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Tetrahedron Letters 45 (2004) 1031–1033
Tetrahedron Letters

Novel pyrrole C-nucleosides by nitrogen extrusion from pyridazine C-nucleosides

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Received 30 September 2003; revised 13 November 2003; accepted 19 November 2003

Abstract—Pyridazine C-nucleosides have been synthesized by [4+2] cycloaddition of alkynyl C-nucleosides with substituted tetrazines. These pyridazines on extrusion of a nitrogen atom afforded novel pyrrole C-nucleosides with good yields. The results of electrochemical and chemical reduction are compared.

1. Introduction

C-Nucleosides bearing five-membered nitrogen heterocycles such as thiazofurin, pyrazomycin, showdomycin etc. and their analogs are known to possess varied biological activities.[1] C-Nucleosides bearing a nitropyrrole are known for their biochemical and pharmacological activities.[2] Recently Burnham et al.[3] reported that pyrrole C-nucleosides also exhibit anticancer activity. Even simple substituted pyrroles are known to exhibit antineoplastic, antileukemic activities.[4]

This led us toward the synthesis of novel functionalized pyrrole C-nucleosides. In the last few years we have successfully developed an electrochemical method for the synthesis of substituted pyrroles from pyridazines.[5] In this process the latter undergo extrusion of a nitrogen atom to afford the corresponding substituted pyrrole derivatives by a controlled potential electroreduction.

This process appears complementary to that of Boger's strategy using Zn/AcOH to achieve the ring contraction of diazaheterocycles.[6]

It was thus obvious to attempt the same methodology toward the synthesis of pyrrole C-nucleosides in order to test their biological activity. Herein we wish to summarize our results on the electrochemical as well as the chemical transformation of pyridazine C-nucleosides to the corresponding pyrrole C-nucleosides.

2. Preparation of pyridazine C-nucleosides 4

In the first place the pyridazine C-nucleosides **4** were prepared by the procedure described by Seitz and co-worker.[7] D-(−)-Ribose (**1**) was converted to furanose **2** by a conventional method. Treatment of intermediate **2** with appropriate alkynyl Grignard's reagents, prepared in situ, and cyclization of the resulting open-chain compound through selective tosylation of the propargylic hydroxy group, afforded the corresponding alkynyl sugars **3a**–**b**, in 25% and 40% overall yields, respectively (Scheme 1). The β-isomer was found to be the major isomer in every case (β:α = 8:2). Having alkynyl sugars in hand, they were converted to pyridazine C-nucleosides **4a**–**b** by inverse demand hetero Diels–Alder reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[8] as described by Seitz and co-worker.[7] By slight changes in the reaction conditions, we were successful in significantly increasing the yields of the individual steps for the synthesis of pyridazine C-nucleosides **4a**–**b**. Thus the

Keywords: Pyridazine C-nucleosides; Ring contraction; Pyrrole C-nucleosides.
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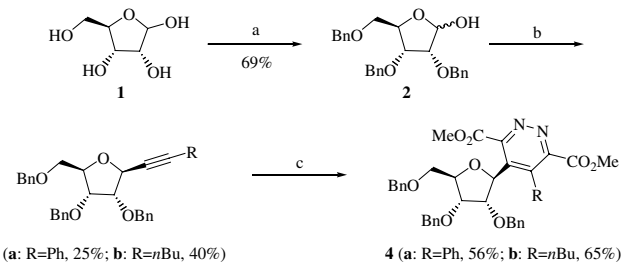
doi:10.1016/j.tetlet.2003.11.088



Scheme 1. Reagents and conditions: (a) (i) MeOH, catalytic H_2SO_4, (ii) NaH, THF/DMF, BnBr, rt, (iii) AcOH, 1 M H_2SO_4, 100 °C; (b) (i) R–C≡C–MgBr, THF, 60 °C, (ii) TsCl, pyridine, 60 °C; (c) dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, toluene, reflux.

yield of the [4+2] cycloaddition reaction was optimized to 56% in the case of **4a** and 65% in the case of **4b**, respectively.[9]

3. Nitrogen extrusion by the electrochemical method

The next step was to convert these pyridazine C-nucleosides **4a**–**b** into the corresponding pyrrole derivatives. In a typical electroreduction experiment, previously optimized in our laboratory,[10] the electrolysis of a solution of the pyridazine derivative in the electrolytic system, comprised of ethanol and acidic buffer, was carried out in the potential range of −0.8 to −1.2 *E*/(*V* vs SCE). The potential range was determined on the basis of the polarograms of the pyridazine derivatives, which indicated two successive bielectronic steps [$E_{1/2} = -0.9$ and −1.1 *E*/(*V* vs SCE)]. Cyclic voltametry was performed at a sweep rate of 0.2 V s^{-1}. The polarogram and the cyclic voltamogram are shown in Figure 1. The mechanism of the electrochemical transformation of pyridazines to pyrrole rings, consisting of a stepwise transfer of four electrons and four protons, has already been described and can be transposed to the pyridazine C-nucleoside precursors.[10] Thus in the case of **4a**, the yield of the reaction was very good (75%) but, surprisingly, in the case of **4b**, the corresponding pyrrole was isolated in only low yield (18%) along with the undesired side products. In the case of **4a**, no formation of side products was observed. The results are summarized in Table 1.

Table 1

Entry	Pyridazine	R	Method	Yield of 5 (%)
1	**4a**	Ph	Electrolysis	74
2	**4b**	*n*-Bu	Electrolysis	18
3	**4a**	Ph	Zn, AcOH, rt, 24 h	63
4	**4b**	*n*-Bu	Zn, AcOH, rt, 24 h	34
5	**4b**	*n*-Bu	Zn, AcOH, 60 °C, 24 h	53
6	**4b**	*n*-Bu	Zn, AcOH, reflux, 15 h	63

4. Nitrogen extrusion by chemical methods

The low yield obtained in the case of **4b** led us to carry out the same transformation by chemical means. Thus, treatment of **4a** with zinc and acetic acid at room temperature for 24 h followed by the work up procedure as described by Boger et al.,[6] and purification of the crude product by column chromatography on silica gel afforded the desired pyrrole derivative, as shown in Scheme 2. In this case, the yield was comparable (63%) to that of the electrochemical method, whereas in the case of **4b**, the desired pyrrole derivative was isolated in only 34% yield. However, improvement in the yield of **4b** was achieved (63%) when the reaction was carried out at a higher temperature. The results are summarized in Table 1.

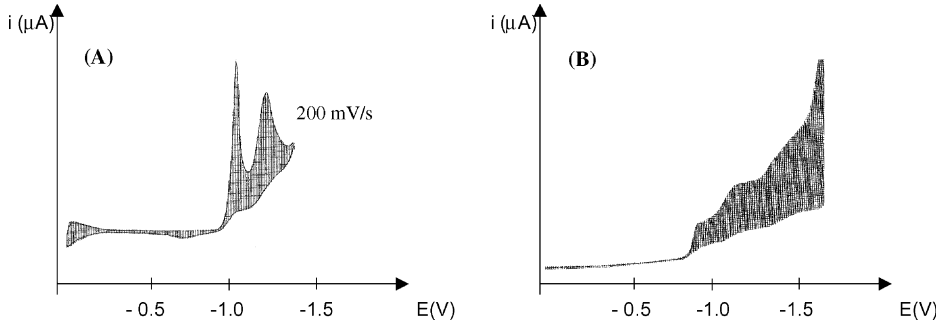
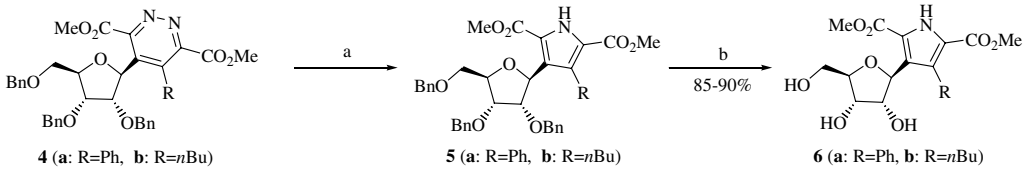


Figure 1. Cyclic voltamogram (A) and polarogram (B) of pyridazine C-nucleosides.



Scheme 2. Reagents and conditions: (a) Zn, AcOH or electrolysis; (b) H_2/Pd–C, ethyl acetate, rt.

In the last step, the benzyl protecting groups were removed by conventional hydrogenolysis of **5a**–**b**, as shown in Scheme 2, to afford the novel pyrrole C-nucleosides[11] (**6a**–**b**) in excellent yields (>85%).

In summary, we have synthesized novel pyrrole C-nucleosides by a nitrogen extrusion strategy. Some exploratory work such as the synthesis of pyridazine C-nucleosides with different substituents and their electrolysis under basic conditions is being undertaken in order to study the behavior of the pyridazine derivatives. The biological evaluation of novel pyrrole C-nucleosides for their anticancer activity, is currently in progress.

Acknowledgements

This work was supported by the 'Ministère de l'Education Nationale de la Recherche et de la Technologie' with a doctoral fellowship to S.J. and a postdoctoral fellowship to U.J. We also thank CNRS and the 'Conseil Régional des Pays de la Loire'.

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11. 2,5-Bis(methoxycarbonyl)-4-phenyl-3-(β-D-ribofuranosyl)-1H-pyrrole **6a**: Mp 83–84 °C (as colorless needles from pet. ether–dichloromethane). $[\alpha]_D^{25}$ −23° (*c* 1.0, $CHCl_3$). IR (neat): 3434, 1708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 1H, OH_5), 3.17 (s, 1H, OH_3), 3.31 (s, 1H, OH_2), 3.48 (dd, 1H, H_{5a}, $J_{5a-5b} = 10.3$, $J_{5a-4} = 2.6$), 3.65 (dd, 1H, H_{5b}, $J_{5b-5a} = 10.3$, $J_{5b-4} = 1.7$), 3.67 (s, 3H, CH_3), 3.78 (m, 1H, H_4), 3.92 (s, 3H, CH_3), 4.05 (m, 1H, H_3), 4.21 (m, 1H, H_2), 4.94 (d, 1H, H_1, $J_{1-2} = 7.8$), 7.29–7.38 (m, 5H, Ph), 9.96 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 52.4, 62.5, 70.6, 75.6, 77.6, 85.5, 121.6, 122.0, 127.5, 127.7, 128.0, 130.5, 132.3, 133.5, 160.5. Anal. Calcd for $C_{19}H_{21}NO_8$: C, 58.31; H, 5.41; N, 3.58. Found: C, 58.63; H, 5.32; N, 3.39.