

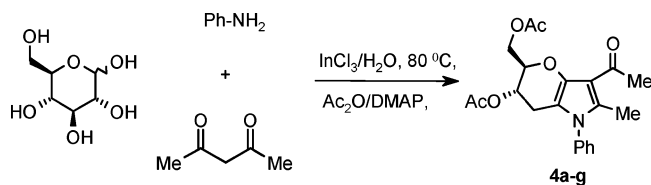
Three-Component Reaction of Aldose Sugars, Aryl Amines, and 1,3-Diones: A Novel Synthesis of Annulated Pyrroles

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Aldose sugars undergo smooth coupling with enamines, generated in situ from aryl amines and 1,3-diketones, in the presence of 10 mol % of InCl_3 in water at 80 °C to furnish annulated pyrrole derivatives in relatively good to high yields. The use of InCl_3 , in combination with water, makes this procedure quite simple, more convenient, and environmentally friendly.

Substituted pyrroles represent an important class of heterocycles which are present in a wide range of natural products such as porphyrins and bioactive molecules including the blockbuster drug atorvastatin calcium as well as important antiinflammatories, antitumor agents, and immunosuppressants.^{1–3} Similarly, polypyrroles are of growing relevance in material science, nonlinear optics, and supramolecular chemistry as

molecular sensors and devices.^{4–7} Therefore, considerable attention has been paid to develop efficient methods for the synthesis of pyrroles.⁸

Naturally occurring carbohydrates and their derivatives have been useful during the last few decades as “chiral pool” constituents in the enantioselective synthesis of biologically active natural and non-natural products.⁹ The ready availability of a wide range of carbohydrates in nature and their multichiral architecture, coupled with their well-defined stereochemistry, make them attractive starting materials in organic synthesis.¹⁰ To the best of our knowledge, there have been no reports in the literature on the formation of annulated pyrroles via condensation of aldose sugars with enamines. In this paper, we disclose a direct and one-pot synthesis of optically pure annulated pyrroles via a novel cyclization of enamines with aldose sugars. While working on the Knoevenagel condensation of D-glucose with β -enaminoketones in the presence of InCl_3 , surprisingly, we have observed the formation of annulated pyrroles. This provided the incentive for an extensive study. Initially, we have examined the reaction of D-glucose with aniline and acetyl acetone in the presence of 10 mol % of InCl_3 . The reaction proceeded well in water at 80 °C and after acetylation; the product **4a** was isolated in 93% yield (Scheme 1).

To establish the structure, the product (dihydroxyl derivative) thus obtained was converted as its nitrobenzoate **5a** and then submitted for extensive NMR studies. In **5a**, the presence of

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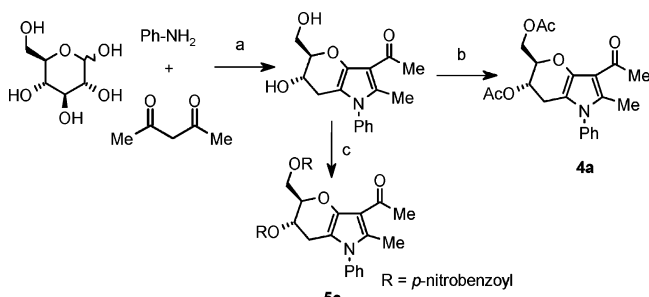
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SCHEME 1



a = InCl₃/H₂O, 80 °C, b = Ac₂O/DMAP, c = 4-NO₂C₆H₄COCl/Et₃N

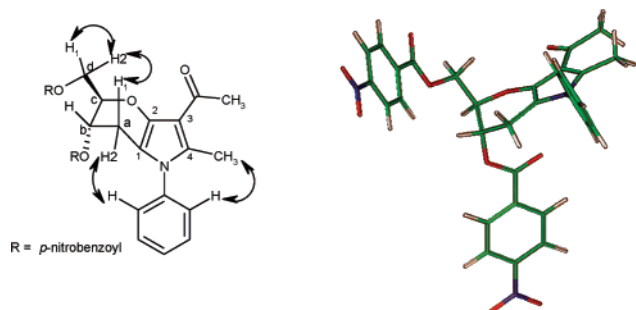


FIGURE 1. Characteristic NOE interactions, the chemical structure, and the energy-minimized structure of **5a**.

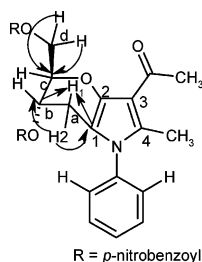


FIGURE 2. Characteristic Long range (²J_{CH} and ³J_{CH}) correlations from the HMBC spectrum of **5a**.

NOE between aH₁ and aH₂ with ortho protons of the *N*-phenyl group of the pyrrole ring confirms that the oxygen in the pyran ring and nitrogen in the pyrrole ring are opposite each other. The energy-minimized structure is shown in Figure 1 and long-range (²J_{CH} and ³J_{CH}) correlations obtained from HMBC spectrum confirming the structure as shown in Figure 2. Figure 1 shows NOE correlations observed from a NOESY spectrum. Further the structure of **5a** was confirmed by molecular mechanics calculations.¹¹ Initially, the structure was minimized with steepest decent and conjugate gradient methods for 10 000 iterations. The distances calculated from the minimized structures are in good agreement with NOE data. The phenyl connected to the nitrogen atom is oriented perpendicular to the plane of the pyrrole ring. The ortho protons of phenyl are close to the methyl group on the fourth carbon of the pyrrole ring as well as to the protons aH₁ and aH₂. These protons are also in proximity to dH₁ and dH₂. The minimized structure of **5a** is shown in Figure 1.

The product **4a** was also obtained from a disaccharide, sucrose, under identical conditions (entry **4a**, Table 1). Similarly,

(11) (a) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187. (b) Structures were calculated by using Insight II/DISCOVER modules on a silicon graphics workstation.

TABLE 1. InCl₃-Catalyzed Synthesis of Pyrroles from Sugars and Enamines

aldose	amine	1,3-dione	product ^a	time [h]	yield ^b [%]
D-glucose	C ₆ H ₅ NH ₂ (1a)	acac	4a	6.0	93
D-glucose	4-MeC ₆ H ₄ NH ₂ (1b)	acac	4b	6.0	90
D-glucose	4-MeO-C ₆ H ₄ NH ₂ (1c)	acac	4c	6.0	87
D-glucose	α-naphthylamine (1d)	acac	4d	6.0	92
D-glucose	3,4-methyleneoxy-C ₆ H ₃ NH ₂ (1e)	NH ₂ (1e)	4e	8.0	87
D-glucose	4-C ₄ H ₉ C ₆ H ₄ NH ₂ (1f)	acac	4f	6.5	86
D-mannose	4-MeO-C ₆ H ₄ NH ₂ (1c)	acac	4g	6.0	93
D-fructose	C ₆ H ₅ NH ₂ (1a)	acac	4h	7.0	85
D-arabinose	C ₆ H ₅ NH ₂ (1a)	acac	4i	6.0	80
D-arabinose	C ₆ H ₅ NH ₂ (1a)	eaa	4j	8.5	79
D-arabinose	4-MeC ₆ H ₄ NH ₂ (1b)	acac	4k	6.5	91
D-arabinose	4-MeO-C ₆ H ₄ NH ₂ (1c)	maa	4l	6.0	81
D-arabinose	3,4-methyleneoxy-C ₆ H ₃ NH ₂ (1e)	NH ₂ (1e)	4m	6.5	91
D-arabinose	4-F-C ₆ H ₄ NH ₂ (1g)	acac	4n	7.0	87
D-xylose	C ₆ H ₅ NH ₂ (1a)	acac	4o	6.0	92
D-xylose	4-Cl-C ₆ H ₄ NH ₂ (1h)	acac	4p	6.0	90
D-sucrose	C ₆ H ₅ NH ₂ (1a)	acac	4a	7.5	47

^a Products were characterized by ¹H NMR, ¹³C NMR, IR, and mass spectrometry. ^b Yield refers to pure products after chromatography. ^c acac: acetyl acetone. eaa: ethyl acetoacetate. maa: methyl acetoacetate.

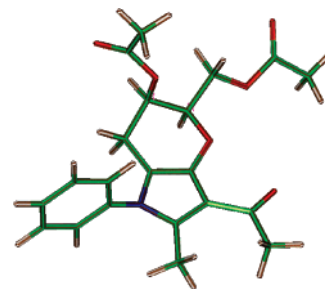


FIGURE 3. The energy minimized structure **4h**.

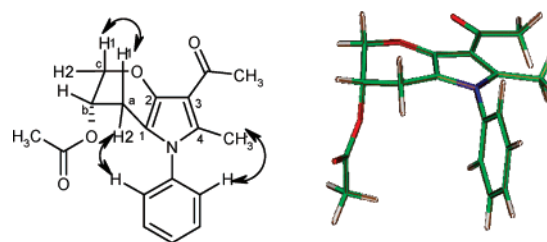
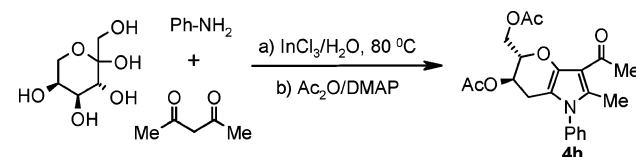


FIGURE 4. Characteristic NOE interactions, the chemical structure, and the energy-minimized structure of **4i**.

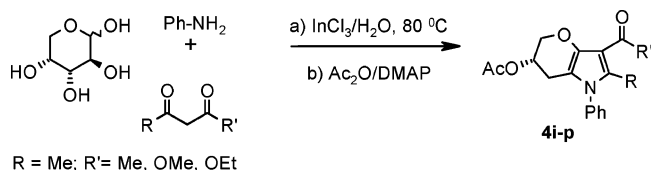
SCHEME 2



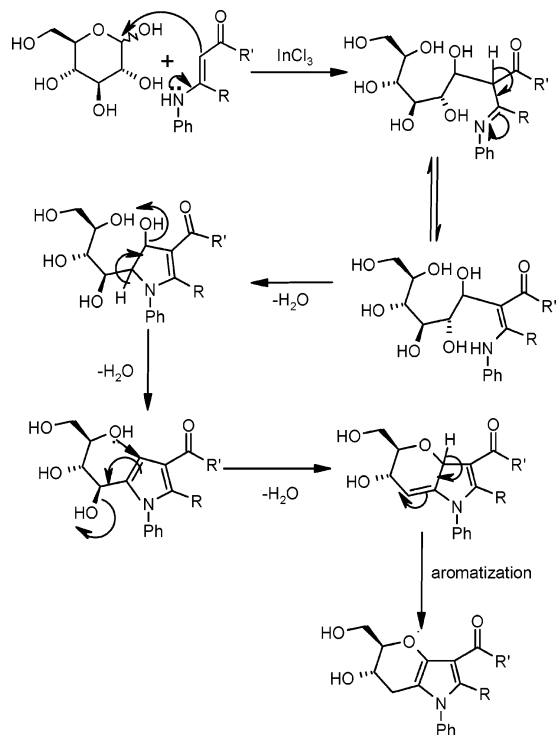
mannose reacted well with enaminoketone to produce the corresponding tetrahydropyrano[3,2-*b*]pyrroles derivative (entry **4g**, Table 1). Like aldose sugars, ketose sugar, for example, fructose, gave the respective annulated pyrrole in 85% yield under similar conditions (entry **4h**, Scheme 2, Table 1).

The structure of **4h** (Figure 3) was established by using various NMR studies. The NMR information (NOE and HMBC)

SCHEME 3



SCHEME 4. A Possible Reaction Mechanism



for **4h** is very similar to that for **4a**. The energy-minimized structure of **4h** is shown in Figure 3.

Like hexose sugars, pentose sugars such as arabinose and xylose also reacted smoothly with β-enaminoketones to produce the corresponding annulated pyrroles in good yields (Scheme 3).

The structure of the product **4i** was determined by NMR studies. Like **5a** and **4h**, in **4i** also NOEs between aH₁, aH₂, and ortho protons of the *N*-phenyl ring of pyrrole are observed. In addition, a long range ω coupling between aH₂ and cH₂

confirms the structure as shown in the energy-minimized structure (Figure 4). In all cases, the reactions were carried out in water at 80 °C and the products were obtained in good to high yields. Only a single stereoisomer was obtained in each case, the structure of which was established by using various NMR studies. The products were characterized by ¹H and ¹³C NMR, IR, and mass spectrometry. As solvent, water appeared to give the best results. Among various Lewis acid catalysts such as BiCl₃, NbCl₅, ZrCl₄, TaCl₅, and CeCl₃·7H₂O tested, InCl₃ was found to be effective in terms of conversion. The scope and generality of this process is illustrated with respect to various aldose sugars, aryl amines, and 1,3-dicarbonyl compounds and the results are presented in Table 1.

Probably, the reaction proceeds via the condensation of enaminoketone with sugar hemi-acetal to give an aldol product that on subsequent cyclodehydrations followed by aromatization would give an annulated pyrrole (Scheme 4).

In conclusion, we have demonstrated a novel, one-pot, and efficient protocol for the preparation of annulated pyrroles via a three-component coupling of aldose sugars, aryl amines, and β-diketones. The use of InCl₃ in water makes this procedure quite simple, more convenient, and environmentally friendly. The novelty and synthetic usefulness of this methodology was demonstrated in the efficient synthesis of some interesting optically pure annulated pyrroles.

Experimental Section

Experimental Procedure. D-Glucose (1 mmol), pentane-2,4-dione (1 mmol), aniline (1 mmol), and InCl₃ (0.1 mmol) in H₂O were stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with water followed by brine and dried over anhydrous Na₂SO₄. Removal of solvent followed by purification on silica gel column with a mixture of ethyl acetate:*n*-hexane (6:4) afforded pure product.

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Supporting Information Available: Characterization data and ¹H and ¹³C NMR spectra for compounds **5a** and **4b–q** and experimental procedure for general reactions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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