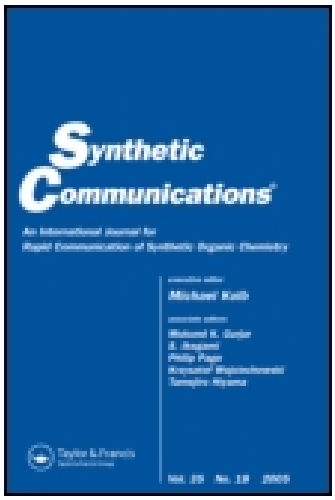

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AN IMPROVED PHASE TRANSFER CATALYZED SYNTHETIC METHOD FOR ONONIN AND ROTHINDIN

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AN IMPROVED PHASE TRANSFER CATALYZED SYNTHETIC METHOD FOR ONONIN AND ROTHINDIN

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ABSTRACT

An improved and mild glycosylation reaction was developed and used for the synthesis of ononin and rothindin, two naturally occurring isoflavone glycosides by a modified phase transfer catalyzed process.

Isoflavones are a class of compounds mainly occurring in species of the *leguminosae* family. Many isoflavones exist naturally as *O*-glycoside conjugates.[1] Isoflavonoid glycosides are common dietary phenolics which may be absorbed from the small intestine of humans,[2] and have been reported to exhibit antitumor, antioxidative, antifungal, and antihaemolytic activities.[1]

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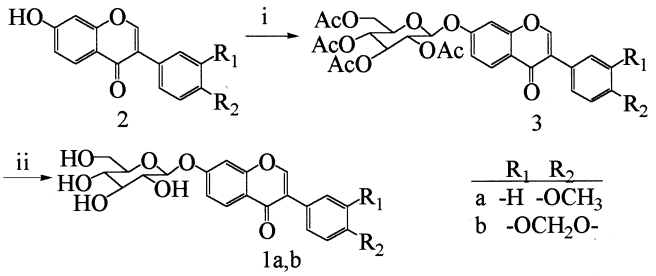
7-*O*-Glucoside isoflavones ononin (1a) and rothindin (1b) are natural products found in numerous sources.[3,4,5] Ononin (1a, 7-*O*-β-D-gluco-4′-methoxy-isoflavone) was first isolated from *G. Uralensis*,[3] which is a principal inhibitor of Epstein–Barr virus early antigen activation *in vitro*,[6] and possesses antibacterial activity and lowering blood sugar.[4] Rothindin (1b) was first isolated from *Rothia indica* Linn which is a copiously branched diffuse annual herb throughout the plains of Indian peninsula.[5]

Previous methods for the synthesis of isoflavone-*O*-glucosides are low-yielding, e.g. ononin (5–48%).[6] It was reported[6] Zemplén's 9% KOH solution 4 used for the base-catalyzed reaction of α-acetylbromoglucose with unprotected hydroxyisoflavones in acetone causes significant isoflavone C-ring cleavage (Waltz reported C-ring cleavage using 5% KOH solution[7]) and anomeric hydrolysis of the α-acetylbromoglucose, but no glycosylation. The low-yielding of previous methods for glycosylation of isoflavones may have two reasons: (1) the previous methods using the system of aqueous $NaOH/CH_2Cl_2^6$ or aqueous KOH/acetone[8] caused C-ring cleavage, deglycosylation and gave many by-products; (2) isoflavones hardly dissolved in the solvent systems.

Herein we introduce a facile and mild glycosylation reaction (as shown in Scheme 1) for the synthesis of ononin (1a) and rothindin (1b) by using anhydrous K_2CO_3 in a solvent mixture of DMF/acetone (3 : 2 v/v) and dodecyltrimethylammonium bromide (DTMAB) as a phase transfer catalyst. 7-*O*-β-D-Acetyl-glucoside isoflavones 3(a,b) were obtained by glycosylation of 2 with α-acetylbromoglucose in higher yields (85% for 3a and 80% for 3b).

We tried to deacetylate 3(a,b) by standard procedure using NaOMe-MeOH,[6] however, we found that the strong basic condition resulted



Reagents and conditions: i) α-acetylbromoglucose/DMF/acetone/K_2CO_3/DTMAB, reflux, 5h, 80–85%; ii) $Zn(OAc)_2$/MeOH, reflux, 7 h, 92–96%.

Scheme 1.

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in cleavage of the isoflavone's C-ring, while $ZnCl_2$/MeOH system led to significant deglycosylation. Finally, complete deacetylation was achieved by using anhydrous $Zn(OAc)_2$ in methanol in good yield.

EXPERIMENTAL

Melting points were measured on a XT_4-100_x apparatus and were uncorrected. IR spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrometer. ^{1}H-NMR and ^{13} C-NMR spectra were recorded on a Bruker AM-400 instrument, using tetramethylsilane as an internal standard, chemical shifts (δ) are measured in ppm and coupling constant *J* are reported in Hz. Multiplicity was simplified such as s = singlet, bs = broad singlet, d = doublet, t = triplet and m = multiplet. Mass spectra were determined with VG ZAB-HS spectrometer through EI or FAB method. All solvents were dried by standard procedures.

7-*O*-β-D-Acetylglucoside Isoflavones (3a)

In a 25 mL round-bottomed flask, anhydrous K_2CO_3 (2 g, 6.3 mmol) was added to the mixture of DMF (9 mL) and acetone (6 mL), then 2a (80 mg, 0.30 mmol), DTMAB (10 mg) and α-acetylbromoglucose (250 mg, 0.60 mmol) were added under stirring, the reaction mixture was refluxed for 5 h (monitored by TLC). Then acetone was removed under vacuum, water (20 mL) was added to the flask. The mixture was extracted with ethyl acetate (5 × 10 mL), the organic layer was washed by 20 mL water and brine, dried over anhydrous $MgSO_4$, then removed the solvent to give the residue which was purified by silica gel flash chromatography (ethyl acetate: petroleum ether 1 : 2 v/v) to give 3a 150 mg, yield: 85%, white solids, mp.191–193°C; IR: (KBr) cm^{-1} 2921, 2854, 1742, 1684, 1659, 1607, 1561, 1439, 1365, 1216, 1026; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 8.24 (1H, d, J = 9.0 Hz, H-5), 7.9 (1H, s, H-2), 7.50 (2H, dd, J = 8.7, 2,0 Hz, H-2′,6′), 7.23 (1H, d, J = 2.3 Hz, H-8), 7.01 (1H, dd, J = 9.0, 2.3 Hz, H-6), 6.98 (2H, dd, J = 8.7, 2.0 Hz, H-3′, 5′), 5.3 (1H, m, H-1″), 5.23 (1H, m, H-3″), 5.20 (1H, m, H-2″), 4.30 (1H, dd, J = 12.0, 2.0 Hz, H-6″a), 4.20 (1H, dd, J = 12.0, 2.0 Hz, H-6″b), 3.97 (1H, m, H-5″), 3.94 (1H, m, H-4″), 3.84 (3H, s, -OCH_3), 2.1 (12H, m, -$COCH_3$); EI-MS (*m*/*z*): 598 (M^+, 1), 330 (9.2), 295 (1.6), 268 (9.4), 266 (4.7), 252 (1.4), 238 (1.6), 228 (2.1), 168 (100), 145 (6.1), 127 (17.5), 109 (51.3).

Using the above procedure, 7-*O*-β-D-acetylglucoside isoflavones 3b was prepared in 80% yield as white solids, mp. 210–213°C; IR: (KBr) cm^{-1} 2955,

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2896, 1754, 1645, 1621, 1490, 1439, 1371, 1239, 1038, 909, 731; ^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 8.24 (1H, d, $J = 8$ Hz, H-5), 7.93 (1H, s, H-2), 7.09 (1H, d, $J = 1.0$ Hz, H-2′), 7.06 (1H, d, $J = 2.0$ Hz, H-6′), 7.03 (1H, d, $J = 6.0$ Hz, H-8), 6.97 (1H, dd, $J = 8.6$, 2.0 Hz, H-6), 6.87 (1H, $J = 8.0$ Hz, H-5′), 6.0 (2H, s, -OCH_2O-), 5.3 (1H, m, H-1″), 5.23 (1H, m, H-3″), 5.20 (1H, m, H-2″), 4.30 (1H, dd, $J = 12.0$, 2.0 Hz, H-6″a), 4.20 (1H, dd, $J = 12.0$, 2.0 Hz, H-6″b), 3.97 (1H, m, H-5″), 3.94 (1H, m, H-4″), 2.1 (12H, m, CH_3CO-); ^{13}C-NMR (100 MHz, $CDCl_3$): δ ppm 175.5 (C-4), 170.4, 170.1, 169.3, 169.2 (-CO-), 169.2 (C-7), 157.3 (C-8a), 152.4 (C-2), 147.8 (C-3′), 147.8 (C-4′), 28.2 (C-5), 125.3 (C-3), 125.3 (C-1′), 122.3 (C-6′), 120.2 (C-4a), 115.3 (C-6), 109.7 (C-2′), 108.4 (C-5′), 104.3 (C-8), 104.2 (C-1″), 101.2 (-OCH_2O-), 77.3 (C-5″), 76.8 (C-3″), 71.0 (C-2″), 68.2 (C-4″), 62.0 (C-6″), 20.6 (-CH_3); EI-MS (m/z): 612 (M^+, 3), 170 (9), 69 (100), 145 (11), 139 (9), 129 (21), 115 (3), 109 (71), 97 (8), 85 (5), 81 (7), 69 (4), 43 (87).

Ononin (1a)

In a 5 mL round-bottomed flask, 3a (65 mg, 0.109 mmol) was dissolved in methanol (2 mL), anhydrous zinc acetate (23 mg, 0.126 mmol) was added to the stirring solution. The mixture was refluxed for 7 h (monitored by TLC). After cooled down at RT the mixture was filtered by cation exchange resin, the solvent was evaporated under vacuum. The residue was purified by silica gel flash chromatography ($CHCl_3$: MeOH 12 : 1 v/v) to get the product 1a 45 mg, yield: 96%, white solids, mp. 203–205°C; IR: (KBr) cm^{-1} 3404, 2924, 2853, 1629, 1570, 1513, 1444, 1252, 1194, 1074, 1017, 819; ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.43 (1H, s. H-2), 8.06 (1H, d, $J = 9.0$ Hz, H-5), 7.53 (2H, dd, $J = 8.7$, 2.0 Hz, H-2′, 6′), 7.23 (1H, d, $J = 2.3$ Hz, H-8), 7.14 (1H, dd, $J = 9.0$, 2.3 Hz, H-6), 6.98 (2H, dd, $J = 8.7$, 2.0 Hz, H-3′, 5′), 5.41 (1H, d, 2″-OH), 5.10–5.13 (1H, m, 3″-OH), 5.06–5.09 (1H, m, 4″-OH), 5.06 (1H, d, $J = 5.2$ Hz, H-1″), 4.58–4.61 (1H, m, 6″-OH), 3.78 (3H, s, -OCH_3), 3.69–3.70 (1H, m, H-5″, 6″a), 3.43–3.48 (1H, m, H-6″b), 3.28–3.32 (1H, m, H-2″, 3″), 3.16–3.20 (1H, m, H-4″); ^{13}C-NMR (100 MHz, DMSO-d_6): δ ppm 174.6 (C-4), 161.4 (C-7), 159 (C-4′), 157.0 (C-8a), 153.5 (C-2), 130.0 (C-2′, 6′), 127.0 (C-5), 124.0 (C-3), 123.3 (C-1′), 118.4 (C-4a), 115.6 (C-6), 113.6 (C-3′, 5′), 103.4 (C-8), 100 (C-1″), 77.2 (C-5)″, 76.4 (C-3″), 73.1 (C-2″), 69.6 (C-4″), 60.6 (C-6″), 55.1 (-OCH_3); FAB-MS (m/z): 430 [M^+].

Using the above procedure, rothindin 1b was obtained in 92% yield as white solids, mp. 213–215°C; IR: (KBr) cm^{-1} 3430, 2926, 1623, 1501, 1439, 1248, 1074, 1014, 920, 810; ^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm 8.45 (1H, s, H-2), 8.05 (1H, d, $J = 9.0$ Hz, H-5), 7.24 (1H, d, $J = 2.0$ Hz, H-2′),

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7.14 (1H, dd, $J=8.1$, 2.0 Hz, H-6′), 7.07 (1H, dd, $J=9.0$, 2.0 Hz, H-6), 7.07 (1H, d, $J=2.0$ Hz, H-8), 6.97 (1H, d, $J=8.1$ Hz, H-5′), 6.04 (2H, s, -OCH_2O-), 5.44–5.46 (1H, m, 2″-OH), 5.15 (1H, d, $J=5.0$ Hz, H-1″), 5.14–5.16 (1H, m, 3″-OH), 5.07–5.11 (1H, m, 4″-OH), 4.60–4.63 (1H, m, 6″-OH), 3.70–3.73 (1H, m, H-6″b), 3.45–3.47 (2H, m, H-5″, 6″a), 3.30–3.32 (2H, m, H-2″, 3″), 3.17–3.25 (1H, m, H-4″); ^{13}C-NMR (100 MHz, DMSO-d_6): δ ppm 174.5 (C-4), 165.1 (C-7), 157.0 (C-8a), 154 (C-2), 147.0 (C-3′), 147.0 (C-4′), 127.0 (C-5), 126.9 (C-3), 125.5 (C-1′), 122.4 (C-6′), 118.4 (C-4a), 115.6 (C-6), 109.3 (C-2′), 108.1 (C-5′), 103.4 (C-8), 101.0 (C-1″), 100.0 (-OCH_2O-), 77.2 (C-5″), 76.5 (C-3″), 73.1 (C-2″), 69.6 (C-4″), 60.6 (C-6″); FAB-MS (m/z): 444[M^+].

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