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EFFICIENT SYNTHESIS OF 2,4-DIOXO-HEXAHYDRO-1,3,5-TRIAZINE O-ACETYL-GLYCOSYL GLUCOSIDES AND THEIR ANTIVIRAL ACTIVITY

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Four 2,4-dioxohexahydro-1,3,5-triazine O-acetylglycosyl glucosides were synthesized through glucoside formation reactions at room temperature using 4-dimethylaminopyridine as a catalyst and triethylamine as a deacidification reagent. Their structure was confirmed by IR, ^{1}H NMR spectra, MS, and elemental analysis. The synthesized compounds are all of β-configuration. The results show that DMAP is an effective catalyst; the yields can reach 83.7%. The above glucosides showed an improved antiviral activity against tobacco mosaic virus.

Keywords: O-acetylglycosyl, O-acetylglycosyl glucoside, 2,4-dioxohexahydro-1,3,5-triazine, DMAP/Et_3N, tobacco mosaic virus.

We have synthesized 2,4-dioxohexahydro-1,3,5-triazine (DHT) derivatives, which possess certain activities against tobacco mosaic virus (TMV) [1-4].

A number of authors have reported the bioactivity of glucosides. They have been used in medicinal chemistry and agriculture [5-12].

4-Dimethylaminopyridine (DMAP) is widely used in organic synthesis as a nucleophilic reaction catalyst [13, 14]. It can efficiently catalyze esterification reactions, but it has been rarely reported as a catalyst for the synthesis of 2,4-dioxohexahydro-1,3,5-triazine O-acetylglycosyl glucosides. In view of the above and in connection with our recent work on the search for new phytoantiviral agents [15-17], we selected DMAP as a catalyst and Et_3N as a deacidification reagent for the preparation of glucosides **1-4** (Scheme 1, Table).

We found that the reactions in the presence of DMAP/Et_3N proceeded quickly and smoothly at room temperature under mild conditions and with a substantially increased yield (up to 83.7%), and a decrease in the reaction time compared with the phase-transfer catalyst (Bu_4NBr) method. This method is simple, and the amount of catalyst DMAP is small. Optimum reaction conditions were as follows: 1.5-2.5 h at 20-25°C with equimolar ratio of reagents (5 ml of Et_3N and 1.5 mmol of DMAP for 0.03 mol of DHT and 0.03 mol of α-O-acetyl-glycosyl bromide).

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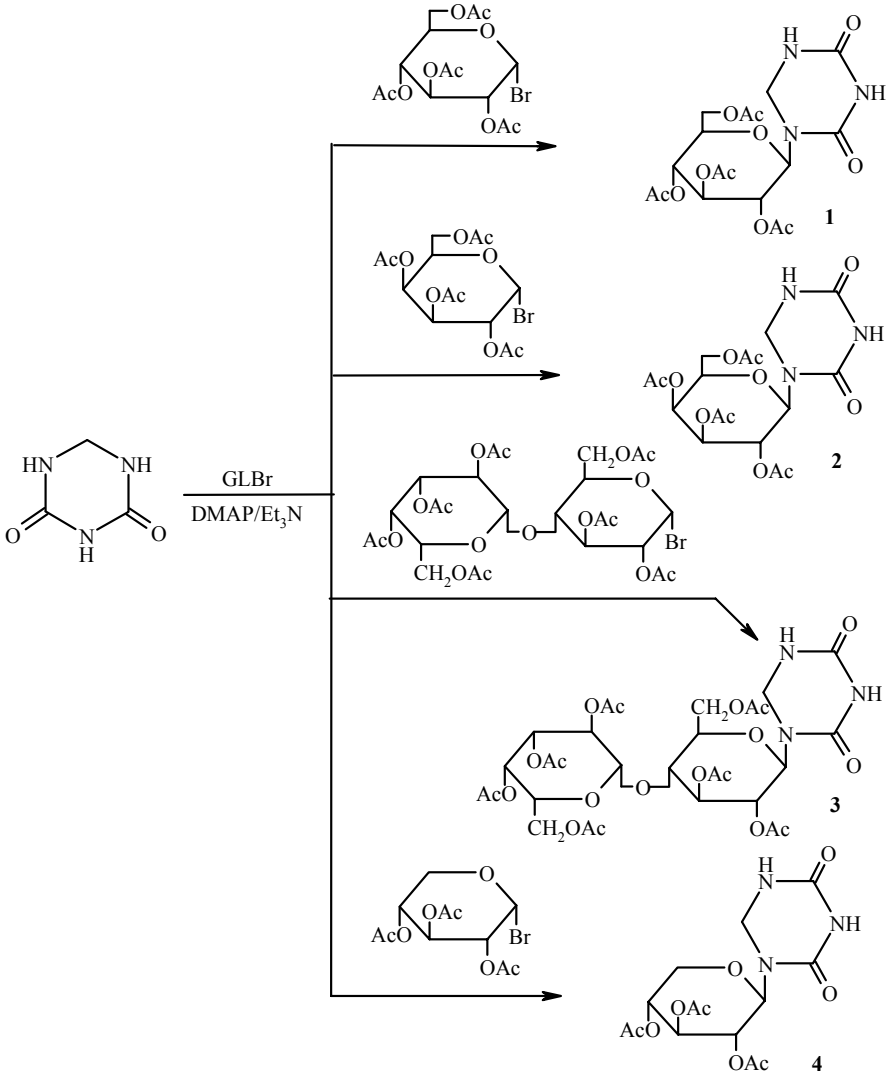
The preliminary biological tests showed that the antiviral activity of 2,4-dioxohexahydro-1,3,5-triazine O-acetylglycosyl glucosides (56.7-68.7% against TMV) is good. The anti-TMV data indicate that the O-acetyl-glycosyl moiety influences the anti-TMV activity of the compounds, and the inhibition rate of xylopyranosyl derivatives is higher than that of glucopyranosyl and galactopyranosyl analogs (Table 1).

Scheme 1
The synthetic route of compounds **1–4**



As far as we know this is the first example of 2,4-dioxohexahydro-1,3,5-triazine O-acetylglycosyl glucoside synthesis using the DMAP/Et_3N method. We propose that the mechanism of DMAP/ET_3N catalytic action is similar to that described in [18]: DMAP firstly reacted with O-acetylglycosyl bromide, quickly forming an unstable intermediate (DMAP salt) with increased electropositivity at the glycosyl ring C-1. Further this salt quickly reacted with 2,4-dioxohexahydro-1,3,5-triazine to give the target product **1-4**. Thus, the reaction can proceed at low temperature. DMAP is released recyclable.

TABLE 1.Yields, Reaction Time, and Antiviral Activity of Compounds **1–4***

Compound	Yield, %		Reaction time, h		Antiviral activity, %**
	a	*b*	*a*	*b*	
1	81.7	76.6	2.0	5.0	59.5
2	83.7	78.5	2.0	5.0	56.7
3	80.8	72.5	2.5	5.0	62.3
4	80.7	71.8	1.5	5.0	68.7

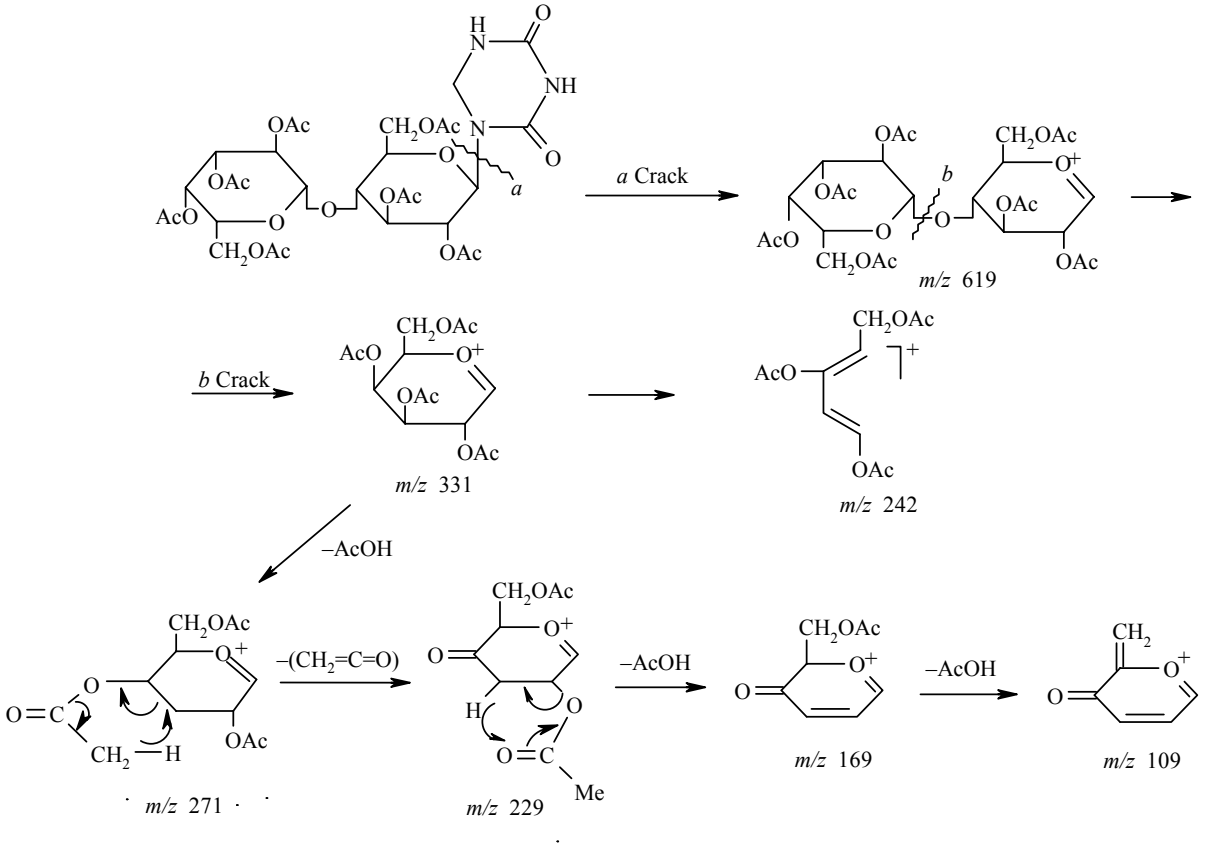
* *a* – DMAP/Et_3N method (20-45°C); *b* – phase-transfer catalyst (Bu_4NBr) method (70-80°C).

*[2]Activity against TMV (calculated from withered spot number on the tobacco leaf at 0.001%, concentration with 80% inhibition for NS83 used as a control).

Triethylamine, being a strong base (p*K*a 10.88), activated 2,4-dioxohexahydro-1,3,5-triazine and bound the released HBr, thus saving the DMAP catalytic activity.

The molecular ion $[M+H]^+$ peaks of glycosides **1-4** were obtained by fast atom bombardment (FAB) because by the electron impact (EI) MS method no molecular ion peaks were obtained. Only a *m/z* 331 peak, which corresponds to a tetraacetylgalactopyranosyl fragment or O-tetraacetylglucopyranosyl fragment, a

Scheme 2
The MS fragmentation of compound **3**



m/z 259 fragment peak, which corresponds to a O-acetylxylopyranosyl fragment, and a *m/z* 619 peak, which corresponded to the O-octaacetyllactosyl fragment, were observed. Some of the 2,4-dioxohexahydro-1,3,5-triazine fragment peaks were obtained both by FAB and EI methods. The fragmentation of compound **3** is shown in Scheme 2.

In the IR spectra of compounds **1-4** two strong and wide bi-shoulder peaks of the pyranoid ring appear at 1000-1100 and 1200-1300 cm^{-1}; absorption about 1750 cm^{-1} is attributed to the carbonyl group. In the ^1H NMR spectra the assignments of the hydrogen atoms in peaks are very obvious; the coupling constant $J_{1,2}$ between H-1 and H-2 of the pyranose ring is 7.2-7.4 Hz, proving the β-configuration of glucoside (usually 7-10 Hz [19]). Moreover, there is only an NH proton signal at 7.5-7.9 and not at 8.95 ppm [20]. As in the standard spectra [20], the NH proton signal of the NH group placed between two carbonyl groups was not observed.

To sum up, compounds **1-4** prepared in the system of DMAP/Et_3N are of the β-configuration. Their structure is the same as compared with the compounds obtained by the phase-transfer catalytic method.

The antiviral activities of the compounds synthesized against TMV are up to 68.7%.

EXPERIMENTAL

IR spectra were obtained using a Shimadzu IR-435 IR spectrometer (thin layer). The elemental analyses were recorded on an Immunomedia MT-3 elemental analyzer. Mass spectra were recorded on an HP5988A GC-MS instrument. ^1H NMR spectra were recorded in acetone-d_6 on a Varian Mercury-VX300 (300 MHz) NMR instrument using TMS as an internal standard.

2,4-Dioxohexahydro-1,3,5-triazine O-Acetylglycosyl Glucosides 1-4 (General Method). 2,4-Dioxohexahydro-1,3,5-triazine (DHT) (0.03 mol), α-O-acetylglycosyl bromide (0.03 mol), and DMAP (1.5 mmol) were dropped into a four-necked round-bottomed flask (250 ml) with DMF (120 ml). Triethylamine (5 ml) was slowly dropped into the reaction system under stirring at 0°C for 30 min, then kept at room temperature for 1.5-2.5 h. As soon as the reaction is finished, the solution was filtered. After separation, the organic phase was washed to neutral with water and dried with anhydrous magnesium sulfate. The dense liquid was obtained by evaporation of the solvent under vacuum distillation conditions. After separation through silica gel chromatography using methanol–chloroform, 1:5 (V/V) as an eluent, compounds **1-4** were obtained after the solvent evaporation.

2,4-Dioxohexahydro-1,3,5-triazine O-Tetraacetylglucopyranosyl Glucoside (1). Red-brown dense liquid. IR spectrum, ν, cm^{-1}: 3479 (NH), 2950 (CH_3), 1760, 1680 (C=O), 1440, 1370 (CN), 1015-1060, 1210-1290 (bi-shoulder peaks of pyranoid ring), 1220, 1030 (C–O pyrane). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.9 (1H, s, DHT NH); 4.21-4.32 (2H, m, DHT CH_2); 5.90-6.00 (1H, d, *J* = 7.2, H-1 pyrane); 5.40-4.75 (3H, m, H-2,3,4 pyrane); 4.08-4.28 (1H, m, H-5 pyrane); 3.40-3.50 (2H, m, H-6 pyrane); 1.28–2.15 (12H, m, CH_3). FAB mass spectrum, *m/z* (I_{rel}, %): 446 $[M+H]^+$ (14). Found, %: C 45.69; H 5.20; N 9.39. $C_{17}H_{23}N_3O_{11}$. Calculated, %: C 45.84; H 5.17; N 9.44.

2,4-Dioxohexahydro-1,3,5-triazine O-Tetraacetylgalactopyranosyl Glucoside (2). Red-brown liquid. IR spectrum, ν, cm^{-1}: 3450 (NH), 2900 (CH_3), 1740, 1665 (C=O), 1385, 1435 (CN), 1020-1090, 1210-1290 (bi-shoulder peaks of pyranoid ring), 1220, 1090 (C–O pyrane). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.5 (1H, s, DHT NH); 4.20-4.39 (2H, m, DHT CH_2); 5.90–6.00 (1H, d, *J* = 7.2, H-1 pyrane); 5.20–5.48 (3H, m, H-2,3,4 pyrane); 4.05-4.15 (H, m, H-5 pyrane); 3.70-3.76 (2H, m, H-6 pyrane); 1.25–2.13 (12H, m, CH_3). FAB mass spectrum, *m/z* (I_{rel}, %): 446 $[M+H]^+$ (14). Found, %: C 45.70; H 5.19; N 9.40. $C_{17}H_{23}N_3O_{11}$. Calculated, %: C 45.84; H 5.17; N 9.44.

2,4-Dioxohexahydro-1,3,5-triazine O-Heptaacetyllactosyl Glucoside (3). Red-brown liquid. IR spectrum, ν, cm^{-1}: 3470 (NH), 2950 (CH_3), 1745, 1660 (C=O), 1370, 1440 (CN), 1020–1090, 1210-1290 (bi-shoulder peaks of pyranoid ring), 1220, 1050 (C–O pyrane). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.9 (1H, s,

DHT NH); 4.19-4.33 (2H, m, DHT CH_2); 5.85-5.95 (1H, d, J = 7.2, H-1 pyrane); 5.50–5.60 (1H, d, J = 7.2, H-1' pyrane); 5.33-4.75 (6H, m, H-2,3,4, H-2',3',4' pyrane); 3.62-3.82 (1H, m, H-5 pyrane); 4.30-4.40 (1H, m, H-5' pyrane); 4.10-4.20 (4H , m, H-6, H-6' pyrane); 2.05-2.26 (24H, m, CH_3). FAB mass spectrum, m/z (I_{rel}, %): 734 $[M+H]^+$ (16). Found, %: C 47.25; H 5.27; N 5.69. $C_{29}H_{39}N_3O_{19}$. Calculated, %: C 47.48; H 5.32; N 5.73.

2,4-Dioxohexahydro-1,3,5-triazine O-Triacetylxylopyranosyl Glucoside (4). Red-brown liquid. IR spectrum, ν, cm^{-1}: 3445 (NH), 2900 (CH_3), 1710, 1740, 1660 (C=O), 1380, 1490 (CN) 1010-1070, 1210-1290 (bi-shoulder peaks of pyranoid ring), 1220, 1050 (C–O pyrane). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.5 (1H, s, DHT NH); 4.20-4.34 (2H, m, DHT CH_2); 5.85-5.95 (1H, d, J = 7.4, H-1 pyrane); 4.70-5.40 (3H, m, H-2,3,4 pyrane); 3.30-3.50 (2H, m, H-5 pyrane), 2.10-2.20 (9H, m, CH_3). FAB mass spectrum, m/z (I_{rel}, %): 374 $[M+H]^+$ (17). Found, %: C 44.92; H 5.01; N 11.19. $C_{14}H_{19}N_3O_9$. Calculated, %: C 45.04; H 5.09; N 11.26.

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