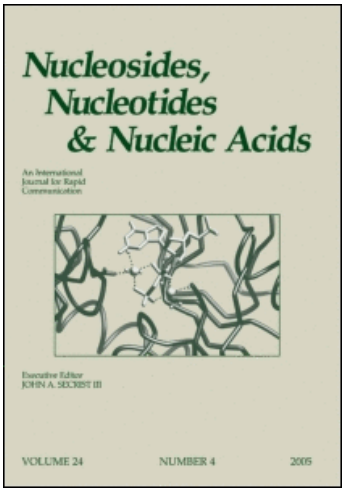

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Synthesis of 1,2,4-Triazole *C*-Nucleosides from Hydrazonyl Chlorides and Nitriles

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SYNTHESIS OF 1,2,4-TRIAZOLE *C*-NUCLEOSIDES FROM HYDRAZONYL CHLORIDES AND NITRILES

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□ *A series of 1,3-diaryl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole nucleosides (**3a–f**) were synthesized via the intermolecular cyclization of hydrazonyl chlorides with peracylated ribofuranosyl cyanide catalyzed by $Yb(OTf)_3$ or $AgNO_3$, respectively. Similarly, the 1,2,4-triazole of glucopyranosyl* C*-nucleosides **5a,b** were prepared from the hydrazonyl chlorides and the nitrile **4**. Alternatively, the 1,2,4-triazole* N*-nucleoside **8** was obtained from cyclization of the unsymmetrical bis[α-(4-methoxyphenyl)aminobenzylidene]-hydrazine with peracylated 1-amino-D-*manno*-pentitol.*

Keywords Hydrazonyl chlorides; C-nucleosides; pharmacological activity; 1,2,4-triazoles

INTRODUCTION

1*H*-1,2,4-Triazoles display important pharmacological activities such as antiasthmatic,[1] antiviral (*ribavirin*),[2] antifungal (*fluconazole*),[3] antibacterial,[4] and hypnotic,[5] (*triazolam*) drugs. Furthermore, various 1,2,4-triazole derivatives have been reported as fungicidal[6] and pesticidal[7] agents. In addition, it was reported that compounds having triazole moieties such as *vorozole*, *letrozole,* and *anastrozole* appear to be very effective aromatase inhibitors, which, in turn, prevent breast cancer.[8–10] Recently, we synthesized several 1,2,4-triazole *C*-nucleosides[11,12] by the cycloaddition of 1-aza-2-azoniaallenes to the glycosyl nitriles.

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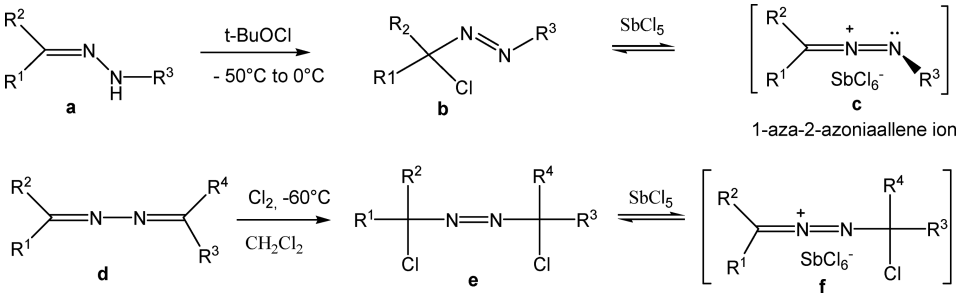


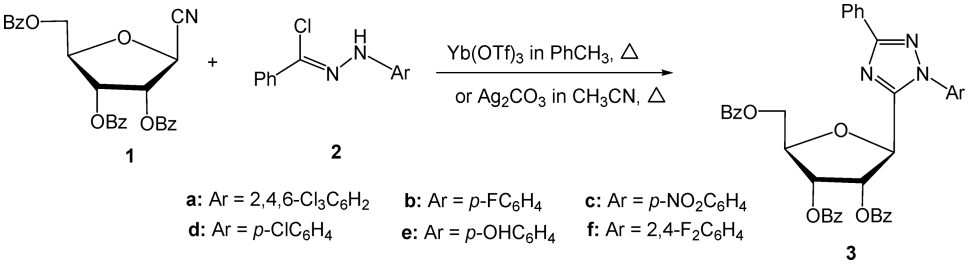
FIGURE 1 Formation of 1-aza-2-azoniaallenes from hydrazones and azines in the presence of $SbCl_5$.

However, it was found the 1-aza-2-azoniaallene reactive intermediates (Figure 1) are very unstable unless used at very low temperature (∼−60°C). As a part of our program for the preparation of novel biological active 1,2,4-triazole compounds,[13] we report here an facile method for synthesis of 1,2,4-triazole *C*-nucleosides from cycloaddition of hydrazonyl chlorides to nitriles in the presence of $Yb(OTf)_3$ or Ag_2CO_3, as mediated catalysts.

RESULTS AND DISCUSSION

In previous work, the 1-chloroalkylazo compounds **b**,[14] prepared by oxidation of the hydrazones **a**[15] with *t*-BuOCl at low temperature, furnished the reactive intermediates 1-aza-2-azoniallene salts on treatment with $SbCl_5$ at −60°C in CH_2Cl_2 used, in situ, in the synthesis of various trisubstituted 1,2,4-triazoles.[16] Alternatively, α,α'-dichloroazo compounds **e**, prepared by chlorination of azines **d**,[17] have been used in preparation of the 1-aza-2-azoniallene salts with a more suitable leaving group ($CClR^3R^4$) **f** (Figure 1). This method included spontaneous rearrangements: the [1,2]-*tert*-butyl group migration followed by elimination processes. This synthetic approach required a more drastic condition in the preparation of the short-lived 1-aza-2-azoniallene salts intermediates, which are unstable even at low temperature. We used here an alternative approach[18] for the synthesis of 2-aryl-5-phenyl-1*H*-1,2,4-triazole *C*-nucleosides from cycloaddition of hydrazonyl chloride and nitriles in the presence of $Yb(OTf)_3$ as reusable Lewis acid. Thus, treatment of the glycosyl nitrile **1** and the hydrazonyl chlorides **2** in the presence of a catalytic amount of $Yb(OTf)_3$ in refluxing MeCN afforded the *C*-nucleosides **3a–f**, in 58–74% yield. The advantages of this method include the facile experimental procedures, that the catalyst may be reused after washing with water, an easier work-up procedure, and the use of reflux temperature for the reaction.

Alternatively, compounds 3a-c were prepared from reaction of **1** with the hydrazonyl chlorides **2a–c** in the presence of 1.2 eq. of Ag_2CO_3[19] (Scheme 1). The product yields (25–40%) were lower than those prepared

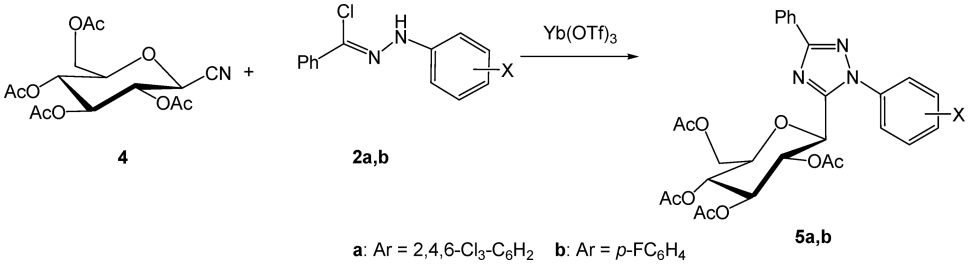


SCHEME 1

in the above method, and might be explained in term of the oxidizing property of Ag_2CO_3, as proposed by Buzykin.[20]

The structures of **3a–f** were determined from the ^{1}H NMR, which showed a close similarity to the *C*-nucleosides prepared previously,[11,12] and from the mass spectra. The ^{1}H NMR of **3a–f** and showed similar patterns since H-1′, H-2′, and H-3′ appeared as doublet and doublet of doublets in the region δ 5.18–6.37 with coupling constants $J_{1',2'}$ 5.18–5.27; $J_{2',3'}$ 6.22–6.37; $J_{3',4'}$ 5.97–6.27. The doublet of doublets, doublet of doublets of doublets, or multiplets appeared in the region δ 4.57–4.87, being attributed to H-4′,H-5′, and H-5″. The geminal coupling $J_{5',5''}$ is ∼13.0 Hz. The aromatic protons appeared between δ 8.02–7.20. Compound **3a** was selected for further NMR study by detection of carbons and protons via HMQC, HMBC, and HSQC experiments. Gradient selected HMBC spectrum allowed via $^2J_{C,H}$ and $^3J_{C,H}$ couplings the assignment of the residual quaternary carbons. The $^2J_{C,H}$ correlation of C-3 at δ_C152.3 and δ_H 5.24 is proof for the *C*-nucleoside formation between C-1′ of the sugar moiety and C-3 of the triazole ring. The triazole ring is verified by the resonance of C-5 carrying the phenyl group at δ 162.9. The rotating nuclear overhauser effect (ROE)[21] between H-1′ and δ_H 5.24 and H-4′ and δ_H 4.80 is an additional proof for β-configuration.

Similarly, glucopyranosyl *C*-nucleosides **5a**,**b** were obtained by following the Su method. Thus, treatment of the nitrile[22] **4** with **2a**,**b** in the presence of catalytic amount of $Yb(OTf)_3$ afforded the 1,2,4-triazole *C*-nucleosides **5a**,**b** in 59% and 65% yield, respectively (Scheme 2). The structures of **5a**,**b** were assigned by the ^{1}H NMR and mass spectra. The aromatic proton



SCHEME 2

signals showed a similar pattern to those of the analogues **3a**,**b**. The large coupling constants of $J_{1',2'}$, $J_{2',3'}$, $J_{3',4'}$, and $J_{4',5'}$ (~9.5 Hz) is indicative of the β-conformation as well as the $^4C_1$-conformation of the sugar moiety.

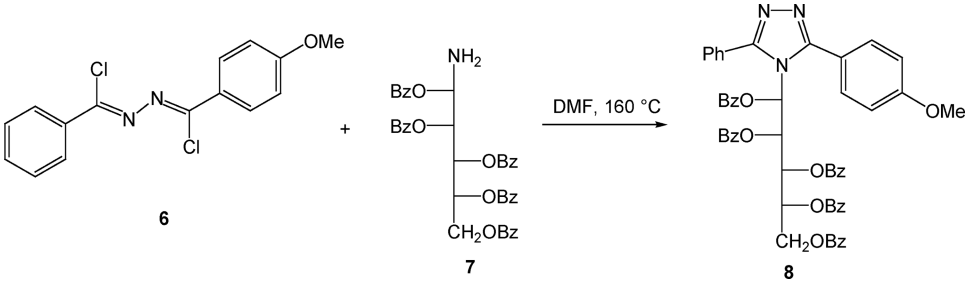
Carlsen et al.[23] have synthesized a series of 3,4,5-trisubstituted-1,2,4-triazoles by cyclization of bis[α-alkylaminobenzylidene]-hydrazine, which, in turn, is obtained by reacting aroyl chlorides with monohydrazides, with alkylamines at refluxing temperature. By following the same procedure, the aminosugar **7**,[24] was treated with the hydrazine derivative[23] **6** in DMF at 160°C to afford, after purification, the *N*-nucleoside **8** in 21% yield (Scheme 3). The low yield of **8** might be explained in term of the decomposition of the sugar moiety at high temperature. The structure of **8** was confirmed by the ^{1}H NMR and mass spectra. In the ^{1}H NMR spectrum, The doublet of doublets at δ 6.74 with J coupling 1.2 Hz being attributed to H-2′ while the multiplet at δ 6.64 was attributed to H-1′ and H-3′. H-4′, and H-5′ were appeared as doublet of doublets at δ 5.64 and δ 4.94 ($J_{4',5''}$ 5.3 Hz, $J_{4',5'}$ 3.5 Hz), respectively. The doublet of doublets at δ 4.65 with J coupling 12.1 Hz was attributed to H-5″. The alkyl phenyl and aryl groups at C-3 and C-5 were assigned.

EXPERIMENTAL

General Procedure

^{1}H NMR spectra were measured on Bruker spectrometer at 250 MHz with TMS as internal standard and on δ scale in ppm. 3-Nitrobenzylalcohol (NBOH) or glycrol were used in the FAB mass measurements as matrices. Some molecular ions were detected by doping the sample with Na^+ ions.

General Procedure for 1-aryl-3-phenyl-5-β-D-glycosyl-1 *H*-1,2,4-triazole nucleosides (3a–f, 5a,b). To a solution of the nitrile **1** or **4** (2.12 mmol) in toluene (15 mL) was added $Yb(OTf)_3$ (0.19 mmol) and hyrazonyl chlorides (1.90 mmol) and the mixture was heated under reflux for 4 hours under nitrogen atmosphere. After cooling, the mixture was evaporated to dryness and the residue was partitioned between water (20 mL) and ethyl acetate (3 × 15 mL). Evaporation of water to dryness gave $Yb(OTf)_3$, which can be



SCHEME 3

used after recrystallization from CH_3CN/CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was poured on SiO_2 column (25 g), using ethyl acetate, in gradient, and toluene (0–30%) as eluent to afford the desired nucleoside as an amorphous solid or oil.

5-(2,3,5-Tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1-(2,4,6-trichlorophenyl)-3-phenyl-1*H*-1,2,4-triazole (3a). From **1** (1.0 g). Yield: 1.2 g (74%). ^{1}H NMR ($CDCl_3$): δ 8.00–7.96 (m, 6 H, Ar-H), 7.49–7.22 (m, 16 H, ArH); 6.25 (dd, 1 H, $J_{2',3'} = 5.2$ Hz, H-2′); 5.97 (t, 1 H, $J_{3',4'} = 6.5$ Hz, H-3′); 5.24 (d, 1 H, $J_{1',2'} = 4.2$ Hz, H-1′); 4.83–4.79 (m, 2 H, H-4′, H-5′); 4.57 (dd, 1 H, $J_{5',5''} = 13.0$ Hz, H-5″). Anal. calcd. for $C_{40}H_{28}Cl_3N_3O_7$ (769.03): C, 62.47; H, 3.67; N, 5.46. Found: C, 62.15; H, 3.54; N, 5.19; MS (FAB) *m/z*: 770/772 $(M+H)^+$.

1-(4-Fluorophenyl)-3-phenyl-5-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1*H*-1,2,4-triazole (3b). From **1** (1.0 g). Yield: 0.95 g (66%). ^{1}H NMR ($CDCl_3$): δ 8.01–7.22 (m, 24H, Ar-H); 6.26 (dd, 1H, $J_{2',3'} = 5.3$ Hz, H-2′); 6.21 (t, 1H, $J_{3',4'} = 6.3$ Hz, H-3′); 5.20 (d, 1H, $J_{1',2'} = 3.2$ Hz, H-1′); 4.57–4.83 (m, 2H, H-4′, H-5′, H-5″). Anal. calcd. for $C_{40}H_{30}FN_3O_7$ (683.68): C, 70.27; H, 4.42; N, 6.15. Found: C, 69.94; H, 4.31; N, 5.93; MS (FAB) *m/z*: 683/685 $(M+H)^+$.

1-(4-Nitrophenyl)-3-phenyl-5-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1*H*-1,2,4-triazole (3c). From **1** (1.0 g). Yield: 0.95 g (63%). ^{1}H NMR ($CDCl_3$): δ 8.22–7.25 (m, 24H, ArH); 6.37 (dd, 1H, $J_{2',3'} = 5.2$ Hz, H-2′); 6.24 (t, 1H, $J_{3',4'} = 6.4$ Hz, H-3′); 5.24 (d, 1H, $J_{1',2'} = 3.2$ Hz, H-1′); 4.80–4.77 (m, 2 H, $J_{4',5'} = 5.2$ Hz, H-4′, H-5′); 4.56 (dd, 1 H, $J_{5',5''} = 12.5$ Hz, H-5″). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.3, 165.2 (C=O); 162.9 (C-5, triazole); 152.3 (C-3, triazole); 141.9, 133.8, 133.6, 133.3, 129.8, 129.7, 129.5, 128.5, 128.4, 125.0, 124.7 (Ar); 80.6 (C-1′); 75.4 (C-4′); 74.9 (C-2′); 72.8 (C-3′); 63.6 (C-5′). Anal. calcd. for $C_{40}H_{30}N_4O_9$ (710.69): C, 67.60; H, 4.25; N, 7.88. Found: C, 67.41; H, 4.16; N, 7.62; MS (FAB) *m/z*: 711 $(M+H)^+$.

1-(4-Chlorophenyl)-3-phenyl-5-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1*H*-1,2,4-triazole (3d). From **1** (1.0 g). Yield: 0.95 g (66%). ^{1}H NMR ($CDCl_3$): δ 8.00–7.20 (m, 24H, ArH); 6.22 (dd, 1H, $J_{2',3'} = 5.2$ Hz, H-2′); 6.19 (t, 1H, $J_{3',4'} = 6.3$ Hz, H-3′); 5.18 (d, 1 H, $J_{1',2'} = 3.1$ Hz, H-1′); 4.56–4.83 (m, 2 H, H-4′, H-5′, H-5″). Anal. calcd. for $C_{40}H_{30}ClN_3O_7$ (700.14): C, 68.62; H, 4.32; N, 6.00. Found: C, 68.31; H, 4.14; N, 5.73; MS (FAB) *m/z*: 700/702 $(M+H)^+$.

1-(4-Hydroxyphenyl)-3-phenyl-5-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-1*H*-1,2,4-triazole (3e). From **1** (1.0 g). Yield: 0.84 g (58%). ^{1}H NMR ($CDCl_3$): δ 8.11–7.27 (m, 24H, ArH); 6.29 (dd, 1H, $J_{2',3'} = 5.3$ Hz, H-2′); 6.21 (t, 1H, $J_{3',4'} = 5.3$ Hz, H-3′); 5.20 (d, 1H, $J_{1',2'} = 3.2$ Hz, H-1′); 4.62–4.86 (m, 2H, H-4′, H-5′, H-5″). Anal. calcd. for $C_{40}H_{31}N_3O_8$ (681.69): C, 70.48; H, 4.58; N, 6.16. Found: C, 70.17; H, 4.39; N, 5.88; MS (FAB) *m/z*: 682 $(M+H)^+$.

1-(2,4-Difluorophenyl)-3-phenyl-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole (3f). From **1** (1.0 g). Yield: 0.95 g (64%). ^{1}H NMR ($CDCl_3$): δ 8.27–7.29 (m, 23H, ArH); 6.31 (dd, 1H, $J_{2',3'} = 5.2$ Hz, H-2′); 6.27 (t, 1H, $J_{3',4'} = 6.4$ Hz, H-3′); 5.27 (d, 1 H, $J_{1',2'} = 3.3$ Hz, H-1′); 4.63–4.87 (m, 2H, H-4′, H-5′, H-5″). Anal. calcd. for $C_{40}H_{29}F_2N_3O_7$ (701.67): C, 68.47; H, 4.17; N, 5.99. Found: C, 68.18; H, 3.98; N, 5.68; MS (FAB) *m/z*: 723/725 $(M+Na)^+$.

3-Phenyl-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-(2,4,6-trichlorophenyl)-1*H*-1,2,4-triazole (5a). From **4** (0.76 g). Yield: 0.82 g (59%). ^{1}H NMR ($CDCl_3$): δ 7.98–7.95 (m, 6H, ArH); 7.46 (dd, $J = 2.2$ Hz, ArH); 5.73 (t, 1H, $J_{2',3'} = 9.5$ Hz, H-2′); 5.41 (t, 1H, $J_{4',5'} = 9.5$ Hz, H-4′); 4.99 (t, 1H, $J_{3',4'} = 9.5$ Hz, H-3′); 4.56 (d, 1H, $J_{1',2'} = 9.6$ Hz, H-1′); 3.85 (m, 1H, H-5′); 3.79 (dd, 1H, $J_{5',6a'} = 4.5$ Hz, H-6′a); 3.75 (dd, 1H, $J_{6a',6'b} = 12.0$ Hz, H-6′b). Anal. calcd. for $C_{28}H_{26}Cl_3N_3O_9$ (654.88): C, 51.35; H, 4.00; N, 6.42. Found: C, 51.10; H, 3.96; N, 6.19; MS (FAB) *m/z*: 676/678 $(M+Na)^+$.

1-(4-Fluorophenyl)-3-phenyl-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1–1*H*-1,2,4-triazole (5b). From **4** (0.76 g). Yield: 0.78 g (65%). ^{1}H NMR ($CDCl_3$): δ 7.97–7.96 (m, 6H, ArH); 7.15 (m, 4H, ArH); 5.71 (t, 1H, $J_{2',3'} = 9.6$ Hz, H-2′); 5.39 (t, 1H, $J_{4',5'} = 9.6$ Hz, H-4′); 4.95 (t, 1H, $J_{3',4'} = 9.5$ Hz, H-3′); 4.53 (d, 1H, $J_{1',2'} = 9.7$ Hz, H-1′); 3.87–3.73 (m, 3H, H- 5′, H-6′a, H-6′b). Anal. calcd. for $C_{28}H_{28}FN_3O_9$ (569.54): C, 59.05; H, 4.96; N, 7.38. Found: C, 58.84; H, 4.87; N, 7.16. MS (FAB) *m/z*: 569/571 $(M+H)^+$.

3-(4-Methoxyphenyl)-5-phenyl-4-(1,2,3,4,5-penta-*O*-benzoyl-D-*manno*-pentitol-1-yl)-1*H*-1,2,4-triazole (**8**). A solution of **7** (0.69 g, 1.0 mmol) in DMF (30 mL) was treated with the hydrazine **6** (0.43 g, 1.2 mmol) was stirred at 160°C for 10 hours. After cooling the solution was evaporated to dryness and the residue was partitioned between CHCl3 (3 × 30 mL) and water (40 mL). The combined organic extracts was dried (Na2SO4), filtered, and evaporated to dryness. The residue was poure on SiO2 column using, in gradient, MeOH (0–5%) and CHCl3 as eluent to give **8** (0.19 g, 21%) as a morphous. 1H NMR (CDCl3): δ 7.97–6.83 (m, 34 H, ArH); 6.64 (dd, 1H, J2′,3′ = 1.2 Hz, H-2′); 6.64 (m, 2H, H-1′, H-3′); 5.64 (dd, 1H, J4′,5′ = 5.3 Hz, H-4′); 4.28 (dd, 1H, J4′,5′ = 3.5 Hz, H-5′); 4.65 (dd, 1H, J4′,5″ = 12.1 Hz, H-5″); 3.71 (s, 3H, OMe). Anal. calcd. for C55H43N3O11 (921.94): C, 71.65; H, 4.70; N, 4.56. Found: C, 71.39; H, 4.57; N, 4.28. MS (FAB) *m/z*: 923 $(M+H)^+$.

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