



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

AN IMPROVED PHASE TRANSFER CATALYZED SYNTHETIC METHOD FOR ONONIN AND ROTHINDIN

Yaping Wang^a, Liangxi Li^a, Qinglian Wang^a & Yulin Li^b

^a National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu, 730000, P. R. China

^b National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu, 730000, P. R. China

Published online: 22 Aug 2006.

To cite this article: Yaping Wang, Liangxi Li, Qinglian Wang & Yulin Li (2001) AN IMPROVED PHASE TRANSFER CATALYZED SYNTHETIC METHOD FOR ONONIN AND ROTHINDIN, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 31:22, 3423-3427, DOI: [10.1081/SCC-100106200](https://doi.org/10.1081/SCC-100106200)

To link to this article: <http://dx.doi.org/10.1081/SCC-100106200>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

SYNTHETIC COMMUNICATIONS, 31(22), 3423–3427 (2001)

AN IMPROVED PHASE TRANSFER CATALYZED SYNTHETIC METHOD FOR ONONIN AND ROTHINDIN

Yaping Wang, Liangxi Li, Qinglian Wang,
and Yulin Li*

National Laboratory of Applied Organic
Chemistry and Institute of Organic Chemistry,
Lanzhou University, Lanzhou,
Gansu 730000, P. R. China

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 antihemolytic activities.¹

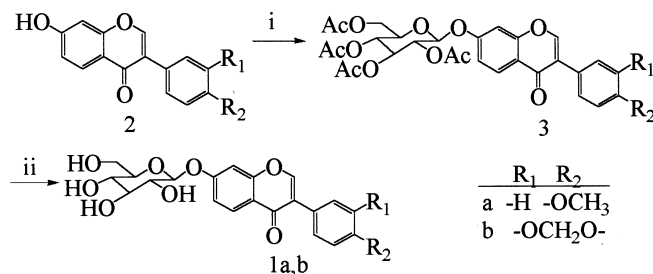
*Corresponding author.

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-glucopyranosyl-7'-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 reported⁶ Zemplen's 9% KOH solution⁴ 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 solution⁷) 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/CH₂Cl₂⁶ or aqueous KOH/acetone⁸ 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 K₂CO₃ 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/K₂CO₃/DTMAB, reflux, 5h, 80–85%; ii) Zn(OAc)₂/MeOH, reflux, 7 h, 92–96%.

Scheme 1.



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

EXPERIMENTAL

Melting points were measured on a $\text{XT}_4\text{-100}_x$ apparatus and were uncorrected. IR spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrometer. ^1H -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), DTMB (10 mg) and α -acetylglucose (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; ^1H -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, $-\text{OCH}_3$), 2.1 (12H, m, $-\text{COCH}_3$); 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,



2896, 1754, 1645, 1621, 1490, 1439, 1371, 1239, 1038, 909, 731; $^1\text{H-NMR}$ (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, $-\text{OCH}_2\text{O}-$), 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, $\text{CH}_3\text{CO}-$); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ ppm 175.5 (C-4), 170.4, 170.1, 169.3, 169.2 ($-\text{CO}-$), 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 ($-\text{OCH}_2\text{O}-$), 77.3 (C-5''), 76.8 (C-3''), 71.0 (C-2''), 68.2 (C-4''), 62.0 (C-6''), 20.6 ($-\text{CH}_3$); 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; $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$): 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, $-\text{OCH}_3$), 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''); $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO}-d_6$): 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 ($-\text{OCH}_3$); 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; $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$): 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'),



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, -OCH₂O-), 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''); ¹³C-NMR (100 MHz, DMSO-d₆): 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 (-OCH₂O-), 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⁺].

REFERENCES

1. Lewis, P.T.; Wähälä, K. Regiospecific 4'-O-β-Glucosidation of Isoflavones. *Tetrahedron Lett.* **1998**, *39*, 9559–9562.
2. Day, A.J.; Dupont, M.S.; Ridley, S.; Rhodes, M.; Rhodes, M.J.C.; Morgan, M.R.A.; Williamson, G. Deglycosylation of Flavonoid and Isoflavonoid Glycosides by Human Small Intestine and Liver-β-glucosidases. *FEBS Lett.* **1998**, *436*, 71–75.
3. Nakanishi, T.; Inada, A.; Kambayashi, K.; Yoneda, K. Flavonoid Glycosides of the Roots of Glycyrrhiza Uralensis (G. Uralensis). *Phytochemistry* **1985**, *24*, 339–341.
4. Jia, S.; Dong, Y.; Zheng, F.; Qiu, G. Isolation and Identification of Isoflavone Glycosides from the Roots of Zhongjian Jinjier (Caragana Intermedia). *Zhong Cao Yao* **1991**, *22*, 441–443. *Chem. Abstr.* *116*, 148213f.
5. Nair, A.G.R.; Subramanian, S.S. Rothindin – A New Isoflavone Glycoside from Rothia Indica Linn. *Indian J. Chem.* **1976**, *14B*, 801–802.
6. Lewis, P.; Haltia, S.; Wähälä, K. The Phase Transfer Catalysed Synthesis of Isoflavone-O-glucosides. *J. Chem. Soc. Perkin Trans. 1* **1998**, *26*, 2481–2484.
7. Walz, E. Isoflavone and Saponin Glucosides in Soja Hispida. *Liebigs Ann. Chem.* **1931**, *489*, 118.
8. Zemplén, G.; Farkas, L.; Bien, A. Synthese des Ononins. *Chem. Ber.* **1944**, *77*, 452–457.

Received in Japan October 6, 2000



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081SCC100106200>