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An Efficient Chemical Synthesis of Nicotinamide Riboside (NAR) and Analogues

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Abstract—A simple and efficient synthesis of nicotinamide riboside (NAR) **1** and derivatives **4** and **5** via trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated *N*-glycosilation followed by spontaneous deacetylation by treating with methanol is reported.

Nicotinamide riboside (NAR) **1** is important as a precursor of nicotinamide mononucleotide (β-NMN) **10**, which is a component for both chemical[1] and enzymatic[2] preparation of nicotinamide adeninedinucleotide (NAD^+) **2**. The importance of NAD^+ and derivatives such as $NADP^+$, NADH, and NADPH as coenzymes for cellular oxidation and reduction reactions is well known.[3] In addition, NAD^+ has been shown to be the precursor to cyclic ADP-ribose (cADPR) **3**, a newly discovered general mediator involved in Ca^{2+} signaling.[4] Although there are numerous cADPR analogues synthesized previously due to their biological importance, to our knowledge, few examples concerning *N*-1-glycosidic derivatives have been reported.[5] To obtain these compounds, there was need for a reliable, practical synthesis of β-NMN and derivatives. Three essentially different pathways to the preparation of β-NMN are known: (i) enzymatic degradation of NAD^+,[6] (ii) condensation of 1-amino sugars with N^1-(2,4-dinitrophenyl)-3-aminocarbonylpyridinium halogenides,[7] and (iii) condensation of peracylated halo sugars with nicotinamide.[8] The biological process is not suitable for analogue synthesis. The chemical synthesis using halo sugars and/or 1-amino sugars was inefficient due to their instability. We describe here a simple and efficient synthesis of NAR **1** and its xylose and arabinose derivatives **4** and **5** using trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated *N*-glycosilation[9] of tetraacetate **6**, **7** and **8** followed by spontaneous deacetylation on treatment with methanol as the key steps.

The synthesis of NAR started from commercially available β-D-ribofuranose 1,2,3,5-tetraacetate **6** (Scheme 1). Reaction of **6** with nicotinamide in the presence of TMSOTf in acetonitrile at room temperature for 1 h followed by the addition of methanol produced N^1-(β-D-ribofuranosyl)-3-aminocarbamoylpyridinium triflate **1** via triacetate **9** (not isolated). The *N*-glycoside **1** thus obtained contained up to 13% of the α-anomer as determined by ^1H NMR spectroscopy. The α-anomer was removed by chromatography on activated charcoal and crystallization to give β-**1** in 58% isolated yield. Along the same reaction pathway, the xylose and arabinose derivatives (β-**4** and α,β-mixture of **5**[10]) were also prepared starting from the corresponding tetraacetate **7** (α/β = 33:67) and **8** (α/β = 63:37)[11] in 67 and 78% yield, respectively (Scheme 2). In the latter case, the α-anomeric isomer was predominantly produced (α/β = 61:39) due to neighboring group participation and the mixture was not separable by chromatography on activated charcoal.

Thus, a simple and efficient method for the chemical synthesis of NAR and derivatives via TMSOTf-mediated *N*-glycosilation followed by spontaneous deacetylation by treating with methanol has been revealed in one-pot manner. Synthetic studies of other NAR derivatives directed toward the synthesis of NAD^+ analogues for the enzymatic studies of ADP-ribosylcyclase and NAD glycohydrolase[4] are currently under investigation.

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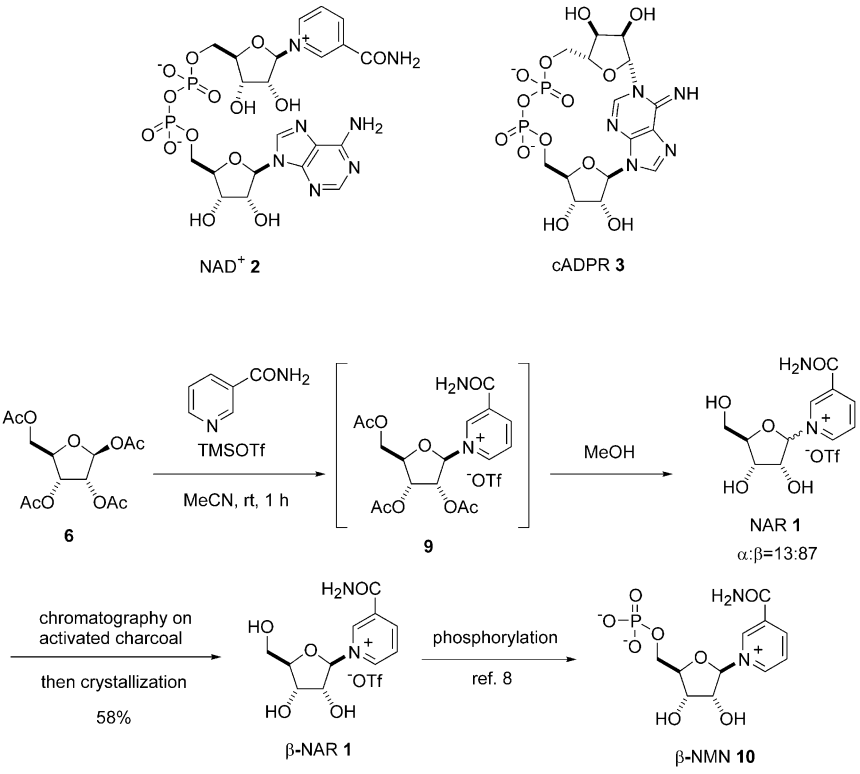
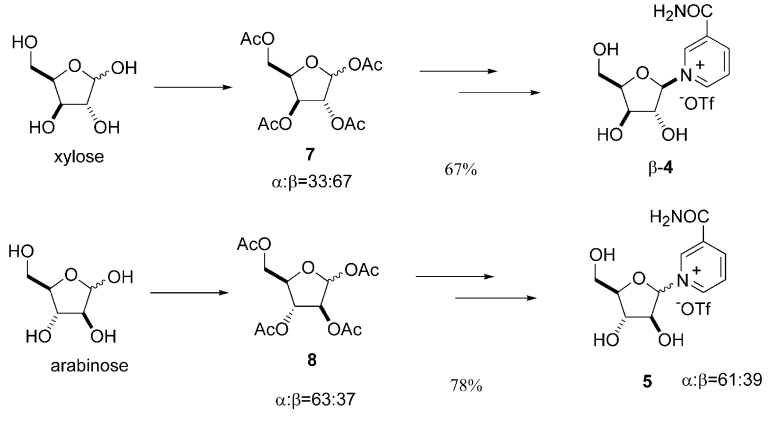
Typical Experimental Procedure

Synthesis of 3-(*N*-D-ribofuranosylcarbamoyl)pyridinium triflate (β-1). To a stirred solution of tetraacetate **6** (0.2 g, 0.63 mmol) and nicotinamide (86 mg, 0.70 mmol) in dry acetonitrile (5 mL), TMSOTf (1.0 mL, 5.17 mmol) was added dropwise at room temperature and the mixture was stirred for 1 h at the same temperature. Methanol (2.5 mL) was added to the mixture and stirred for 30 min, then the solvent was evaporated in vacuo. The residue was chromatographed on activated charcoal (eluted with H_2O to 10% MeOH in H_2O) to give a colorless syrup after removal of the solvent. The syrup was dissolved in minimum amount of methanol and then ethyl acetate was added to produce β-**1** (0.15 g, 58%) as a white solid. $R_f = 0.41$ (*n*-BuOH/H_2O/AcOH = 5:3:2); IR ν_{max} cm^{-1}: 3410, 3101, 2934, 2112, 1739, 1698, 1639, 1591, 1553, 1411, 1229, 1167, 1100, 1032, 913, 840, 763, 679, 642, 577, 520; ^1H NMR δ (D_2O): 9.23 (1H, s, H-2), 8.96 (1H, d, $J = 6.1$ Hz, H-4), 8.81 (1H, d, $J = 7.9$ Hz, H-6), 8.06 (1H, dd, $J = 6.7$, 7.6 Hz, H-5), 5.70 (1H, d, $J = 8.9$ Hz, H-1′), 4.13–4.08 (1H, m, H-2′), 3.96–3.87 (2H, m, H-3′, H-4′), 3.78 (1H, dd, $J = 12.2$, 12.5 Hz, H-5′), 3.63 (1H, dd, $J = 2.6$, 9.0 Hz, H-5′); TOF-MS (DHBA): *m*/*z* 255.2 ($[M-OTf]^+$).



Scheme 1.



Scheme 2.

3-(*N*-D-Xylofuranosylcarbamoyl)pyridinium triflate (β-4). $R_f = 0.32$ (*n*-BuOH/H_2O/AcOH = 5:3:2); ^{1}H NMR δ (D_2O): 9.33 (1H, s, H-2), 8.99 (1H, d, $J = 6.1$ Hz, H-4), 8.82 (1H, d, $J = 8.8$ Hz, H-6), 8.10 (1H, dd, $J = 7.0$, 7.3 Hz, H-5), 5.58 (1H, d, $J = 8.5$ Hz, H-1′), 4.12 (1H, dd, $J = 5.4$, 11.5 Hz, H-2′), 3.64–3.85 (1H, m, H-4′), 3.54–2.95 (3H, m, H-3′, H-5′); TOF-MS (DHBA): *m*/*z* 254.6 ([M−OTf]$^+$).

3-(*N*-D-Arabinofuranosylcarbamoyl)pyridinium triflate (α,β-5). $R_f = 0.38$ and 0.27 (*n*-BuOH/H_2O/AcOH = 5:3:2); ^{1}H NMR δ (D_2O): 9.33 (0.6H, s, H-2), 9.22 (0.4H, s, H-2), 9.03–8.97 (1H, m, H-4), 8.83 (0.4H, d, $J = 7.9$ Hz, H-6), 8.75 (0.6H, d, $J = 5.3$ Hz, H-6), 8.09 (0.6H, dd, $J = 7.0$, 7.3 Hz, H-5), 8.00 (0.4H, dd, $J = 7.3$, 7.3 Hz, H-5), 6.16 (0.4H, d, $J = 3.1$ Hz, H-1′), 5.52 (0.6H, d, $J = 8.5$ Hz, H-1′), 4.46 (0.4H, dd, $J = 5.4$, 8.7 Hz, H-4′), 4.32 (0.6H, dd, $J = 3.4$, 4.3 Hz, H-4′), 4.13–4.05 (1H, m, H-2′), 3.88 (0.6H, s, H-3′), 3.83 (0.4H, s, H-3′), 3.79–3.70 (1H, m, H-5′), 3.69–3.60 (1H, m, H-5′); TOF-MS (DHBA): *m*/*z* 255.9 ([M−OTf]$^+$).

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