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Mild and regioselective nitration of 1-deazapurine nucleosides using TBAN/TFAA

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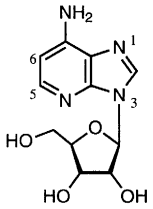
Abstract

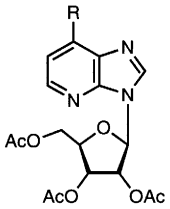
To obtain selectively functionalized 1-deazapurine nucleosides, the nitrating mixture tetrabutylammonium nitrate/trifluoroacetic anhydride (TBAN/TFAA) has been studied. This mixture demonstrated several merits: the use of an easy to handle reagent, mild reaction conditions and high selectivity for nitration in the pyridine ring. Nitration occurred at the α or β-position with respect to the pyridine nitrogen atom, depending on the substituents in the ring. Electron withdrawing substituents in the pyridine ring showed a positive effect on this nitration.

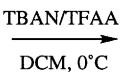
Keywords: nitration; nucleosides.

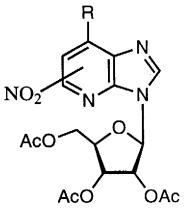
Modified nucleosides have been extensively investigated due to their biological activity e.g. as enzyme inhibitors and antitumor agents and their affinity for adenosine receptors. For instance 1-deazaadenosine (7-amino-imidazo[4,5-*b*]pyridine riboside) is a nucleoside with considerable biological activity[1] which we used as a target for the development and synthesis of new analogs containing substituents at the 5- or 6-position.



1-deazaadenosine







R = H, Cl, NO_2

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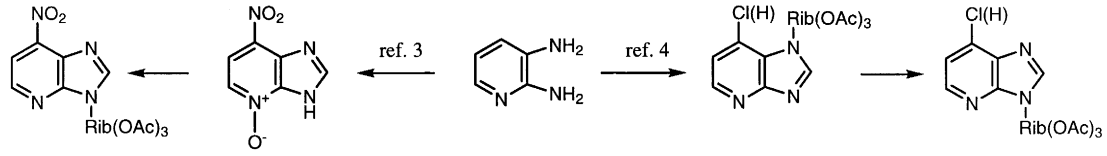
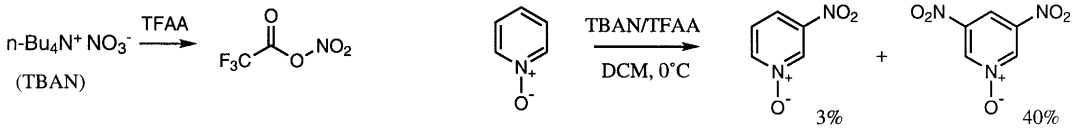
Literature procedures for the synthesis of the anticipated C-5 and C-6 functionalized imidazo[4,5-*b*]pyridine ribosides (1-deaza-purine ribosides) are in general based on introduction of substituents in the pyridine ring, prior to construction of the imidazole ring and attachment of the sugar moiety. Since several good syntheses are available for the synthesis of imidazo[4,5-*b*]pyridine ribosides, we investigated the possibilities for functionalization of the pyridine ring in a later stage of the synthesis, by using a recently reported selective nitration of benzocycloheptapyridines[2] with TBAN/TFAA.[3]

The acetate protected nucleoside substrates required for this nitration reaction were prepared as is shown in Scheme 1, starting from 2,3-diaminopyridine. The 7-nitro substituted nucleoside, which is used as precursor of 1-deazaadenosine itself, is readily available.[4] The corresponding *N*-1 ribosylated derivatives and some of the pyridine *N*-oxides were prepared according to literature procedures.[5]



Scheme 1.

Nitration reactions: Since, in general, nitration of pyridines is difficult, it is especially noteworthy that the TBAN/TFAA mixture is capable of nitrating some benzocycloheptane substituted pyridines exclusively at the β-position, albeit in moderate yield (<50%).[2] The observation that a normal benzene ring, present in the same molecule, was unreactive with TBAN/TFAA, makes a radical mechanism[6] more probable than a classical, electrophilic type of reaction (Scheme 2). Some precedent for this unusual selectivity can be found in the nitration of pyridine-*N*-oxide with benzoyl nitrate to give mixtures of 3-nitro- and 3,5-dinitropyridine-*N*-oxides in 10–20% yield.[7] On the other hand, nitration of pyridine-*N*-oxide under acidic conditions produces the 4-nitro isomer in high yield.[8] Application of the TBAN nitrating conditions to pyridine-*N*-oxide resulted in fast formation of 3,5-dinitropyridine-*N*-oxide in 40% yield, together with minor amounts of the mono-nitro product. It should be noted that pyridine itself is not nitrated under these conditions.[9]



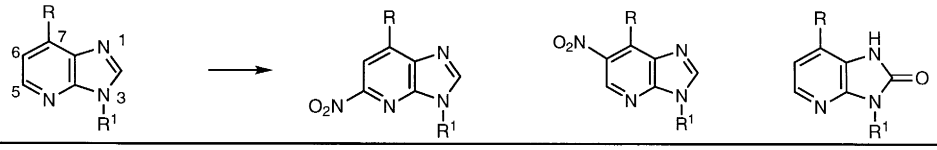
Scheme 2.

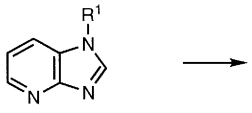
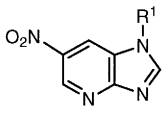
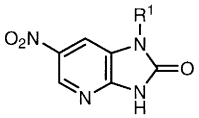
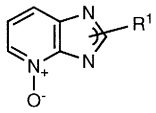
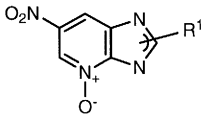
Only a few nitration reactions of nucleosides are known in the literature[10,11] due to the instability of the glycosidic linkage towards acidic conditions and/or high temperatures.

Nitrations with the TBAN/TFAA reagent are in general performed at 0°C in DCM, and one equivalent of TFA is formed during the substitution reaction. The results of the nitration reactions with imidazo[4,5-*b*]pyridine ribosides are shown in Table 1. Nucleosides with a 7-chloro or 7-nitro-substituent (entries 1 and 2) were cleanly nitrated at C-5 with comparable reaction rates (3 h, 0°C), indicating the absence of any de-activating influence of the electron withdrawing nitro substituent on the reaction. Nitration of the unsubstituted systems (entries 3 and 4) however suffered from a side reaction[12] in the imidazole ring and only trace amounts of pyridine-ring nitration products were observed. The position of the nitro group in these examples is β to the pyridine nitrogen.

The nitration of unsubstituted substrates could be effectively directed to the pyridine ring, by oxidizing the pyridine nitrogen atom to give the corresponding *N*-oxide (entries 5 and 6). Addition of cesium

Table 1
Nitration of imidazo[4,5-*b*]pyridine nucleosides with TBAN/TFAA



Entry[a]		C-5	C-6	C-2
1[b]	R = NO_2	73%	-	-
2	R = Cl	72%	-	-
3	R = H	-	3%	47%
4		-	 10%	 32%
		-		-
5[c]	N-3 tri-*O*-acetylribofuranosyl		45% (85% with Cs_2CO_3)	
6	N-1 tri-*O*-acetylribofuranosyl		39% (64% with Cs_2CO_3)	

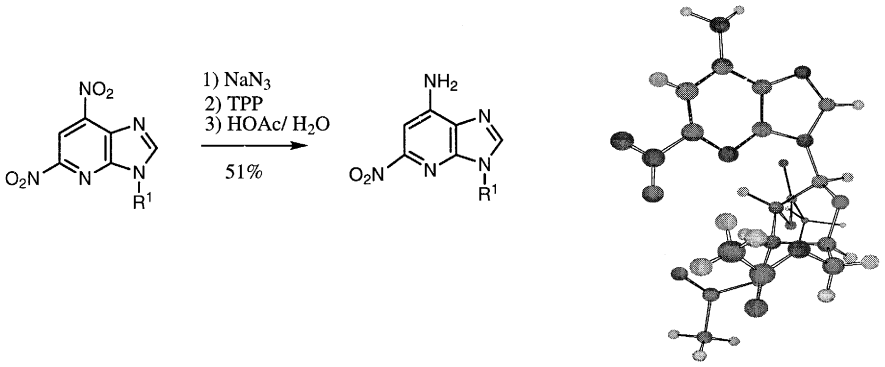
[a] R1 = (2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl). For a general method of nitration see reference 13. [b] Spectroscopic data: ^{1}H NMR ($CDCl_3$): δ 1.99, 2.05, 2.06 (3×s, 9H, $COCH_3$), 4.50 (m, 3H, H-4' and H-5'), 5.65 (m, 1H, H-3'), 5.82 (m, 1H, H-2'), 6.35(d, 1H, *J* = 4.9 Hz, H-1'), 8.79 (s, 1H, H-2), 8.92 (s 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 170.2, 169.5, 169.4, 151.4, 150.9, 147.6, 144.0, 132.06, 108.44, 87.65, 80.95, 73.53, 70.52, 62.9, 20.5, 20.3, 20.1; HRMS(FAB$^+$) obs. mass 468.0998, calcd mass for $C_{17}H_{18}O_{11}N_5$ (M+1) 468.1003. [c] Spectroscopic data: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.15, 2.18, 2.20 (3×s, 9H, $COCH_3$), 4.42 (m, 2H, H-5'), 4.59 (m, 1H, H-4'), 5.36 (dd, *J* = 5.0, *J* = 5.0 Hz, 1H, H-3'), 5.51 (dd, *J* = 5.2, *J* = 5.2 Hz, 1H, H-2'), 6.13 (d, 1H, *J* = 5.0 Hz, H-1'), 8.52 (s, 1H, H-2), 8.57 (d, 1H, *J* = 1.7 Hz, H-7), 9.18 (d, *J* = 1.7 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 170.0, 169.5, 169.4, 151.1, 145.4, 141.5, 131.1, 126.8, 106.9, 88.3, 81.8, 73.6, 69.4, 62.2, 20.6, 20.3, 20.2.

carbonate as an inert base to the reaction mixture improved the yield even further, probably by preventing protonation of the *N*-oxide. Further studies are required to establish the exact mechanism.

Structure analysis of the 6-substituted nitro compounds (entries 3–6) was easily performed by ^{1}H NMR (J_{meta}=1.7 to 2 Hz). Nitration at C-5 in entries 1 and 2 was confirmed by long-range ^{13}C-^{1}H NMR correlation experiments.[14]

Definitive proof of the site of nitration was obtained by X-ray analysis of 5-nitro-7-amino-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3*H*-imidazo[4,5-*b*]pyridine, prepared by selective replacement of the 7-nitro group by an amino substituent, as is shown in Scheme 3.

In summary, a selective nitration procedure for protected imidazo[4,5-*b*]pyridine nucleosides (1-deaza-purine nucleosides) was developed, by using a mild and easy to handle nitrating mixture. Introduction of electron withdrawing substituents in the pyridine ring showed a positive effect on the reaction, which excludes an electrophilic process. These new nitro substituted nucleosides will be converted into a



Scheme 3.

variety of deaza-adenosine analogs and will be screened for their biological activity in several adenosine dependent systems.

Acknowledgements

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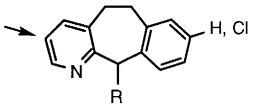
2. For selective nitration of benzocycloheptapyridines, see:



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12. Probably the unstable 2-nitro isomer is formed, which is hydrolyzed during work-up.

13. General procedure for nitration with TBAN/TFAA (see also Refs. 2, 3 and 6): TFAA (1.2 mmol) was added to a solution of TBAN (1.2 mmol) in dry DCM (5 mL) at 0°C and the mixture was stirred for 10 min. This solution was added to the substrate (1 mmol) in 5 mL of DCM at 0°C. After 2 to 3 h the reaction mixture was poured into saturated $NaHCO_3$ and extracted with DCM. Chromatographic separation gave the pure nitro compounds.
14. Long-range ^{13}C–^{1}H NMR correlation studies showed coupling between carbon and hydrogen atoms through three bonds (J=10 Hz). In the 5,7-dinitro compound for instance, the following correlation's were observed: H-1′⇆C-2, H-2⇆C-1a, H-6⇆C-1a.