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Synthesis of Ribosylated 1,2,3-Triazole Derivatives

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ABSTRACT: *Ribosylated 1,2,3-triazole* **4** *and* **5** *were synthesized in moderate yields by the reaction of aroyl-substituted heterocyclic ketene aminals* **1** *or* **2** *with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide (***3***). Their structures were determined by elemental analyses and spectroscopic methods.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:487–490, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10167

INTRODUCTION

Heterocyclic ketene aminals are versatile intermediates for the synthesis of a wide variety of new heterocycles and fused heterocycles [1,2]. The reactions of heterocyclic ketene aminals with 1,3-dipolar reagents, such as azides [3–11], nitrile imines [12,13], benzonitrile oxides [14,15], or its precursor [16,17], have been reported. A series of polysubstituted 1,2,3-triazoles have been synthesized by the reaction of heterocyclic ketene aminals with azides, and when glucopyranosyl azide was used, a kind of glucosylated 1,2,3-triazole derivatives were obtained [9,11] which were found to be biologically active [18]. Considering that the ribosides may change or enhance their biological activities, the ribosylated 1,2,3-triazole derivatives were synthesized. In this paper, we report the results of the reaction between aroyl-substituted heterocyclic ketene aminals and 2,3,5-tri-*O*-β-D-ribofuranosyl azide.

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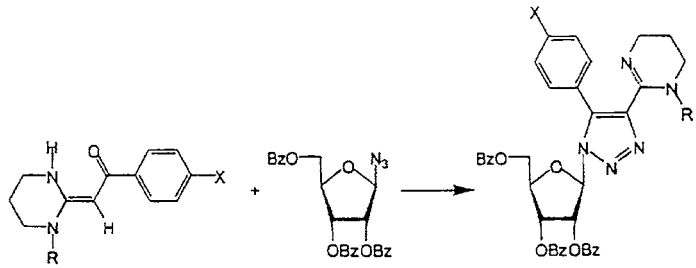
RESULTS AND DISCUSSION

The aroyl-substituted heterocyclic ketene aminals **1** and **2** used were prepared by the reaction of aroyl-substituted ketene-*S,S*-diacetals with 1,3-propanediamine or *N*-methyl-1,3-propanediamine, according to the literature procedure [19]. Ketene aminals **1** or **2** reacted with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (**3**) [20] to give the *N*-ribosylic triazoles **4** or **5** (Scheme 1). The reaction conditions, yields, and melting points of **4** and **5** are listed in Table 1.

The structures of compounds **4** and **5** were determined by IR, ^{1}H, and ^{13}C NMR and also by MS and elemental analyses. The constitutions of **4** and **5** were confirmed by MS and elemental analyses, which indicated that a reaction took place between **1** or **2** with **3** in 1:1 molar ratio, accompanied by the loss of 1 mol of water. The disappearance of the aroy carbonyl absorption (ca. 1610 cm^{-1}) in the IR spectra and of the carbonyl signal (δ ca. 180–190 ppm) in the ^{13}C NMR of compounds **4** and **5**, the appearance of benzoxy carbonyl bands/signals in the IR and NMR spectra, and the disappearance of the ethylenic proton signal in the ^{1}H NMR spectra are all consistant with the structures shown for compounds **4** and **5**. The ^{1}H NMR and ^{13}C NMR signals, especially those of the ribofuranose ring, were assigned by ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectrum of **4b**. The β-configuration of ribofuranosyl ring was confirm by the H_1–H_2 coupling constants ($J_{H1,H2}$ = 5.4–6.8 Hz) for **4** and **5** [21].



1, 2, 4, 5	a	b	c	d	e	f
X	H	CH_3	OCH_3	Cl	F	Br

SCHEME 1

The above results are similar to those of the reaction of benzoyl-substituted heterocyclic ketene aminals with phenyl azides. The polysubstituted 1,2,3-triazoles are formed by the nucleophilic attack of the α-carbon of the ketene aminal to the terminal nitrogen atom of the azide, the reaction then being completed by cyclocondensation and aromatization sequences [8].

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Analytical Laboratory of the Institute. Mass spectra were obtained on a KYKY-ZHT-5 instrument. IR spectra were recorded with Bruck IFS 2s spectrometer for KBr tablets. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 200 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard.

TABLE 1 Reaction Conditions, Yields, and Melting Points of Compounds **4** and **5**

	Reaction Conditions			
Compd.	*Temp. (°C)*	*Time (d)*	*Yield [a] (%)*	*m.p. (°C)*
4a	35	4	62	95–97
4b	35	5	68	86–88
4c	35	4	75	82–84
4d	35	6	58	93–95
4e	35	6	60	105–107
4f	35	6	63	121–123
5a	35	8	53	89–91
5b	35	12	65	98–100
5c	35	8	70	80–82
5d	35	14	50	80–82

[a]Isolated yield.

General Procedure for the Synthesis of Compounds **4** *and* **5**

A mixture of benzoyl-substituted heterocyclic ketene aminals **1** or **2** (1 mmol) and 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (**3**) (1 mmol) in 20 ml anhydrous ethylene chloride was stirred at 35°C and monitored by TLC. After removal of solvent, the products were purified with a neutral aluminium oxide column, using chloroform as eluant.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-phenyl-1,2,3-triazole (**4a**). IR (KBr): 3400 (N—H), 1729 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.00–7.20 (m, 20H, Ar-H), 6.52–6.47 (m, 1H, rib-H_3), 6.16–6.10 (m, 1H, rib-H_2), 6.01 (d, 2H, $J_{H1,H2} = 6.8$ Hz, rib-H_1), 5.73–5.60 (m, 1H, rib-H_4), 4.37–4.04 (m, 2H, rib-H_5), 3.35 (t, 4H, $J = 5.7$ Hz, N—CH_2), 1.77 (quin, 2H, $J = 5.7$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.8, 164.5, 147.7, 140.4, 137.5, 133.4, 130.5, 129.9, 129.8, 129.7, 129.5, 129.4, 129.1, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.2, 125.8, 81.8, 68.4, 68.0, 66.6, 64.0, 41.5, 20.4; FABMS: 672 $(M+1)^+$. Anal. Calcd for $C_{38}H_{33}N_5O_7$: C, 67.95; H, 4.95; N, 10.43. Found: C, 67.32; H, 4.82; N, 9.80.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-(p-methylphenyl)-1,2,3-triazole (**4b**). IR (KBr): 3416 (N—H), 1727 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.97–7.26 (m, 19H, Ar-H), 6.52–6.07 (m, 1H, rib-H_3), 6.16–6.11 (m, 1H, rib-H_2), 6.03 (d, 2H, $J_{H1,H2} = 6.6$ Hz, rib-H_1), 5.73–5.67 (m, 1H, rib-H_4), 4.38–4.04 (m, 2H, rib-H_5), 3.38 (t, 4H, $J = 5.9$ Hz, N—CH_2), 2.46 (s, 3H, CH_3), 1.79 (quin, 2H, $J = 5.9$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.1, 164.6, 164.3, 147.2, 140.6, 139.7, 137.2,

133.3, 130.2, 130.1, 129.6, 129.5, 129.1, 129.0, 128.7, 128.3, 128.2, 122.8, 81.4, 68.3, 67.9, 66.5, 63.8, 41.6, 21.4, 20.5; FABMS: 686 $(M+1)^+$. Anal. Calcd for $C_{39}H_{35}N_5O_7$: C, 68.31; H, 5.15; N, 10.21. Found: C, 68.26; H, 5.22; N, 9.31.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-(p-methoxyphenyl)-1,2,3-triazole (***4c***).* IR (KBr): 3429 (N—H), 1729 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.97–7.00 (m, 19H, Ar-H), 6.52–6.48 (m, 1H, rib-H_3), 6.16–6.11 (m, 1H, rib-H_2), 6.03 (d, 2H, $J_{H1,H2} = 6.6$ Hz, rib-H_1), 5.75–5.68 (m, 1H, rib-H_4), 4.38–4.09 (m, 2H, rib-H_5), 3.89 (s, 3H, OCH_3), 3.37 (t, 4H, $J = 5.5$ Hz, N—CH_2), 1.79 (quin, 2H, $J = 5.5$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.7, 164.5, 160.8, 147.9, 140.0, 137.5, 133.4, 133.3, 132.0, 129.7, 129.6, 129.5, 129.1, 128.6, 128.4, 128.3, 128.2, 117.4, 114.0, 81.7, 68.4, 68.0, 66.7, 64.0, 55.3, 41.5, 20.4; FABMS: 702 $(M+1)^+$. Anal. Calcd for $C_{39}H_{35}N_5O_8$: C, 66.75; H, 5.03; N, 9.98. Found: C, 66.80; H, 5.13; N, 9.88.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-(p-chlorophenyl)-1,2,3-triazole (***4d***).* IR (KBr): 3416 (N—H), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.04–7.22 (m, 19H, Ar-H), 6.52–6.24 (m, 1H, rib-H_3), 6.18–6.12 (m, 1H, rib-H_2), 6.00 (d, 2H, $J_{H1,H2} = 6.4$ Hz, rib-H_1), 5.74–5.67 (m, 1H, rib-H_4), 4.36–4.05 (m, 2H, rib-H_5), 3.32 (t, 4H, $J = 5.5$ Hz, N—CH_2), 1.72 (quin, 2H, $J = 5.5$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.7, 164.4, 147.4, 140.7, 136.3, 136.0, 133.4, 133.3, 133.0, 131.9, 129.7, 129.5, 129.4, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 127.8, 124.3, 81.7, 68.3, 67.8, 66.5, 63.9, 41.5, 20.4; FABMS: 706 $(M+1)^+$. Anal. Calcd for $C_{38}H_{32}ClN_5O_7$: C, 64.63; H, 4.57; N, 9.92. Found: C, 64.53; H, 4.69; N, 9.45.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-(p-fluorophenyl)-1,2,3-triazole (***4e***).* IR (KBr): 3430 (N—H), 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96–7.16 (m, 19H, Ar-H), 6.51–6.47 (m, 1H, rib-H_3), 6.15–6.10 (m, 1H, rib-H_2), 5.98 (d, 2H, $J_{H1,H2} = 6.1$ Hz, rib-H_1), 5.75–5.68 (m, 1H, rib-H_4), 4.37–4.08 (m, 2H, rib-H_5), 3.38 (t, 4H, $J = 5.2$ Hz, N—CH_2), 1.82 (quin, 2H, $J = 5.2$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.7, 164.4, 147.2, 140.8, 136.3, 133.4, 133.3, 132.8, 132.6, 129.7, 129.6, 129.5, 129.3, 129.2, 129.0, 128.8, 128.4, 128.3, 122.0, 115.8, 115.3, 81.7, 68.3, 67.9, 66.6, 64.0, 41.6, 20.5; FABMS: 690 $(M+1)^+$. Anal. Calcd for $C_{38}H_{32}FN_5O_7$: C, 66.18; H, 4.68; N, 10.15. Found: C, 65.76; H, 4.75; N, 10.37.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(2-tetrahydropyrimidinyl)-5-(p-bromophenyl)-1,2,3-triazole (***4f***).* IR (KBr): 3420 (N—H), 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96–7.20 (m, 19H, Ar-H), 6.53–6.49 (m, 1H, rib-H_3), 6.17–6.12 (m, 1H, rib-H_2), 5.97 (d, 2H, $J_{H1,H2} = 6.6$ Hz, rib-H_1), 5.75–5.68 (m, 1H, rib-H_4), 4.36–4.09 (m, 2H, rib-H_5), 3.37 (t, 4H, $J = 5.7$ Hz, N—CH_2), 1.78 (quin, 2H, $J = 5.7$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.7, 164.4, 147.1, 140.9, 136.2, 133.5, 133.4, 133.3, 132.2, 131.6, 129.7, 129.6, 129.5, 129.0, 128.5, 128.3, 125.0, 124.4, 81.7, 68.4, 67.9, 66.5, 64.0, 41.6, 20.5; FABMS: 750 $(M+1)^+$. Anal. Calcd for $C_{38}H_{32}BrN_5O_7$: C, 60.81 H, 4.30; N, 9.33. Found: C, 60.73; H, 4.68; N, 8.79.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl-4-(N-methyl-2-tetrahydropyrimidinyl)-5-phenyl-1,2,3-triazole (***5a***).* IR (KBr): 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00–7.20 (m, 20H, Ar-H), 6.57–6.53 (m, 1H, rib-H_3), 6.19 (d, 2H, $J_{H1,H2} = 5.9$ Hz, rib-H_1), 6.12–6.06 (m, 1H, rib-H_2), 5.73–5.67 (m, 1H, rib-H_4), 4.42–4.14 (m, 2H, rib-H_5), 3.40 (t, 2H, $J = 5.7$ Hz, N—CH_2), 3.20 (t, 2H, $J = 5.7$ Hz, N—CH_2), 2.60 (s, 3H, N—CH_3), 1.88 (quin, 2H, $J = 5.7$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.3, 164.7, 164.6, 149.8, 140.1, 137.2, 133.4, 133.3, 129.9, 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 128.9, 128.7, 128.4, 128.3, 128.2, 125.6, 122.5, 82.3, 68.4, 67.8, 66.7, 64.0, 48.0, 44.2, 39.2, 21.4; FABMS: 686 $(M+1)^+$. Anal. Calcd for $C_{39}H_{35}N_5O_7$: C, 68.31; H, 5.15; N, 10.21. Found: C, 68.34; H, 5.36; N, 9.74.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl-4-(N-methyl-2-tetrahydropyrimidinyl)-5-(p-methylphenyl)-1,2,3-triazole (***5b***).* IR (KBr): 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.98–7.20 (m, 19H, Ar-H), 6.58–6.54 (m, 1H, rib-H_3), 6.19 (d, 2H, $J_{H1,H2} = 5.6$ Hz, rib-H_1), 6.12–6.06 (m, 1H, rib-H_2), 5.75–5.69 (m, 1H, rib-H_4), 4.42–4.16 (m, 2H, rib-H_5), 3.40 (t, 2H, $J = 5.6$ Hz, N—CH_2), 3.19 (t, 2H, $J = 5.6$ Hz, N—CH_2), 2.60 (s, 3H, N—CH_3), 2.45 (s, 3H, CH_3), 1.87 (quin, 2H, $J = 5.6$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.7, 164.6, 149.8, 141.6, 140.0, 137.1, 133.3, 133.2, 129.7, 129.6, 129.5, 129.3, 129.1, 128.5, 128.3, 128.2, 128.1, 122.5, 82.1, 68.3, 67.7, 66.6, 63.8, 47.9, 44.2, 39.0, 21.4, 21.3; FABMS: 700 $(M+1)^+$. Anal. Calcd for $C_{40}H_{37}N_5O_7$: C, 68.66; H, 5.33; N, 10.01. Found: C, 68.70; H, 5.39; N, 9.77.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl-4-(N-methyl-2-tetrahydropyrimidinyl)-5-(p-methoxyphenyl)-1,2,3-triazole (***5c***).* IR (KBr): 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06–7.00 (m, 19H, Ar-H), 6.59–6.55 (m, 1H, rib-H_3), 6.17 (d, 2H, $J_{H1,H2} = 5.6$ Hz, rib-H_1), 6.14–6.08 (m, 1H, rib-H_2), 5.75–5.69 (m,

1H, rib-H_4), 4.43–4.16 (m, 2H, rib-H_5), 3.88 (s, 3H, OCH_3), 3.40 (t, 2H, $J = 5.5$ Hz, N—CH_2), 3.22 (t, 2H, $J = 5.5$ Hz, N—CH_2), 2.63 (s, 3H, N—CH_3), 1.88 (quin, 2H, $J = 5.5$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.4, 164.8, 164.7, 160.9, 150.3, 140.8, 137.4, 133.4, 133.3, 132.7, 131.1, 129.8, 129.7, 129.6, 129.2, 128.9, 128.7, 128.4, 128.3, 117.3, 114.4, 113.0, 82.4, 68.4, 67.7, 66.8, 64.0, 55.3, 48.1, 43.7, 39.3, 21.2; FABMS: 716 $(M+1)^+$. Anal. Calcd for $C_{40}H_{37}N_5O_8$: C, 67.12; H, 5.21; N, 9.78. Found: C, 67.11; H, 5.18; N, 9.53.

*1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl-4-(N-methyl-2-tetrahydropyrimidinyl)-5-(p-chlorophenyl)-1,2,3-triazole (***5d***).* IR (KBr): 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.00–7.20 (m, 19H, Ar-H), 6.57–6.53 (m, 1H, rib-H_3), 6.14 (d, 2H, $J_{H1,H2} = 5.4$ Hz, rib-H_1), 6.13–6.07 (m, 1H, rib-H_2), 5.75–5.69 (m, 1H, rib-H_4), 4.40–4.16 (m, 2H, rib-H_5), 3.38 (t, 2H, $J = 5.4$ Hz, N—CH_2), 3.20 (t, 2H, $J = 5.4$ Hz, N—CH_2), 2.64 (s, 3H, N—CH_3), 1.86 (quin, 2H, $J = 5.4$ Hz, C—CH_2—C); ^{13}C NMR ($CDCl_3$): δ 165.2, 164.6, 164.5, 149.5, 141.9, 136.1, 133.4, 133.3, 133.2, 131.0, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.6, 128.4, 128.3, 128.2, 128.0, 124.0, 82.3, 68.2, 67.5, 66.5, 63.9, 47.9, 44.1, 39.1, 21.2; FABMS: 720 $(M+1)^+$. Anal. Calcd for $C_{39}H_{34}ClN_5O_7$: C, 65.05; H, 4.76; N, 9.72. Found: C, 65.30; H, 5.60; N, 9.65.

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