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EFFICIENT SYNTHESIS OF BENZIMIDAZOLYL-PHENOXYACETIC ACID O-ACETYLXYLOPYRANOSYL AND O-ACETYLGALACTOPYRANOSYL ESTERS AND THEIR ANTIVIRAL ACTIVITY

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Six benzimidazolylphenoxyacetic acid O-acetylxylopyranosyl and O-acetylgalactopyranosyl esters were synthesized through esterification 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 63.6%. The above esters showed improved antiviral activity against tobacco mosaic virus.

Keywords: O-acetylgalactopyranosyl esters, O-acetylxylopyranosyl esters, benzimidazolyl-phenoxyacetic acid esters, tobacco mosaic virus, DMAP/Et_3N.

A number of authors have reported the bioactivity of benzimidazole and its derivatives. They are applied widely in medicinal chemistry, agriculture, and also as plant virus inhibitors [1-4].

4-Dimethylaminopyridine (DMAP) is widely used in organic synthesis as a nucleophilic reaction catalyst [5, 6]. It can efficiently catalyze esterification reactions, but it has been rarely reported as a catalyst for the synthesis of benzimidazolylphenoxyacetic acid esters. In view of the above, and in connection with our recent work on the search for new phytoantiviral agents [7, 8], we selected DMAP as a catalyst and Et_3N as a deacidification reagent for the preparation of saccharide esters **1-6**.

The reactions are shown in Scheme 1, and the results are summarized in Table 1. 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 63.6%), and decrease in reaction time compared with the phase-transfer catalyst (Bu_4NBr) method. This method is simple; 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 (1 ml of Et_3N and 0.3 mmol of DMAP for 5.25 mmol of acid).

The antiviral activity of benzimidazolylphenoxyacetic acid esters (43-58%) against tobacco mosaic virus (TMV) is higher than that of the parent acids (about 30% [8]), xylopyranosyl derivatives being more active than galactopyranosyl analogues (Table 1).

As far as we know, this is the first example of benzimidazolylphenoxyacetic acid saccharide esters synthesized using the DMAP/Et_3N method. We propose (Scheme 2) that DMAP first reacted with O-acetylglycosyl bromide, quickly forming an unstable intermediate (DMAP salt), with increased

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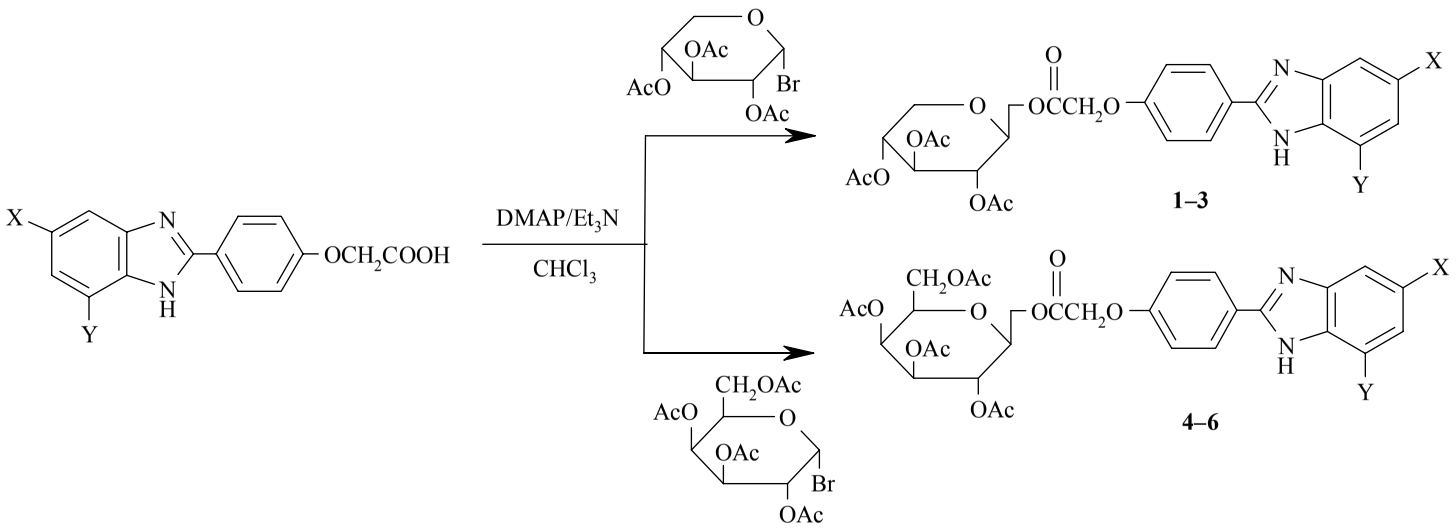
Scheme 1



1,4 X = Y = H; **2,5** X = NO_2, Y = H; **3,6** X = CF_3, Y = NO_2

TABLE 1. Reaction Time, Yields, and Antiviral Activity of Esters **1-6***

Compound	Reaction time, h		Yield, %		Antiviral activity, %*[2]
	a	b	a	b	
1	2.5	5.0	61.7	21.3	50.2
2	2.0	4.5	63.6	23.5	54.7
3	1.5	4.0	60.8	19.2	58.6
4	2.5	5.5	50.7	26.8	43.3
5	2.0	5.0	52.2	27.5	46.9
6	1.5	4.5	58.0	30	48.6

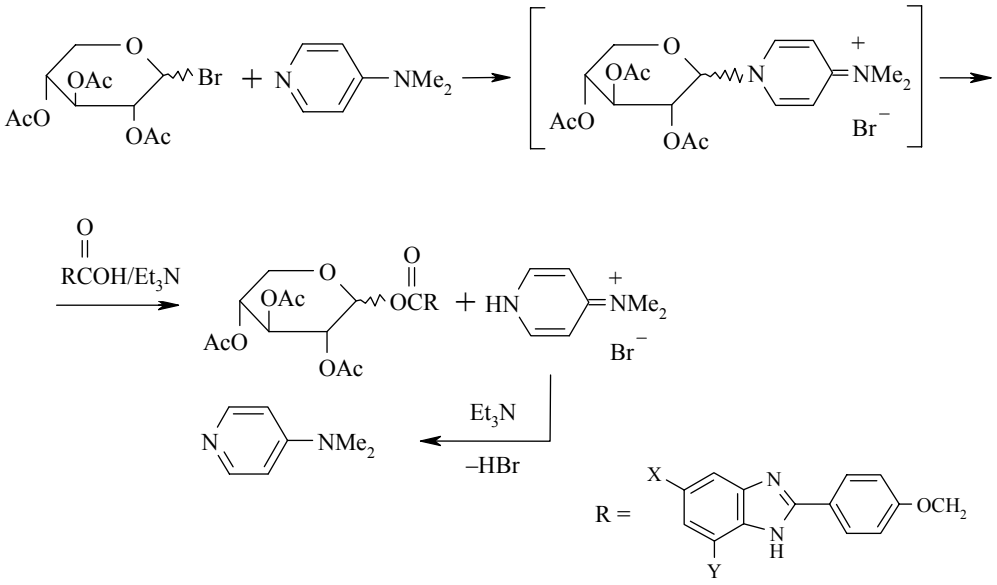
* a – DMAP/Et_3N method; b – phase-transfer catalyst (Bu_4NBr) method.
*[2] Activity against TMV (calculated from withered spot number on the tobacco leaf at 0.001% concentration with 80% inhibition for NS83 used as a control).

electropositivity at the glycosyl ring $C_{(1)}$. Further this salt quickly reacted with substituted benzimidazolylphenoxyacetic acid to give the target product **1-6**. Thus the reaction can proceed at low temperature. DMAP is released recyclable.

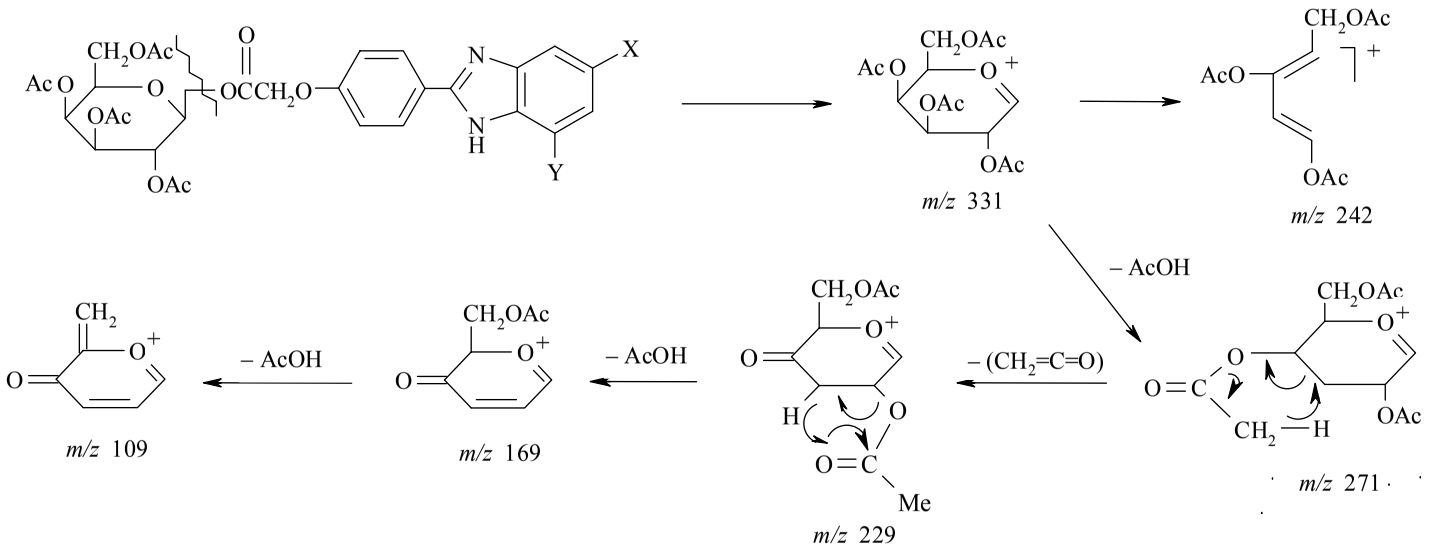
Triethylamine, being a strong base (pK_a = 10.88), activated the benzimidazolylphenoxyacetic acid and binded the released HBr, so saving the catalytic activity of DMAP.

The molecular ion $(M+H)^+$ peaks of esters **1-6** were obtained by FAB (fast atom bombardment) because by the EI (electron impact) MS method, no molecular ion peaks were obtained. Only a 331 (*m/z*) fragment peak, which corresponds to a tetraacetylgalactopyranosyl fragment, and a 259 (*m/z*) fragment peak, which corresponds to an O-acetylxylopyranosyl fragment, were observed. Some of benzimidazolylphenoxyacetic acid fragment peaks were obtained both by FAB and EI methods. The fragmentation of compounds **4-6** is shown in Scheme 3.

Scheme 2
The mechanism of DMAP/Et_3N catalytic action



Scheme 3
MS fragmentation of compounds **4-6**



In the IR spectra of compounds **1-6** 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, and the coupling constant $J_{1,2}$ between H-1 and H-2 of pyranose ring is 7.2-7.4 Hz, proving the β-configuration of saccharide esters (usually 7-10 Hz [9]).

To sum up, compounds **1-6** prepared in the system of DMAP/Et_3N are of β-configuration. Their structure is the same as compared with compounds obtained by the phase-transfer catalytic method.

The antiviral activities of the synthesized compounds against tobacco mosaic virus are up to 58.6%.

EXPERIMENTAL

IR spectra were obtained using a Shimadzu IR-435 IR spectrometer. 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.

Preparation of substituted benzimidazolylphenoxyacetic acid saccharide esters 1-6 (General Procedure). α-O-Acetylglycosyl bromide (5.25 mmol) dissolved in 30 ml of $CHCl_3$ was dropped into chloroform (30 ml) solution of acid (5.25 mmol) and DMAP (0.3 mmol) under stirring in a 250 ml four-necked round-bottomed flask. Triethylamine (1 ml) was slowly dropped into the reaction system under stirring in 30 min at 0°C, then kept at room temperature for 1.5-2.5 h. As soon as the reaction ended, 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 condition. After separation through silica gel chromatography using ethyl acetate as an eluent, compounds **1-6** were obtained after evaporation of the solvent.

4-[2-Benzimidazol-2-yl]phenoxyacetic Acid O-Acetylxylopyranosyl Ester (1). Light brown dense liquid. IR (thin layer), ν, cm^{-1}: 2940 (NH), 1743 (C=O), 1612 (C=C), 1647 (C=N), 1110-1161 (COPh), 1015-1060, 1210-1300 (bi-shoulder peaks pyrane). ^1H NMR, δ, ppm (*J*, Hz): 5.70-5.80 (1H, d, *J* = 7.2, H-1 pyrane); 5.41-4.62 (3H, m, H-2,3,4 pyrane); 3.42-3.05 (2H m, H-5 pyrane); 2.03-2.31 (9H, m, CH_3); 7.20-7.40 (2H, d, *J* = 8.8); 6.91-6.71 (2H, m); 8.00-8.30 (4H, m, ArH); 4.70 (2H, s, $OC(O)CH_2O$); 3.31 (1H, s, NH). Found, %: C 59.24; H 4.90; N 5.30. $C_{26}H_{26}N_2O_{10}$. Calculated, %: C 59.32; H 4.94; N 5.32. FAB mass spectrum, *m/z* (I_{rel}, %): 527 $[M+H]^+$ (12).

4-[2-(5-Nitrobenzimidazol-2-yl)]phenoxyacetic Acid O-Acetylxylopyranosyl Ester (2). Light brown dense liquid. IR (thin layer), ν, cm^{-1}: 2940 (NH), 1761 (C=O), 1615 (C=N), 1510, 1365 (NO_2), 1220, 1030 (COPh), 1210-1300, 1020-1050 (bi-shoulder peaks of pyranoid ring); ^1H NMR, δ, ppm (*J*, Hz): 5.80-5.90 (1H d, *J* = 7.2, H-1 pyrane); 5.41-4.52 (3H m, H-2,3,4 pyrane); 3.42-3.14 (2H, m, H-5 pyrane); 2.01-2.21 (9H, m, CH_3); 7.02-7.23 (2H, d, *J* = 9.1); 6.90 (1H, s); 8.30-8.50 (4H, m, ArH); 4.80 (2H, s, $OC(O)CH_2O$); 3.20 (1H, s, NH). Found, %: C 54.57; H 4.30; N 7.32. $C_{26}H_{25}N_3O_{12}$. Calculated, %: C 54.64; H 4.38; N 7.36. FAB mass spectrum, *m/z* (I_{rel}, %): 572 $[M+H]^+$ (15).

4-[2-(7-Nitro-5-trifluoromethylbenzimidazol-2-yl)]phenoxyacetic Acid O-Acetylxylopyranosyl Ester (3). Yellow dense liquid. IR (thin layer), ν, cm^{-1}: 2950 (NH), 1740 (C=O), 1612 (C=C), 1540, 1330 (NO_2), 1150 (CF), 1020-1090, 1200-1280 (bi-shoulder peaks of pyranoid ring). ^1H NMR, δ, ppm (*J*, Hz): 5.80-5.90 (1H, d, *J* = 7.2, H-1 pyrane); 5.52-4.61 (3H, m, H-2,3,4 pyrane); 3.32-3.03 (2H, m, H-5 pyrane); 2.10-2.31 (9H, m, CH_3); 7.20 (1H, s); 7.40 (1H, s); 8.00-8.30 (4H, m, ArH); 4.61 (2H, s, $OC(O)CH_2O$); 3.01 (1H, s, NH). Found, %: C 50.63; H 3.71; N 6.52. $C_{27}H_{24}F_3N_3O_{12}$. Calculated, %: C 50.70; H 3.76; N 6.57. FAB mass spectrum, *m/z* (I_{rel}, %): 640 $[M+H]^+$ (14).

4-[2-Benzimidazol-2-yl]phenoxyacetic Acid O-Acetylgalactopyranosyl Ester (4). Light yellow dense liquid. IR (thin layer), ν, cm^{-1}: 2962 (NH), 1747 (C=O), 1612 (C=C), 1649 (C=N) 1010-1070, 1215-1280 (bi-shoulder peaks of pyranoid ring), 1100-1161 (COPh).^{1}H NMR, δ, ppm (*J*, Hz): 5.80-5.90 (1H, d, *J* = 7.4, H-1 pyrane); 4.70-5.53 (3H, m, H-2,3,4 pyrane); 3.41-4.25 (1H, m, H-5 pyrane); 4.05-4.41 (2H, d, $J_{5,6}$ = 5.5, $J_{6,6}$ = 12.2); 1.29-2.14 (12H, m, CH_3); 7.30-7.50 (2H. d, *J* = 8.9); 6.91-6.72 (2H, m); 7.90-8.21 (4H, m, ArH); 4.60 (2H, s, $OC(O)CH_2O$); 3.20 (1H, s, NH). Found, %: C 58.12; H 5.00; N 4.65. $C_{29}H_{30}N_2O_{12}$. Calculated, %: C 58.19; H 5.02; N 4.68. FAB mass spectrum, *m/z* (I_{rel}, %): 599 $[M+H]^+$ (14).

4-[2-(5-Nitrobenzimidazol-2-yl)]phenoxyacetic Acid O-Acetylgalactopyranosyl Ester (5). Light brown dense liquid. IR (thin layer), ν, cm^{-1}: 2952 (NH), 1741 (C=O), 1610 (C=N), 1502, 1346 (NO_2), 1232, 1068 (COPh), 1210-1280, 1030-1120 (bi-shoulder peaks of pyranoid ring). ^{1}H NMR, δ, ppm (*J*, Hz): 5.70-5.80 (1H, d, *J* = 7.2, H-1 pyrane); 4.75-5.58 (3H, m, H-2,3,4 pyrane); 3.45-4.20 (1H, m, H-5 pyrane); 4.00-4.35 (2H, d, $J_{5,6}$ = 5.2, $J_{6,6}$ = 12.3); 1.25-2.10 (12H, m, CH_3); 6.90 (1H, s); 7.80-8.01 (4H, m, ArH); 4.70 (2H, s, $OC(O)CH_2O$); 3.10 (1H, s, NH). Found, %: C 54.09; H 4.49; N 6.50. $C_{29}H_{29}N_3O_{14}$. Calculated, %: C 54.12; H 4.51; N 6.53. FAB mass spectrum *m/z* (I_{rel}, %): 644 $[M+H]^+$ (13).

4-[2-(7-Nitro-5-trifluoromethylbenzimidazol-2-yl)]phenoxyacetic Acid O-Acetylgalactopyranosyl Ester (6). Light yellow dense liquid. IR (thin layer), ν, cm^{-1}: 2960 (NH), 1740 (C=O), 1620 (C=C), 1535, 1340 (NO_2), 1345, 1130 (CF), 1050-1120, 1200-1080 (bi-shoulder peaks of pyranoid ring).^{1}H NMR, δ, ppm (*J*, Hz): 5.90-6.10 (1H, d, *J* = 7.2, H-1 pyrane); 4.73-5.57 (3H, m, H-2,3,4 pyrane); 3.47-4.30 (1H, m, H-5 pyrane); 4.02-4.40 (2H, d, $J_{5,6}$ = 5.3, $J_{6,6}$ = 12.0); 1.27-2.13 (12H, m, CH_3); 7.00 (1H, s); 7.20 (1H, s); 8.00-8.40 (4H, m, ArH); 4.71 (2H, s, $OC(O)CH_2O$); 3.10 (1H, s, NH). Found, %: C 50.60; H 3.91; N 5.87. $C_{30}H_{28}F_3N_3O_{14}$. Calculated, %: C 50.63; H 3.94; N 5.91. FAB mass spectrum, *m/z* (I_{rel}, %): 712 $[M+H]^+$ (16).

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