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Carbohydrate Research 331 (2001) 229–232

CARBOHYDRATE RESEARCH

Rapid Communication

A new synthetic method for preparing indole derivatives from 2-keto glycosides

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Received 10 January 2001; accepted 5 February 2001

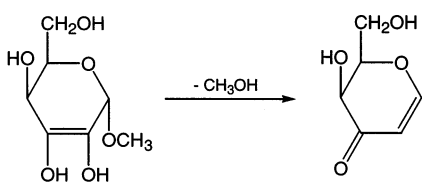
Abstract

In this article, a new reaction of the addition of two molecules of aniline to 2-keto glycosides (glycoside 2-uloses, 2-ulosides) is reported. A possible pathway for the reaction is presented. This reaction provides a novel one-pot method for the synthesis of indole derivatives from sugars. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: 2-Keto glycoside; Glycoside-2-ulose; Indole derivative

1. Introduction

2-Oxo derivatives of glycosides, called 2-keto glycosides or glycoside 2-uloses (2-ulosides), are biologically important in carbohydrate metabolism[1,2] and are very useful in the synthesis of branched-chain sugars[3,4] and amino sugars.[5,6] Very little is known of their chemistry because of the high susceptibility of these compounds to degradation in solution, and in particular their instability to base. Thus it is important to study the reactivities of 2-keto glycosides. In a previous paper,[7] we reported the transformation of 2-keto glycosides in pyridine solution. During the transformation of 2- and 3-keto glycosides, a demethoxylation reaction of the enol intermediate was shown to take place simultaneously with elimination to give the hex-1-enopyran-3-ulose (Scheme 1).



Scheme 1.

Recently, we found a similar demethoxylation process in studying the nucleophilic addition of aniline to 2-keto glycosides. The more interesting result is that when we changed the conditions, indole-like compounds were obtained (Scheme 2).

2. Results and discussion

In previous research we found that 2-deoxy-2-arylamino 3-keto glycosides were easily prepared under mild conditions when the 2-keto glycoside was reacted with an equivalent of aniline. However, the reaction with an excess of *p*-methoxyaniline (4.0 equiv) in refluxing

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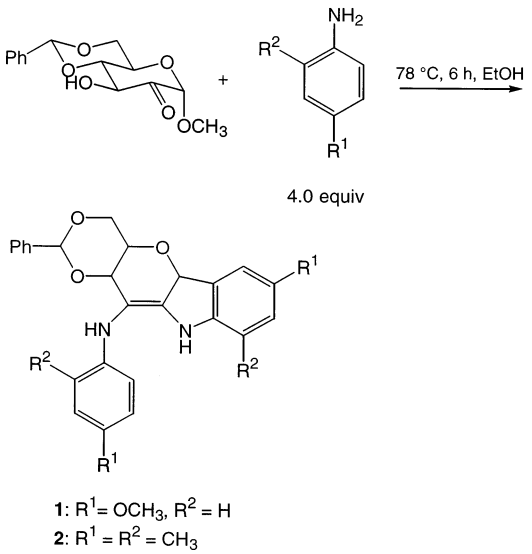
PII: S0008-6215(01)00048-9



Scheme 2.

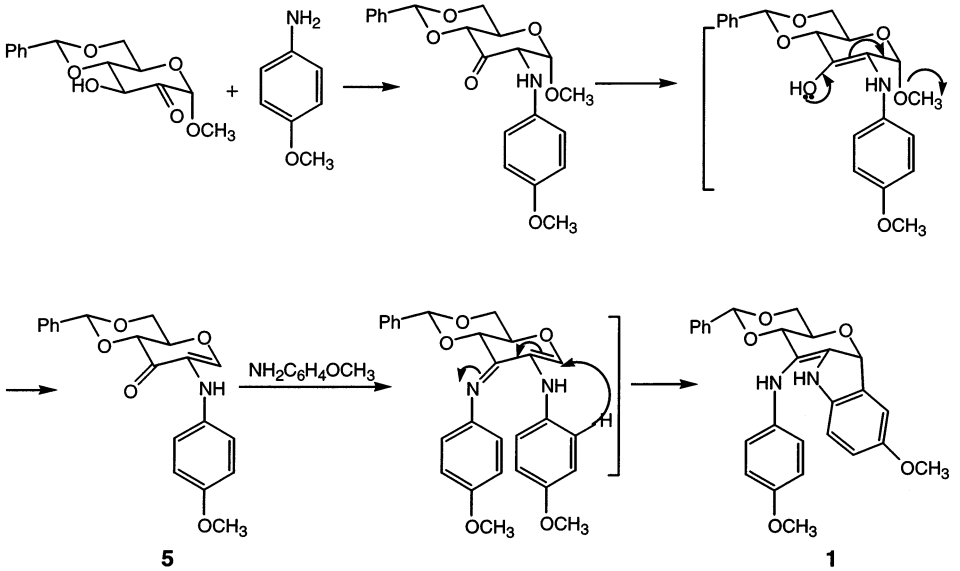
absolute ethanol gave compound **1** in a yield of 54% as the major product, which is an indole derivative produced by the double molecular addition of aniline to the 2-keto glycoside. Among the anilines we have examined, 2,4-dimethylaniline is another example for which such a reaction took place. New compounds were characterized by EIMS, ^{1}H NMR, ^{13}C NMR, 2D NMR, IR and elemental analysis. The ^{1}H NMR spectral data are presented in Table 1.

EIMS of compound **1** gave the M^+ and $[M - PhCHO]^+$ at m/z 458 and 352, respectively. This, together with the elemental analysis, suggested that the molecular formula is $C_{27}H_{26}N_2O_5$. In the ^{1}H NMR spectrum of compound **1**, the protons on C-1 and C-4 appear at a lower field [δ 7.51 (s) and 5.04 (d, J 8.8 Hz)] than those of 2-keto glycosides due to the deshielding effect of the aromatic ring and olefinic bond. Compared with the 2-arylamino-2-deoxy-3-uloside, there are three additional protons: δ 7.77 (1 H, d, J 8.8 Hz), 7.09 (1 H, dd, J 8.8, 2.4 Hz), 6.79 (1 H, d, J 2.4 Hz). These three protons obviously belong to a single spin system of a 1,2,4-trisubstituted aromatic ring. At the same time, there are eight quaternary carbon signals in the ^{13}C NMR spectrum, which were assigned by a DEPT spectrum. All the assignments were confirmed by 2D NMR spectra. Therefore, we conclude that the structure of the compound is that shown in Scheme 2. A possible pathway for the formation of the indole derivatives is shown in Scheme 3.

Table 1
^{1}H NMR data and elemental analyses of compounds **1**–**4**

Compound	^{1}H NMR (δ ppm)	Elemental analysis (%) [a]		
		C	H	N
1	7.77 (1 H, d, J 8.8 Hz, ArH), 7.56–7.40 (5 H, m, ArH), 7.51 (1 H, s, H-1), 7.09 (1 H, dd, J 8.8, 2.4 Hz, Ar–H), 7.02–6.88 (4 H, m, ArH), 6.79 (1 H, d, J 2.4 Hz, ArH), 5.85 (1 H, s, PhCH), 5.04 (1 H, d, J 8.8 Hz, H-4), 4.72 (1 H, dt, J 9.6, 5.2 Hz, H-5), 4.53 (1 H, dd, J 10.8, 5.2 Hz, H-6), 3.97 (1 H, t, J 10.4 Hz, H-6), 3.84 (3 H, s, –OCH_3), 3.80 (3 H, s, –OCH_3)	70.93 (70.73)	5.80 (5.72)	6.11 (6.11)
2	7.55–7.38 (5 H, m, Ar–H), 7.37 (1 H, s, H-1), 7.18–7.00 (5 H, m, ArH), 5.86 (1 H, s, PhCH), 5.17 (1 H, d, J 10.4 Hz, H-4), 4.78 (1 H, dt, J 10.4, 5.2 Hz, H-5), 4.56 (1 H, dd, J 10.4, 5.2 Hz, H-6), 4.02 (1 H, t, J 10.4 Hz, H-6), 2.73 (3 H, s, –CH_3), 2.41 (3 H, s, –CH_3), 2.31 (3 H, s, –CH_3), 1.76 (3 H, s, –CH_3)	76.58 (76.63)	6.60 (6.65)	6.14 (6.16)
3	7.88 (2 H, d, J 8.8 Hz, ArH), 7.61 (1 H, s, H-1), 7.54–7.37 (5 H, m, ArH), 6.75 (2 H, d, J 8.8 Hz, ArH), 5.61 (1 H, s, PhCH), 4.62–4.52 (3 H, m, H-4, 5, 6), 4.32 (2 H, m, J 7.2 Hz, –CH_2), 4.12 (1 H, t, J 10.8 Hz, H-6), 1.36 (3 H, t, J 7.2 Hz, –CH_3)	66.73 (66.83)	5.33 (5.35)	3.45 (3.54)
4	7.55 (1 H, s H-1), 7.53–7.36 (5 H, m, ArH), 7.30 (1 H, d, J 2.0 Hz, ArH), 7.06 (1 H, dd, J 8.8, 2.0 Hz, ArH), 6.65 (1 H, d, J 8.8 Hz, ArH), 5.06 (1 H, s, PhCH), 4.60–4.52 (3 H, m, H-4,5,6), 4.10 (1 H, t, J 9.6 Hz, H-6)	58.10 (58.18)	3.79 (3.85)	3.52 (3.57)

[a] Anal. Found (Calcd).

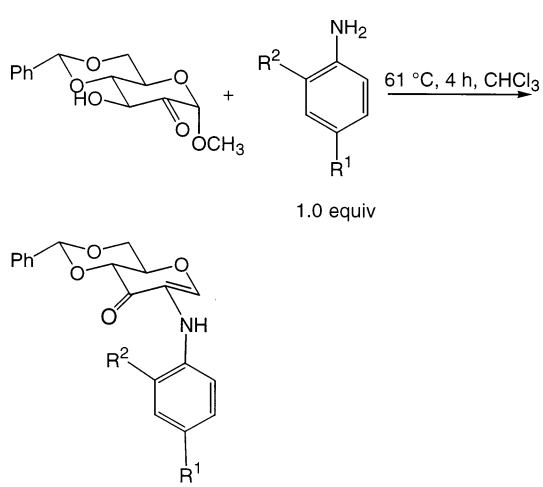


Scheme 3.

Since the alkalinity of the solution was increased by addition of an excess amount of aniline, it is envisaged that an α,β-unsaturated ketone intermediate is formed by the demethoxylation reaction in the enol rearrangement as shown in Scheme 1. Then another molecule of aniline attacked the 3-carbonyl of the intermediate formed, and compound **1** is obtained through the electron shifts shown in Scheme 3.

In order to clarify the mechanism of the reaction, we attempted to isolate intermediate **5**, but failed; however, the α,β-unsaturated ketones were synthesized successfully when we chose the other two anilines: benzocarine and 2,4-dichloroaniline (Scheme 4). In refluxing chloroform, benzocarine (0.47 g, 2.84 mmol) reacted with 2-keto glycoside (0.80 g, 2.82 mmol) for 4 h, to give compound **3** in 51% yield. The compound was characterized by ^{1}H NMR, IR spectroscopy, and by elemental analysis. In its IR spectrum, the absorption of the carbonyl group is at 1692 cm^{-1}, which is shifted to a lower frequency by 49 cm^{-1} compared with that of the corresponding 2-arylamino-2-deoxy-3-uloside. The shift arises through conjugation of the carbonyl group with the double bond between C-1 and C-2. This reaction provides evidence for our proposed mechanism. We propose that the α,β-unsaturated ketones formed would be useful in the synthesis of *C*-glycosylic (*C*-glycosides) via Michael addition reactions.

In summary, a reaction involving the addition of two molecules of aniline to a 2-keto glycoside to prepare indole derivatives has never been reported before. It provides a convenient one-pot method for the synthesis of new types of indole derivatives that are potentially biologically active. This reaction is currently being applied to synthesis of other indole compounds.



Scheme 4.

Acknowledgements

We are grateful to NSFC of PRC (project 296772030) for financial support of this work.

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