# Efficient Synthesis of Sugar Iminopyrrolidine Derivatives via an Intramolecular Staudinger–aza-Wittig-Type Reaction

Hélène Ducatel,[a] Albert Nguyen Van Nhien,[a] Serge Pilard,[b] Denis Postel*[a]

[a] Laboratoire des Glucides (UMR 6219), Faculté des Sciences, Université de Picardie Jules Verne, 33 rue Saint Leu, 80039 Amiens, France
Fax +33(3)22827568; E-mail: denis.postel@u-picardie.fr

[b] Plateforme Analytique, Université de Picardie Jules Verne, Faculté des Sciences, 33, rue Saint Leu, 80039 Amiens, France

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**Abstract:** We report herein the first example of a Staudinger–aza-Wittig-type reaction on a substituted furanoside in which a β-azido glyco-α-aminonitrile was converted into fused iminopyrrolidines in good yields, and the following hydrolysis gave the corresponding conformationally restricted glycoamino acids.

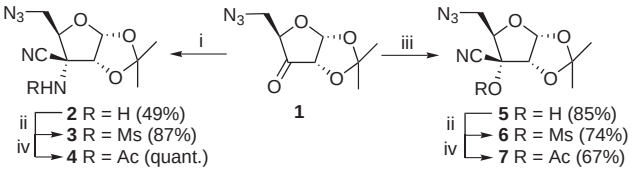
**Key words:** aza-sugars, Wittig reactions, glycoamino nitrile, glycoamino acids, iNOS

Nitric oxide (NO) is an endogenous chemical mediator that plays a role in various physiological processes, such as endothelium-dependent vasodilatation, cell-to-cell communication and cytotoxicity of phagocytes.[1] Three isoforms of nitric oxide synthase are involved in the NO biosynthesis which includes the nNOS and eNOS constitutive forms and iNOS inducible form.[2] The inducible NOS (iNOS) gene is expressed as a result of stimulation by inflammatory cytokines and is an important component in the body's immune defense. During inflammation, the iNOS enzyme is expressed in many tissues and produces NO at levels 1,000 times greater than nNOS or eNOS and in fact represents a major contributor to the pathophysiology of many human diseases.[3] Many different types of NOS inhibitors which have been described in the past few years have focused on structural analogues of L-arginine including either the guanidine or amidine moieties.[4] Since 1996, 2-iminoazaheterocycles have been reported to be potent inhibitors of NOS. This series included cyclic amidines ranging from five- to nine-membered rings, of which 2-iminopiperidine and 2-homopiperidine were the most potent inhibitors for human inducible nitric oxide synthase and the parent iminopyrrolidine ring was a modest inhibitor of hiNOS.[5,6a–c] Several synthetic methods have been used to synthesize iminopyrrolidine rings, one of which involved a lactam as a key intermediate. This heterocyclic intermediate gave the amidine via an iminoether using trimethyloxonium tetrafluoroborate, by treatment with sulfuryl chloride isocyanate[7] or through conversion of the carbonyl into a thiocarbonyl group and subsequent treatment with an amine and $HgCl_2$.[8a,8b] Surprisingly, the route which consists of nucleophilic addition of an amino group on the electrophilic carbon of a cyano or imino group appears not to have been extensively explored,[8c] in contrast to a much more intensive investigation of similar chemistry on the carbonyl group. Of particular note in respect of the latter is the Staudinger–aza-Wittig reaction, which involves a one-pot $N_3$ reduction and subsequent addition of the amino group to a carbonyl to give a cyclic imine as exemplified recently by Spagnolo and coworkers who described a radical reaction of $Bu_3SnH$ with azidonitriles. This involved a 5-*exo* cyclization onto the cyano moiety to give an aminoiminyl radical that was reduced to give an amidine.[9]

Our interest in the chemistry of glyco-α-aminonitriles[10] and their use in heterocyclic chemistry prompted us to explore the feasibility of the Staudinger–aza-Wittig reaction to enable a one-pot 5-*exo* cyclization of an azido nitrile to provide a sugar amidine.

In this paper, we report our initial results of the treatment of various α-substituted γ-azido nitriles with either $Ph_3P$ or $Me_3P$ in THF.

The glycoderivatives **3** and **4** were each synthesized in 87% yield by stereoselective aminocyanation of the ulose (**1**)[11] using $NH_3$–MeOH/TMSCN/Ti(O*i*-Pr)$_4$ (49%) followed by classical mesylation or acetylation, respectively (Scheme 1).




**Scheme 1** *Reagents*: (i) a) Ti(O*i*-Pr)$_4$, MeOH–$NH_3$ 7 N; b) TMSCN; (ii) MsCl, DMAP, pyridine; (iii) $NaHCO_3$, KCN, $H_2O$–$Et_2O$; (iv) $Ac_2O$, pyridine.

Treatment of **1** with NaCN and $NaHCO_3$ in biphasic $H_2O$–$Et_2O$ media gave the *ribo*-cyanohydrine **5** in 85% yield which upon subsequent mesylation and acetylation accordingly gave the corresponding derivatives **6** (74%) and **7** (67%).

Treatment of **2** using classical Staudinger conditions ($Me_3P$–THF) for one hour gave quantitatively the heterocyclic iminopyrrolidine **8** and iminophosphorane intermediate **9** with inseparable traces of $(Me)_3P{=}O$ (Figure 1). Longer treatment with $NH_3$–MeOH allowed quantitative conversion of **9** into the final compound **8** (Figure 1).

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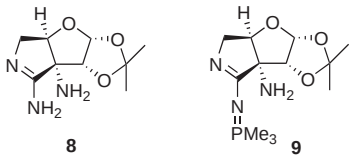


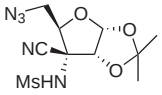
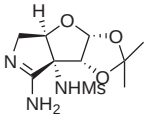
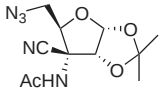
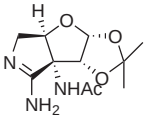
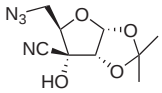
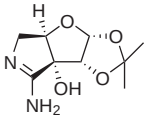
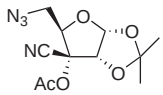
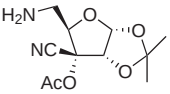
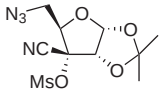
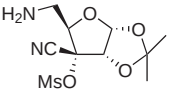
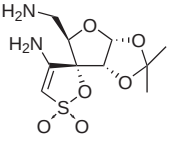
**Figure 1**

Compounds **8** and **9**[13] were characterized by NMR spectroscopy and mass spectrometry (**8**: *m*/*z* = 214.12 [M – H$^+$]; **9**: *m*/*z* = 288.14 [M – H$^+$]).

The use of triphenylphosphine instead of $Me_3P$ allowed convenient removal of the triphenylphospine oxide during the work-up ($Et_2O$–$H_2O$) to afford **8** in 89% yield after five hours.[12]

In order to study the role of the α-substituent in the aza-Wittig reaction, these conditions were applied to the cyanohydrine **5** and the N- (or O-) substituted derivatives **3**, **4**, **6** and **7** (Table 1).

**Table 1** Reaction of N- (or O-) Substituted Derivatives **3**, **4**, **6** and **7** with Phosphine

| Substrate | Phosphine | Yield (%) | Reaction product |
|---|---|---|---|
|  **3** | $PPh_3$ | 76 |  **12** |
|  **4** | $PPh_3$ | 77 |  **13** |
|  **5** | $PMe_3$ | 69 |  **10** |
|  **7** | $PPh_3$<br>$PMe_3$ | 55<br>64 |  **14** |
|  **6** | $PPh_3$ | – |  **15** |
| | $PMe_3$ | 76 |  **16** |

The functionalized aminonitriles **3** and **4** reacted similarly to the unsubstitued compound **2**, to give the corresponding cyclic pyrrolidines **12** and **13** in 76% and 77% yields, respectively.

Contrary to the amino derivatives, the reactivity of the cyanohydrin seemed to be conditioned by the nature of the O-substituent.

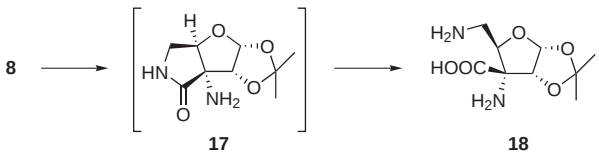
Starting from **5**, the corresponding amidine **10** was formed in 69% yield (isolated as the corresponding acetylated amidine **11**). Surprisingly, the aza-Wittig reaction failed with the functionalized derivatives **6** and **7**. Treatment of acetylated **7** with either $PPh_3$ or $PMe_3$ gave exclusively the Staudinger reaction product **14** in 55–64% yield. The Staudinger reaction was also observed with $PPh_3$ and the mesylated cyanohydrine **6**, but in this case the reduced amino derivative **15** was unstable and could not be isolated.

The use of the more basic trimethylphosphine instead of $PPh_3$ led to the heterocyclic compound **16** (76%) resulting from a Staudinger reduction and subsequent intramolecular carbanionic cyclization (CSIC reaction)[10d] between the mesyl and the cyano groups.

These results demonstrated that the Staudinger–aza-Wittig reaction seems to be independent of the electronegativity of the heteroatom in the α-position but should be ineffective when the α-substituent is an oxygenated electron-withdrawing group. In this case, the product resulted in a Staudinger reduction.

With a view to obtaining a convenient route to glycodiaminoacids (GDAs), the iminopyrrolidine **8** was hydrolyzed in a refluxing basic aqueous media using NaOH (2 N; Scheme 2).

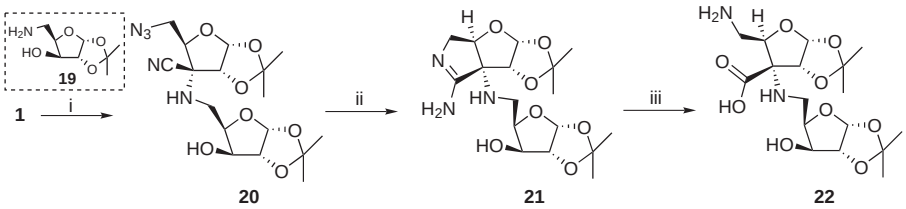
The reaction proceeded via an α-amino lactam intermediate (**17**)[14] to give the GDA **18**[15] quantitatively after 48 hours.



**Scheme 2** *Reagents and conditions*: $H_2O$–NaOH (2 N), reflux; then IRA-120.

The lactam intermediate **17** was isolated using a lower NaOH concentration (0.1 N vs. 2 N) in 49% yield after 12 hours.

Similarly, this route was applied to the synthesis of the pseudodisaccharide **22** (Scheme 3). Treatment of **20** with $Ph_3P$ in THF gave the amidine **21**[16] in 80% yield. Subsequent hydrolysis with NaOH (2 N) and then with acidic resin (Amberlite IRA-120) led, quantitatively, to the corresponding bis-glycoamino acid in which the pseudodisaccharidic linkage is the α-amino acid function.[17]



**Scheme 3** *Reagents and conditions*: (i) a) **19**, Ti(O*i*-Pr)$_4$, MeOH, b) TMSCN; (ii) a) $PPh_3$, THF, b) $NH_3$–MeOH; (iii) $H_2O$–NaOH (2 N), reflux; then IRA-120.

In conclusion we reported the first example of a Staudinger–aza-Wittig reaction on a furanoside, which gave a convenient access to fused iminopyrrolidines in good yields. Further experiments are in progress to explore the influences of the substituent in the α-position regarding the electronic effect and the hard and soft balance between the N-nucleophilic center of the iminophosphorane and C-electrophilic center of the cyano group.

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(12) **(1*R*,3*R*,4*R*,5*R*)-5,6-Diamino-3,4-*O*-isopropylidene-7-aza-2-oxabicyclo[3.3.0]oct-6-ene (8).**
To a solution of compound **2** (0.20 g, 0.85 mmol) in 10 mL of THF–$H_2O$ (4:1) was added 0.25 g (0.93 mmol) of $PPh_3$. After stirring overnight at r.t., the reaction mixture was evaporated and extracted with $Et_2O$ and $H_2O$. The aqueous layer was evaporated to give 0.16 g (89%) of **8** as a slight yellow syrup; $[\alpha]_D^{20}$ 20 (*c* 0.17, $CHCl_3$). IR (ATR): 2988, 1655, 1374, 1217, 1165, 1086, 1007, 877, 733 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 5.80 (d, 1 H, H-1, $J_{1,2}$ = 3.9 Hz), 4.60 (d, 1 H, H-2), 4.30 (d, 1 H, H-4, $J_{4,5a}$ = 3.0 Hz), 3.72 (dd, 1 H, H-5a, $J_{5a,5b}$ = 14.0 Hz), 3.67 (d, 1 H, H-5b), 1.53 (s, 3 H, $CH_3$), 1.35 (s, 3 H, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ = 168.2 (C=N), 112.9 ($CH_3CCH_3$), 106.1 (C-1), 85.1 (C-4), 82.2 (C-2), 74.1 (C-3), 55.5 (C-5), 27.6, 27.3 (2 × $CH_3$). HRMS: *m*/*z* calcd for $C_9H_{16}N_3O_3$ $[M + H]^+$: 214.1192; found: 214.1196. Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.54; H, 6.95; N, 19.60.
(13) **Key Data for Compound 9.**
$^{13}$C NMR ($CDCl_3$): δ = 173.4 (C=N, $J^2_{C\text{-}P}$ = 9.0 Hz), 75.4 (C-3, $J^3_{C\text{-}P}$ = 17.2 Hz), 14.4 [P($CH_3$)$_3$, $J^1_{CH3\text{-}P}$ = 66.0 Hz). MS: *m*/*z* = 288.14 $[M + H]^+$.
(14) **3-Amino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofurano-sidurono-3,5-lactam (17).**
White solid, mp 159–162 °C; $[\alpha]_D^{20}$ 18 (*c* 0.11, $CHCl_3$). $^1$H NMR ($CD_3OD$): δ = 5.81 (d, 1 H, H-1, $J_{1,2}$ = 3.9 Hz), 4.60 (d, 1 H, H-2), 4.40 (d, 1 H, H-4, $J_{4,5a}$ = 3.5 Hz), 3.65 (dd, 1 H, H-5a, $J_{5a,5b}$ = 11.8 Hz), 3.32 (d, 1 H, H-5b), 1.56 (s, 3 H, $CH_3$), 1.38 (s, 3 H, $CH_3$). $^{13}$C NMR ($CD_3OD$): δ = 176.4 (1 C, C=O), 112.8 (1 C, $CH_3CCH_3$), 106.1 (1 C, C-1), 81.9 (1 C, C-2), 81.8 (1 C, C-4), 68.8 (1 C, C-3), 45.6 (1 C, C-5), 26.4, 26.0 (2 C, $CH_3$). IR (ATR): ν = 2959, 2932, 1716, 1659, 1465, 1382, 1233, 1166, 1098, 1082, 1001 cm$^{-1}$. HRMS: *m*/*z* calcd for $C_9H_{14}N_2O_4Na$: 237.0851 $[M + Na]^+$; found: 237.0850.

(15) **3,5-Diamino-3-*C*-carboxy-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (18).**
White solid, mp 200 °C; $[\alpha]_D^{20}$ 77 (*c* 0.21, $H_2O$). $^1$H NMR ($D_2O$): δ = 5.88 (d, 1 H, H-1, $J_{1,2}$ = 3.6 Hz), 4.55 (d, 1 H, H-2), 3.94 (dd, 1 H, H-4, $J_{4,5a}$ = 1.8 Hz), 3.13 (dd, 1 H, H-5a, $J_{5a,5b}$ = 13.3 Hz), 2.78 (dd, 1 H, H-5b, $J_{5b,4}$ = 9.9 Hz), 1.44 (s, 3 H, $CH_3$), 1.27 (s, 3 H, $CH_3$). $^{13}$C NMR ($D_2O$): δ = 175.1 (1 C, C=O), 113.4 (1 C, $CH_3CCH_3$), 105.9 (1 C, C-1), 83.3 (1 C, C-2), 80.3 (1 C, C-4), 68.5 (1 C, C-3), 40.1 (1 C, C-5), 26.1, 25.7 (2 C, $CH_3$). IR (ATR): ν = 2987, 2917, 1614, 1540, 1409, 1381, 1230, 1163, 1069, 1015, 883, 809 cm$^{-1}$. HRMS: *m*/*z* calcd for $C_9H_{16}N_2O_5Na$: 255.0957 $[M + Na]^+$; found: 255.0950.

(16) **(1*R*,3*R*,4*R*,5*R*)-5-{[1,2-*O*-Isopropylidene-α-D-xylofuranos-5-yl]amino}-6-amino-3,4-*O*-isopropylidene-7-aza-2-oxabicyclo[3.3.0]oct-6-ene (21).**
White solid, mp 125–128 °C; $[\alpha]_D^{20}$ 18.2 (*c* 0.36, $CHCl_3$). IR (ATR): 2989, 2901, 1655, 1384, 1217, 1167, 1073, 1014, 879, 858 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ = 5.89 (d, 1 H, H-1, $J_{1,2}$ = 3.6 Hz), 5.77 (d, 1 H, H-1′, $J_{1',2'}$ = 3.7 Hz), 4.62 (d, 1 H, H-2′), 4.52 (s, 1 H, H-4), 4.38 (d, 1 H, H-2), 4.14 (d, 1 H, H-4′, $J_{4',3'}$ = 2.7 Hz), 4.05 (d, 1 H, H-3′), 3.56 (s, 2 H, H-5′), 3.06 (d, 1 H, H-5a, $J_{5a,5b}$ = 11.7 Hz), 2.77 (dd, 1 H, H-5b, $J_{5b,4}$ = 3.5 Hz), 1.48 (s, 3 H, $CH_3$), 1.39 (s, 3 H, $CH_3$), 1.29 (s, 3 H, $CH_3$), 1.20 (s, 3 H, $CH_3$). $^{13}$C NMR ($CDCl_3$): δ = 164.9 (1 C, CN), 112.9, 111.5 (2 C, $CH_3CCH_3$), 105.2, 104.8 (2 C, 2 C-1), 85.6 (1 C, C-2), 83.1 (1 C, C-4), 82.2 (1 C, C-2′), 77.9 (1 C, C-4′), 76.5 (2 C, C-3′, C-3), 58.2 (1 C, C-5′), 42.4 (1 C, C-5), 27.3 (1 C, $CH_3$), 27.1 (1 C, $CH_3$), 26.7 (1 C, $CH_3$), 26.1 (1 C, $CH_3$). HRMS: *m*/*z* calcd for $C_{17}H_{28}N_3O_7$: 386.1927 $[M + H]^+$; found: 386.1908. Anal. Calcd for $C_{17}H_{27}N_3O_7$: C, 52.98; H, 7.06; N, 10.90. Found: C, 52.91; H, 7.04; N, 10.87.

(17) **3,5-Diamino-3-*C*-carboxy-3,5-dideoxy-3-*N*-[1′,2′-*O*-isopropylidene-α-D-xylofuranos-5′-yl]-1,2-*O*-isopropylidene-α-D-ribofuranose (22).**
White solid, mp 254–256 °C; $[\alpha]_D^{25}$ 8.0 (*c* 0.21, $CHCl_3$). IR (ATR): 2987, 2900, 1589, 1394, 1215, 1066 cm$^{-1}$. $^1$H NMR ($CD_3OD$): δ = 5.99 (d, 1 H, H-1′, $J_{1',2'}$ = 3.6 Hz), 5.95 (d, 1 H, H-1, $J_{1,2}$ = 3.8 Hz), 5.01 (d, 1 H, H-2), 4.49 (d, 1 H, H-2′), 4,22 (m, 2 H, H-4′, H-3′), 3.98 (t, 1 H, H-4, $J_{4,5}$ = 6.8 Hz), 3.12 (d, 2 H, H-5), 3.56 (dd, 2 H, H-5a′, $J_{5a,5b}$ = 11.7 Hz, $J_{5a,4}$ = 6.3 Hz), 2.71 (dd, 1 H, H-5b′, $J_{5b,4}$ = 7.3 Hz), 1.56 (s, 3 H, $CH_3$), 1.47 (s, 3 H, $CH_3$), 1.38 (s, 3 H, $CH_3$), 1.31 (s, 3 H, $CH_3$). $^{13}$C NMR ($CD_3OD$): δ = 174.6 (1 C, C=O), 112.3, 111.6 (2 C, $CH_3CCH_3$), 106.8, 105.4 (2 C, C-1′, C-1), 85.2 (1 C, C-2′), 81.2 (1 C, C-2), 80.8 (1 C, C-4′), 77.8 (1 C, C-4), 76.5 (2 C, C-3′, C-3), 43.1 (1 C, C-5′), 40.9 (1 C, C-5), 26.4 (1 C, $CH_3$), 26.2 (1 C, $CH_3$), 25.7 (1 C, $CH_3$), 25.5 (1 C, $CH_3$). HRMS: *m*/*z* calcd for $C_{17}H_{28}N_2O_9Na$: 427.1693 $[M + Na]^+$; found: 427.1685.