Catalytic synthesis of benzimidazolyl-phenoxyacetic acid *O*-acetyllactosyl saccharide esters by DMAP/Et_3N and antiviral activity against TMV

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Benzimidazolyl-phenoxyacetic acid *O*-acetyllactosyl saccharide esters were synthesised in good yields at room temperature using DMAP/Et_3N. The compounds show better antiviral activity against tobacco mosaic virus (TMV).

Keywords: benzimidazolyl-phenoxyacetic acid, *O*-acetyllactosyl saccharide esters, DMAP/Et_3N

4-Dimethylaminopyridine (DMAP) has light straw coloured or colourless crystals, which were discovered in the 1960s as a new type of nucleophilic reaction catalyst. They have been applied widely in organic synthesis.[1,2] A number of authors have reported the bioactivity of benzimidazole and its derivatives, and of the aryloxy carboxylic acids. They are applied widely in agriculture and medicinal chemistry, as well as plant virus inhibitors.[3-6]

DMAP can efficiently catalyse esterification reactions but it has been rarely reported as a catalyst for the synthesis of benzimidazolyl-phenoxyacetic acid saccharide esters by using glycosyl bromide as the active group and nitro or trifluoromethyl substituted benzimidazolyl-phenoxyacetic acid (the compounds **1**, **2**, **3**) as lead compounds. In view of the above, and in conjunction with our recent work on search for new phytoantiviral agents,[7,8] the three saccharide carboxylates (the compounds **4**–**6**) were synthesised using the system DMAP/Et_3N. Experimental results show that DMAP is an efficient catalyst with yields of over 50%, The biological test results indicate that the antiviral activities of the synthesised compounds against tobacco mosaic virus are up to 53.2%. The synthetic route is as follows.

We found that the with DMAP/Et_3N proceeded quickly and smoothly at room temperature under mild conditions and with a substantially increased yield and decrease in reaction time compared with the phase transfer catalytic method (Table 1).

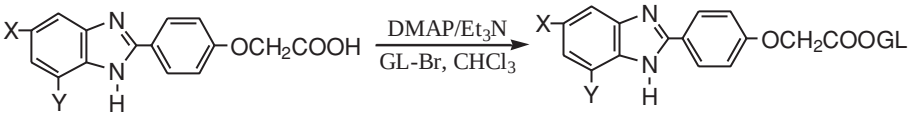
The activity of benzimidazolyl-phenoxyacetic acid saccharide esters are higher than those of benzimidazolyl-phenoxyacetic acids. The inhibiting percentages of benzimidazolyl-phenoxyacetic acid compounds against tobacco mosaic virus are 30% or so.[8] The inhibiting percentage against TMV was expressed by calculating the Withered spot number in the tobacco leaf, with a dosage of 0.001% and NS83 (its inhibiting percentage reachs to 80%) as control. The results are shown in Table 1.

As far as we know, this is the first example of benzimidazolyl-phenoxyacetic acid saccharide esters synthesised using the DMAP/Et_3N method. The mechanism of the reaction is shown in Scheme 2.

The molecular ions $(M+H)^+$ were obtained from fast atom bombarment of the saccharide ester. By the EI method, no molecular ion peaks were obtained with the exception of a fragment peak at 619, which corresponding to the *O*-acetyllactosyl fragment, another fragment peak at 331, which corresponding to a tetraacetyl-glucose fragment. We obtained some fragment peaks of benzimidazolyl-phenoxyacetic acid. The cracking of compound **4** is shown as follow.

Experimental

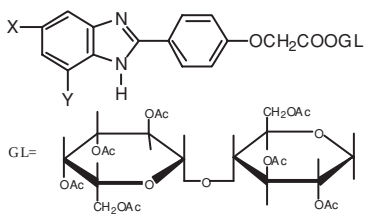
IR spectra were obtained using a Shimadzu IR-435 IR spectrometer. The elemental analyses were recorded on an Immunomedia MT-3 elemental analyzer. Mass spectra were recorded on an HP5988A



Compound **1**–**3** Compound **4**–**6**

Scheme 1

Table 1 Preparation of the compounds **4–6** and activity against TMV

Compounds **4–6**	Substituent		Product	Yield[a]/%	Yield[b]/%	(Reaction time/h)		Activity/%
	X	Y				Method a	Method b	
4	NO_2	H		52.7	27.5	3.5	6	48.5
5	CF_3	NO_2		55.8	28	2.5	5.5	53.2
6	H	H		53	23.9	3.6	6.5	45.6

Activity (%) is antiviral activity against tobacco mosaie virus. [a]Yield obtained using DMAP/Et_3N method. [b]Yield obtained using the phase transfer catalyst (Bu_4NBr) method.

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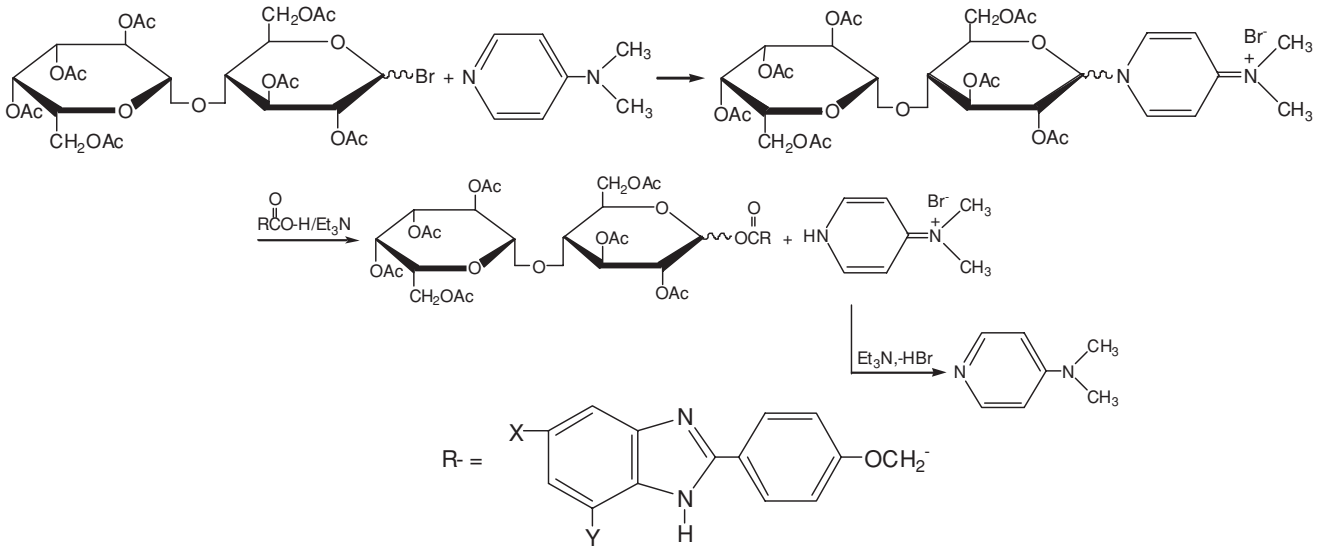


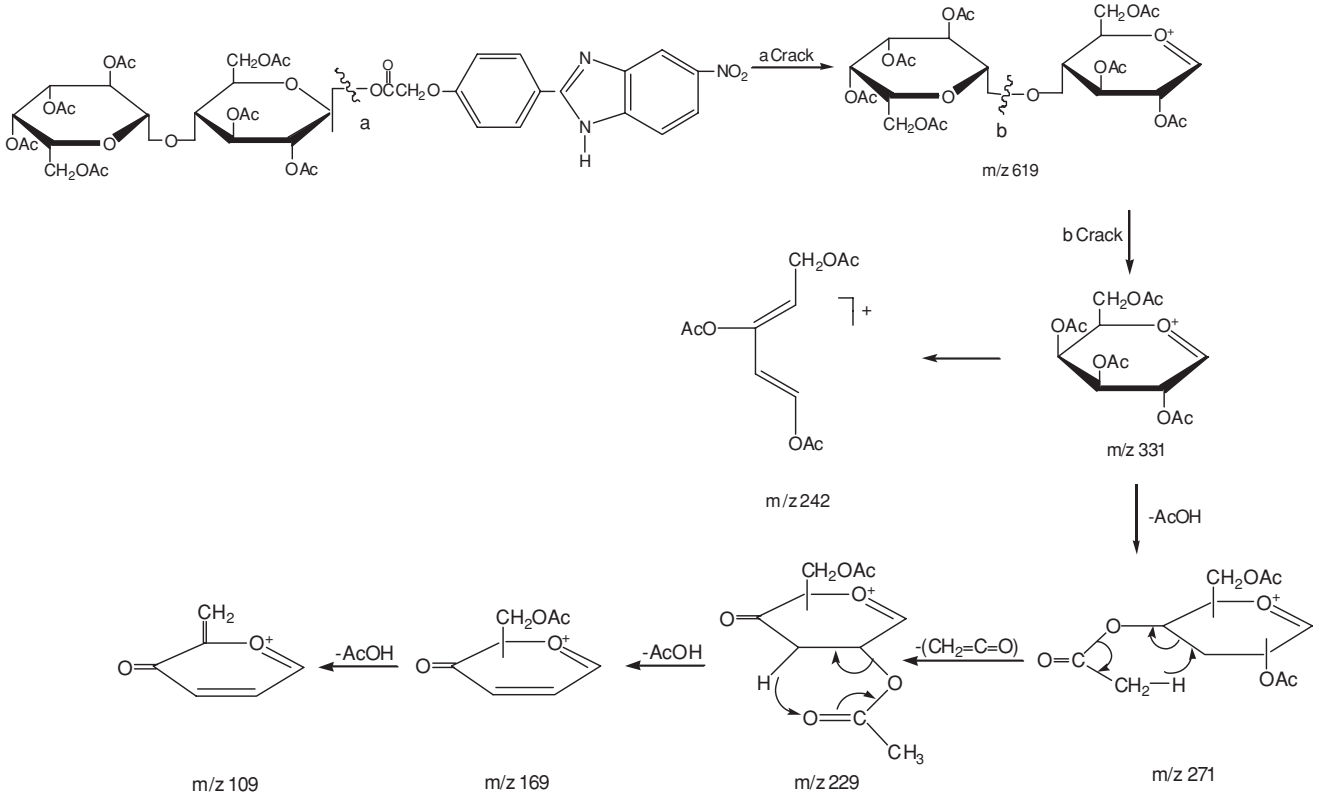
Scheme 2

GC-MS instrument. ^{1}H NMR spectra were recorded in acetone-d_6 on a Varian Mercury-VX300 (300MHz) NMR instrument, using TMS, as internal standard.

General procedure for the preparation of substituted benzimidazolylphenoxyacetic acid saccharide ester (compounds **4–6***)*: 5.25 mmol substituted 4-(benzimidazol-2-yl)phenoxyacetic acid, 5.25 mmol octa-*O*-acetyllactosyl bromide, 0.2g DMAP, $CHCl_3$ 30 ml were added into a four-necked, round-bottomed flask. The temperature was kept constant with a water bath, 2 ml triethylamine were slowly dropped into reaction system under stirring in 30 min at 0°C, then kept reaction at 25–30°C for 3.5h. As soon as the reaction finished, the solution was filtrated. After separation, the yellow dense liquid was obtained by the vaporisation of solvent under condition of vacuum distillation. Further hydrolysis of the product with ethyl acetate and separation through silica gel chromatography by using ethyl acetate as eluent), 4-[2-(5-nitrobenzimidazol-2-yl)]phenoxyacetic acid octa-*O*-acetyllactosyl saccharide ester (compound **4**) was obtained by the vaporisation of the solvent. The compounds **5** and **6** were prepared similarly.

4: Light brown dense liquid, major ^{1}H NMR data, δ_H 5.8–5.9 (d, *J*=7.4Hz 1H), 5.40–5.51 (d, *J*=9.60Hz 1H) (C_1–H_1 of pyranoid ring), 7.1–7.3 (d, 2H), 8.4–8.6 (m, 4H) (Ar–H), 4.8 (s, 2H, –OC(O)CH_2O–), 3.2 (s, 1H, N–H); ν/cm^{-1}: 2941 (N–H), 1740 (C=O), 1612 (C=N), 1500, 1360 (–NO_2), 1230, 1040 (C–O–C of benzene), 1210–1240, 1030–1170 (bi-shoulder peaks of pyranoid ring); Found: C, 52.76; H, 4.80; N, 4.48; Required for $C_{41}H_{45}N_3O_{22}$: C, 52.85; H, 4.83; N, 4.51%.

5: Yellow dense liquid, major ^{1}H NMR data, δ_H 5.8–5.9 (d, *J*=7.2Hz 1H), 5.4–5.5 (d, *J*=9.40Hz 1H) (C_1–H of pyranoid ring), 7.1–7.3 (d, 2H), 8.4–8.6 (m, 4H) (Ar–H), 4.7 (s, 2H, –OC(O)CH_2O–), 3.1 (s, 1H, N–H); ν/cm^{-1}: 2962 (N–H), 1751 (C=O), 1611 (C=C), 1531, 1371(–NO_2), 1330, 1130 (C–F), 1020–1058, 1210–1240 (bi-shoulder



Scheme 3

peaks of pyranoid ring); Found: C, 50.40; H, 4.37; N, 4.16; Required for $C_{42}H_{44}F_3N_3O_{22}$: C, 50.45; H,4.40; N,4.20%.

6: Light brown dense liquid; major ^{1}H NMR data δ_H 5.7–5.8 (d, *J*=7.5Hz 1H), 5.41–5.52 (d, *J*=9.72Hz 1H) (C_1–H of pyranoid ring), 7.1–7.3 (d, 2H), 8.3–8.6 (m, 4H) (Ar–H), 4.9 (s, 2H, –OC(O)CH_2O), 3.0 (s, 1H, N–H); ν/cm^{-1}: 2937 (N–H), 1730 (C=O), 1608 (C=C), 1634 (C=N), 1116–1153 (C–O–C of benzene), 1020–1050, 1215–1240 (bi-shoulder peaks of pyranoid ring); Found: C, 55.50; H, 5.15; N, 3.12; Required for $C_{41}H_{46}N_2O_{20}$: C, 55.53; H,5.19; N, 3.16%.

Compounds **4–6** have the β-configuration in the system of DMAP and Et_3N. Their structure is the same as obtained using a phase transfer catalytic method.

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