]pyrrole-1-carboxylate 24. Following the general procedure, compound 3 (0.4 g, 1.03 mmol) was converted to yield compound 24 (Yield: 0.22 g, 65%).
converted to yield compound 30 (Yield: 0.91 g, 72%). Colorless jelly. [α]D28 26° +34.5° (c 0.625, THF). 1H NMR (DMSO-d6): δ 1.17 (t, 3H, J = 7.0 Hz); 1.27 (s, 3H); 1.41 (s, 3H); 3.95 (d, 1H, J = 2.8 Hz); 4.07–4.15 (m, 3H); 4.33 (d, 1H, J = 12.4 Hz); 4.70 (d, 1H, J = 3.6 Hz); 5.61 (d, 1H, J = 2.8 Hz); 5.99 (d, 1H, J = 3.6 Hz); 6.28 (s, 1H); 6.94–6.96 (m, 3H); 7.19–7.21 (m, 3H); 11.74 (bs, 1H). 13C NMR: δ 14.5, 26.5, 26.9, 59.9 (CH3), 71.0 (CH2), 76.6, 82.0 (CH), 83.1, 104.3, 110.8, 111.1, 117.9, 123.1, 126.5, 126.7, 127.7, 128.4, 138.3. HRMS (ES+), m/z calcd for (M + Na)+ C18H18N2O4Na+: 399.1532. Found: 399.1530.

Ethyl 4-[(3aR,5R,6S,6aR)-6-Methoxy-2,2-dimethyltetrahydrofurano[2,3-d]1,3]dioxol-5-yl]-1H-pyrole-2-carboxylate 31. Following the general procedure, compound 10 (0.248 g, 0.57 mmol) was converted to yield compound 31 (Yield: 0.18 g, 81%). White crystal. Mp: 87–89 °C (decomposed). [α]D28 30° +39.3° (c 1.0, THF). 1H NMR (DMSO-d6): δ 1.23–1.26 (m, 6H); 1.43 (s, 3H); 3.81 (d, 1H, J = 2.4 Hz); 4.17–4.28 (m, 3H); 4.49 (d, 1H, J = 12.0 Hz); 4.75 (d, 1H, J = 3.6 Hz); 5.05 (d, 1H, J = 2.4 Hz); 5.90 (d, 1H, J = 3.6 Hz); 6.84 (s, 1H); 7.02 (s, 1H); 7.13–7.15 (m, 2H); 7.25–7.27 (m, 3H); 11.78 (bs, 1H). 13C NMR: δ 14.7 (CH3), 55.9 (CH3), 60.2 (CH2), 64.6 (CH), 68.9 (CH2), 74.6 (CH), 96.6 (CH), 101.3 (CH), 118.0 (CH), 118.5 (C), 119.8 (C), 124.2 (C), 126.8 (CH), 128.5 (CH), 129.3 (CH), 138.2 (C), 160.3 (C). HRMS (ES+), m/z calcd for (M + Na)+ C17H17NO5Na+: 368.1100. Found: 368.1100.

Ethyl 4-((1R)-1,2-Dimethoxyethyl)-1H-pyrole-2-carboxylate 32. Following the general procedure, compound 11 (0.53 g, 1.25 mmol) was converted to yield compound 32 (Yield: 0.395 g, 83%). White solid. Mp: 144–145 °C. [α]D28 29° +18.7° (c 0.725, THF). 1H NMR (CDCl3): δ 1.27 (t, 3H, J = 7.0 Hz); 3.63–3.66 (m, 3H); 3.73–3.78 (m, 1H); 4.26 (q, 2H, J = 7.2 Hz); 4.47 (d, 1H, J = 12.0 Hz); 4.60–4.65 (m, 3H); 5.37–5.40 (m, 1H); 6.43–6.44 (m, 1H); 6.91–6.92 (m, 1H); 7.29–7.37 (m, 10H); 9.03 (bs, 1H). 13C NMR: δ 14.4, 60.4 (CH2), 70.8 (CH2), 73.0 (CH2), 73.8, 74.4 (CH2), 109.8, 111.1, 119.5, 122.7, 127.4 (2 × C), 127.6, 127.8, 128.1, 128.3 (2 × C), 129.7, 138.7, 138.9, 160.4. HRMS (ES+), m/z calcd for (M + Na)+ C18H18N2O4Na+: 402.1681. Found: 402.1672.

Diethyl 3,4-[(4R,5R)-2,2-Dimethyl-1,3-dioxolane-4,5-diyli]bis(1H-pyrole-2-carboxylate) 33. Following the general procedure, compound 12 (0.1 g, 0.21 mmol) was converted to yield compound 33 (Yield: 0.75 g, 92%). Colorless jelly. [α]D28 26° +31.5° (c 0.625, THF). 1H NMR (DMSO-d6): δ 1.17 (t, 6H, J = 7.0 Hz); 1.45 (s, 6H); 3.96–4.05 (m, 2H); 4.07–4.15 (m, 2H); 5.51 (s, 2H); 6.31 (d, 2H, J = 2.4 Hz); 6.91 (d, 2H, J = 2.4 Hz); 11.74 (bs, 2H). 13C NMR: δ 14.6, 27.7, 26.9, 59.8 (CH2), 76.3, 107.7, 109.5, 120.1, 123.3, 126.6, 160.8. HRMS (ES+), m/z calcd for (M + Na)+ C21H19NO6Na+: 368.1100. Found: 368.1115.

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Supporting Information Available: Experimental procedures, full spectroscopic data of selected compounds, and CIF files of 22. This material is available free of charge via the Internet at http://pubs.acs.org.