Pergamon

Tetrahedron Letters, Vol. 36, No. 46, pp. 8363-8366, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01826-3

An Efficient and Stereospecific Synthesis of Novel Pyrazine C-nucleosides

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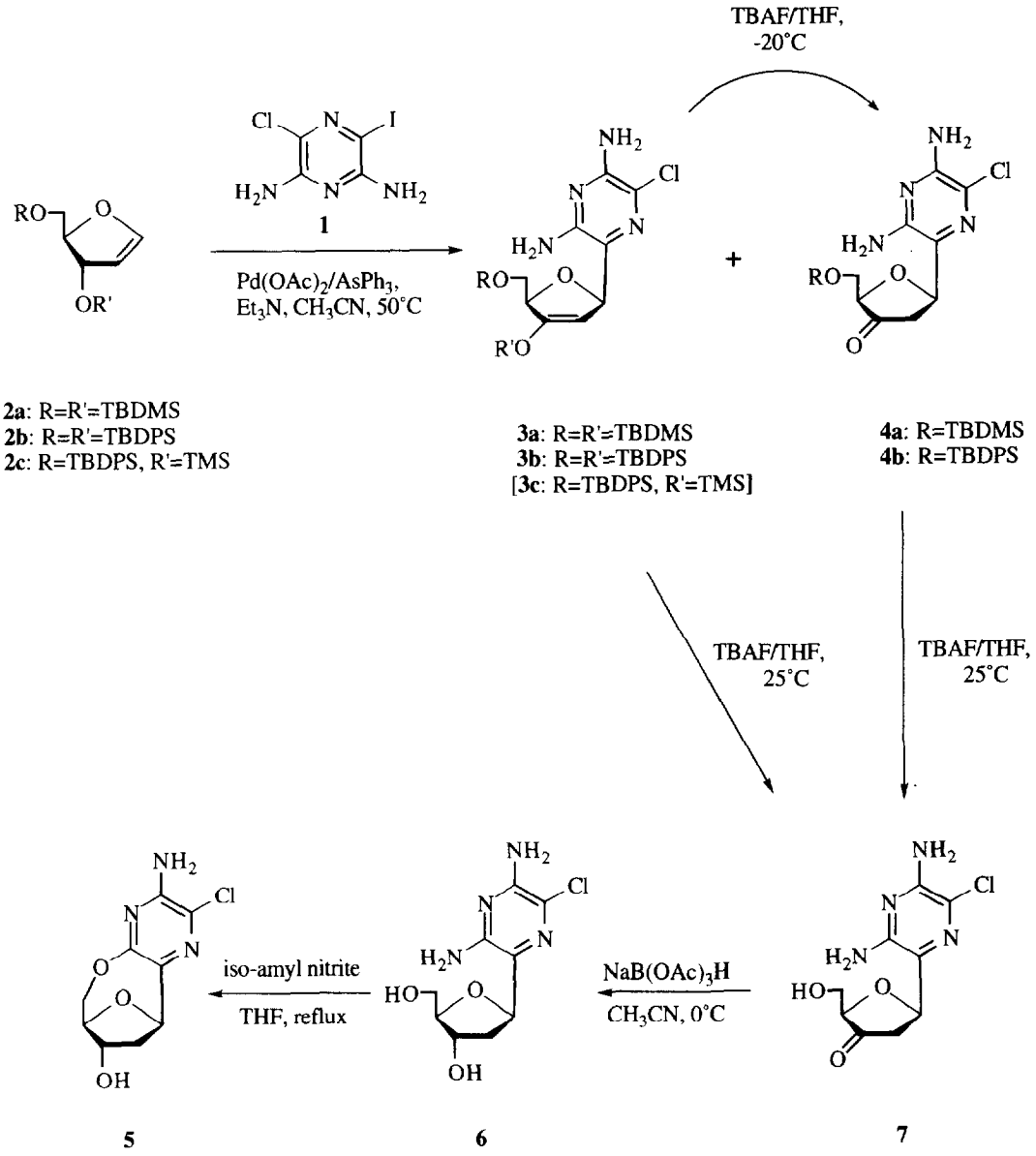
Abstract: A novel 2′-deoxy-ß-D-ribofuranosyl pyrazine C-nucleoside (**6**) was synthesized via a stereospecific palladium(0)-mediated cross-coupling reaction. The ß-configuration of this nucleoside was established by NOE analysis and the formation of a 5,5′-anhydro nucleoside **5**. The compound **4a**, obtained via the cross-coupling reaction and selective deprotection, is a versatile intermediate for the preparation of other pyrazine C-nucleoside analogues.

While bearing a structural resemblance to the N-linked nucleosides, C-nucleosides are by virtue of their unique structural features different in their physicochemical and biochemical properties.[1] It should be noted that some C-nucleosides have shown interesting biological properties.[2] Thus, the chemistry of C-nucleosides has been an active research area during the past two decades.[1-4] C-Nucleosides of a number of different heterocycles, e.g. purine, pyrimidine, pyridazine, and pyridine, have been intensively studied.[1] However, until recently no C-nucleoside analogues of pyrazine, a close isomer of the biologically important pyrimidine nucleosides, had been reported. While our studies were in progress, the preparation of 6-amino-5-(β-D-ribofuranosyl)-3-methylpyrazin-2-one, a pyrazine C-nucleoside analogue of isocytidine, was reported.[5] The preparation of pyrazine 2′-deoxy-C-nucleosides is still unreported and has prompted us to present our studies which are designed to afford this class of compounds.

The two major synthetic approaches to C-nucleosides used to date[1,3] are: 1) coupling of appropriate sugar derivatives with preformed heterocycles, and 2) introduction of a functional group at the anomeric position of a carbohydrate derivative, followed by the construction of a heterocyclic base. The construction method, which was utilized to synthesize the pyrazine isostere of isocytidine,[5] is rather long and does not easily lend itself to structural modification. Conversely, the coupling method appears to be a more efficient and straightforward procedure for the pyrazine 2'-deoxy-C-nucleosides.

Of the coupling methods reported,[3] we chose to investigate the palladium(0)-mediated cross-coupling methodology.[6] The regio- and stereospecific cross-coupling reaction between a ribofuranoid glycal (**2**)[7] and an iodopyrazine agylcon (**1**)[8] would afford the pyrazine C-nucleosides directly. Although in previous studies,[9] ribofuranoid glycals with a bulky protecting group only at the 3-position have generally been used to optimize the cross-coupling reaction to give β-products, we have now found that ribofuranoid glycals with both the 3- and 5-positions protected gave almost exclusively β-products. As shown in the table, whether the 3′ and 5′-positions were both protected by bulky TBDPS (*t*-butyldiphenylsilyl) groups or TBDMS (*t*-butyldimethylsilyl) groups,[7a] or

SCHEME


TBAF/THF,
-20°C
Pd(OAc)2/AsPh3,
Et3N, CH3CN, 50°C
1
2a: R=R'=TBDMS
2b: R=R'=TBDPS
2c: R=TBDPS, R'=TMS
3a: R=R'=TBDMS
3b: R=R'=TBDPS
[3c: R=TBDPS, R'=TMS]
4a: R=TBDMS
4b: R=TBDPS
TBAF/THF,
25°C
TBAF/THF,
25°C
iso-amyl nitrite
THF, reflux
NaB(OAc)3H
CH3CN, 0°C
5
6
7

the 5′-position was protected by a bulky TBDPS group and the 3′-position was protected by a much smaller TMS (trimethylsilyl) group,[7b] the cross-coupling reaction in all cases gave only a trace amount of the α-products. These observations were consistent with those noted by Daves.[6] A comparison of these ribofuranoid glycals revealed that **2a**, with the di-TBDMS protecting groups, was the best candidate for this cross-coupling reaction due to its surprising stability.[10]

In previous studies[11] involving the cross-coupling reaction between ribofuranoid glycals and amino-substituted iodo-aglycons, it was found necessary to protect the amino functionality to form C-nucleosides. In our study we observed no problems with using an unprotected aminopyrazine in the cross-coupling reaction. This may be due to the weak basicity of the amino nitrogen on the electron deficient pyrazine ring or our use of 3′,5′-diprotected ribofuranoid glycals in the cross-coupling reaction.

TABLE: Comparison of Cross-Coupling Reactions between **1** and Protected **2**

Ribofuranoid Glycal	3'-Protecting group	5'-Protecting group	Product	Yield (%)	β : α
2a	TBDMS	TBDMS	**4a**[a]	73	>99 : < 1
2a	TBDMS	TBDMS	**7**[b]	69	>99 : < 1
2b	TBDPS	TBDPS	**3b**[c]	33	>99 : < 1
2b	TBDPS	TBDPS	**7**[d]	20	>99 : < 1
2c	TMS	TBDPS	**4b**[e]	44	>99 : < 1

a) Both **3a** & **4a** were observed in the cross-coupling reaction between **1** and **2a**, but the silyl enol ether **3a** was not stable (see discussion in the text), thus **4a** was obtained as the product via a selective TBAF (tetrabutylammonium fluoride) deprotection;
b) Compound **7** was obtained as the final product of the cross-coupling reaction by a complete deprotection (TBAF) of the **3a** & **4a** mixture;
c) The silyl enol ether **3b** was a stable compound and could be separated from the cross-coupling between **1** and **2b** without the detection of **4b**;
d) Compound **7** was obtained as the final product of the cross-coupling reaction by a complete deprotection (TBAF) of **3b**;
e) The silyl enol ether **3c** was never observed, and **4b** was the only product isolated from the cross-coupling reaction between **1** and **2c**.

Ribofuranosyl C-nucleosides **3a-c**, bearing silyl enol ether functionalities, as shown in the scheme, were supposed to be the direct products of the coupling reactions according to previous studies.[6,11] However, we have found that in our hands some of these silyl enol ether derivatives were not very stable to the cross-coupling reaction conditions (table). For example, the cross-coupling reaction between the aglycon **1** and the ribofuranoid glycal **2c** only resulted in the isolation of the 2′-deoxy-3′-keto-C-nucleoside **4b** instead of the silyl enol ether derivative **3c**. Similarly, the silyl enol ether derivative **3a** gradually converted to **4a**, and both **3a** and **4a** were the products from the cross-coupling reaction between **1** and **2a**. Interestingly, the silyl enol ether **3b** seemed to be fairly stable when compared to **3a** and **3c** in the same conditions. We have also found that the 3′-silyl group of the silyl enol ethers **3a** and **3b** can be selectively deprotected by the fluoride ion at low temperature to give us the 5′-protected 2′-deoxy-3′-keto-C-nucleoside **4a** and **4b**, respectively. This led us to the central intermediates **4a** and **4b** from which 2′-deoxy-D-ribofuranoside, 2′-deoxy-D-xylofuranoside and D-ribofuranoside analogues of pyrazine C-nucleosides can be synthesized via simple manipulations.

As shown in the scheme, the 2′-deoxy-β-D-ribofuranoside **6** was prepared via the complete deprotection of compound **3a**, **3b**, **4a**, or **4b** with tetrabutylammonium fluoride to afford **7**, followed by a stereospecific reduction using sodium triacetoxyborohydride.[12] The β-configuration of compounds **4a** and **6** was confirmed by

NOE analysis[13] and was further proven via the formation of the 5,5′-anhydro-2′-deoxyribofuranoside **5**[14] isolated from a diazotization reaction between **6** and iso-amyl nitrite.

The synthesis of other pyrazine C-nucleosides is being pursued in our laboratory. The biological data of these compounds will be published elsewhere.

ACKNOWLEDGMENT: This work was supported by Grant R01-CA56842, awarded by the National Institutes of Health, National Cancer Institute. The authors are grateful to J. M. Hinkley for the preparation of some starting materials

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10. We have found that compound **2a** was the most stable one among these glycals. Whereas **2b** decomposed to a 2-siloxymethylfuran, as determined by ^{1}H NMR, in 24 hours at room temperature, **2a** was found to be stable for at least a week (reference 7(a)).
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14. Compound **5** exhibited similar ^{1}H NMR and ^{13}C NMR spectra to other cyclized 2′-deoxy-D-ribofuranosides, see reference 13 for an example.

(*Received in USA* 27 *July* 1995; *revised* 15 *September* 1995; *accepted* 21 *September* 1995)