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Facile Synthesis of Flavonoid 7-*O*-Glycosides

Ming Li,[†] Xiuwen Han,[†] and Biao Yu*[,‡]

State Key Laboratory of Catalyst, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China, and State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

byu@mail.sioc.ac.cn

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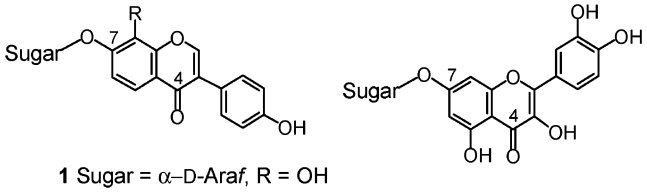
Abstract: Highly regioselective removal of the 7-*O*-acyl groups of the peracylated flavones, isoflavones, and flavonols (PhSH, imidazole, NMP) followed by effective glycosylation with glycosyl trifluoroacetimidates (BF_3·Et_2O) and cautious deprotection of the acyl groups under basic conditions afforded the desired 7-*O*-flavonoid glycosides in satisfactory yields.

The flavonoids are a very large and important group of polyphenolic natural products, which are united by their derivation from the aromatic heterocycle, flavone, namely, 2-phenyl-4*H*-1-benzopyran-4-one.[1,2] Conjugation with sugars is a common form for the natural occurrence of flavonoids. Flavonoid glycosides, as well as their aglycones, play a variety of essential roles in the growth and development of plants. Besides their contribution to attract pollination (via the plant color) and protect against UV-B radiation and microbial and animal feeding, these molecules transfer signals between species such as in the infection of legume roots by *Rhizobium* bacteria and in the feeding of silkworms on mulberry leaves. Flavonoids and flavonoid glycosides are also important to human health, not only because those in fruits and vegetables make up the human diet but also because a number of those molecules have exhibited significant biological activities such as antitumor, antimicrobial, and radical-scavenging properties. Flavonoid *O*-glycosides often bear the sugar moiety at the 7-hydroxy position.[1,2] Notably, among the over 500 flavone *O*-glycosides and over 100 isoflavone *O*-glycosides so far recorded, the majority are 7-*O*-glycosides.[2] Among the over l000 flavonol glycosides recorded, some 40% contain a 7-*O*-glycosidic linkage.[2] Compounds **1**−**3** are selected as examples. 4′,8-Dihydroxyisoflavone 7-*O*-α-D-arabinofuranoside (A-76202, **1**) is isolated from *Rhodococcus* sp. SANK 61694, which demonstrates a very strong inhibition (IC_{50} at the ng/mL level) against α-glucosidases I and II occurring in endoplasmic reticulum and participating in the processing of secretory-, cell membrane-, and virus surface-glycoproteins.[3] Daidzein 7-*O*-β-D-glucopyranoside (daidzin, **2**) is a characteristic isoflavone in the Leguminosae plants possessing a range of bioactivities, such as a potent selective inhibition against hamster liver mitochondria aldehyde dehydrogenase (IC_{50} = 0.04 μM).[4] Daidzin **2** has been added to commercial formulations to act as a radical scavenger, dermal angiogenesis inhibitor, and antiproliferic agent against melanomas.[5] Quercetin 7-*O*-β-D-glucopyranoside (Quercimeritrin, **3**) shows inhibitory effects on IL-5 (IC_{50} = 27.3 μM),[6] cAMP PDE (IC_{50} = 13.9 × 10^{-5} M),[7] and rat aldose reductase (44.4% at 10^{-5} M).[8] In contrast to the wide occurrence and importance of flavonoid *O*-glycosides, synthetic studies toward those molecules are only sporadic and mostly rely on conventional transformations.[9] Here we report an efficient procedure for the synthesis of flavonoid 7-*O*-glycosides, including compounds **1**−**3**.



1 Sugar = α–D-Ara*f*, R = OH
2 Sugar = β–D-Glu*p*, R = H
3 Sugar = β–D-Glu*p*

The 7-hydroxyl group on the polyphenolic flavonoids, which is para to the electron-withdrawing pyrone carbonyl function, possesses the highest acidity in the molecule and therefore generates most easily the corresponding phenolate.[9e] Taking advantage of this fact, conventional methods distinguished the 7-OH by a preferential nucleophilic substitution-upon-deprotection of the flavonoid acetates.[9c−f] Recently, Needs et al.[10] and

* Fax: (86)21-64166128.
[†] Dalian Institute of Chemical Physics.
[‡] Shanghai Institute of Organic Chemistry.

(1) (a) Harborne, J. B. *The Flavonoids: Advances in Research since 1986*; Chapman and Hall: London, 1994. (b) Harborne, J. B. *The Flavonoids: Advances in Research since 1980*; Chapman and Hall: London, 1988. (c) Harborne, J. B.; Mabry, T. J. *The Flavonoids: Advances in Research*; Chapman and Hall: London, 1982. (d) Harborne, J. B.; Mabry, T. J.; Mabry, H. *The Flavonoids*; Chapman and Hall: London, 1975.

(2) Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*: John Wiley & Son: Chichester, UK, 1999; Vols. 1 and 2.

(3) (a) Shiozaki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1477. (b) Watanabe, Y.; Shiozaki, M.; Kamegai, R. *Carbohydr. Res.* **2001**, *335*, 283.

(4) Rooke, N.; Li, D.-J.; Li, J.; Keung, W.-M. *J. Med. Chem.* **2000**, *43*, 4169.

(5) (a) Ichimaru Farukosu, K. K. Japanese Patent 58 225 004/1983; *Chem. Abstr.* **1984**, *100*, 126730. (b) Brunke, R. A. GP 443 2947/1996; *Chem. Abstr.* **1996**, *124*, 2411803.

(6) Park, K. Y.; Lee, S.-H.; Min, B.-K.; Lee, K.-S.; Choi, J.-S.; Chung, S. R.; Min, K. R.; Kim, Y. *Planta Med.* **1999**, *65*, 457.

(7) Sakamoto, Y.; Ohmoto, T.; Nikaido, T.; Koike, K.; Tomimori, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2450.

(8) Shimizu, M.; Ito, T.; Terrashima, S.; Hayashi, T.; Arisawa, M.; Morita, N.; Kurokawa, S.; Ito, K.; Hashimoto, Y. *Phytochemistry* **1984**, *23*, 1885.

(9) (a) Farkas, L.; Mezey-Vándor, G.; Nógrádi, M. *Chem. Ber.* **1969**, *102*, 2583. (b) Farkas, L.; Vermes, B.; Nógrádi, M. *Chem. Ber.* **1972**, *105*, 3505. (c) Farkas, L.; Mezey-Vándor, G.; Nógrádi, M. *Chem. Ber.* **1974**, *107*, 1518. (d) Farkas, L.; Mezey-Vándor, G.; Nógrádi, M. *Chem. Ber.* **1974**, *107*, 3878. (e) Mezey-Vándor, G.; Farkas, L.; Nógrádi, M. In *Flavonoids and Bioflavonoids Current Research Trends*; Farkas, L., Gábor, M., Kállay, F., Eds.: Elsevier: Amsterdam, 1977; pp 187−192. (f) Mezey-Vándor, G.; Farkas, L.; Kanzel, I.; Nógrádi, M. *Chem Ber.* **1980**, *113*, 1945. (g) Demetzos, C.; Skaltsounis, A. L.; Tillequin, F.; Koch, M. *Carbohydr. Res.* **1990**, *207*, 131. (h) Alluis, B.; Dangles, O. *Helv. Chim. Acta* **1999**, *82*, 2201. (i) Alluis, B.; Dangles, O. *Helv. Chim. Acta* **2001**, *84*, 1133. (j) Kondo, T.; Oyama, K.-I.; Yoshida, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 894.

(10) Needs, P. W.; Williamson, G. *Carbohydr. Res.* **2001**, *330*, 511.

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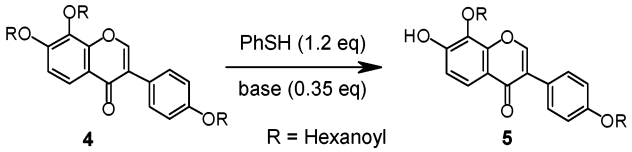
TABLE 1. Regioselective Deprotection of the 7-*O*-Hexanoyl Group of Isoflavone 4

entry	base	solvent	*T* (°C)	time (h)	yield[a] (%, **5**)	recovery yield[a] (%, **4**)
1	DBU	NMP	0	2.5	52	no
2	K_2CO_3	NMP	0	6	67	no
3	2,6-lutidine	NMP	25	24	35	57
4	imidazole	NMP	0	4.5	90	no
5	imidazole	NMP	25	2	87	no
6	imidazole	NMP	−25	5	63	30
7[b]	imidazole	NMP	25	5	87	no
8	imidazole	THF	25	24	68	12
9	imidazole	CH_2Cl_2	25	24	43	19

[a] Isolated yields. [b] Used 0.18 equiv of imidazole.

SCHEME 1



Kim et al.[11] were able to selectively hydrolyze the 7-*O*-acetate in the presence of the 4′-*O*- or 5-*O*-acetate of daidzein and chrysin (substrates **8b** and **6b**), respectively. These results encouraged us to explore a general procedure for selective release of the 7-OH on the peracylated flavonoids. More recently, Chakraborti et al. demonstrated that aromatic thiols in the presence of K_2CO_3 in dipolar aprotic solvents constituted an efficient protocol for the selective cleavage of aryl esters over alkyl esters.[12] Furthermore, we found that using DBU as a base was more efficient for the selective deprotection of an aryl ester in the presence of an alkyl ester.[13] Therefore, we envisioned the combination of an aromatic thiol and a base with suitable basicity a choice for selective removal of the most electrophilic 7-*O*-acyl group on the peracylated flavoinoids. Isoflavone trihexanoate **4** was selected as a substrate for screening the conditions for selective deprotection of 7-*O*-hexanoate over the neighboring 8-*O*- as well as the 4′-*O*-hexanoate on the B ring (Scheme 1). Some results are listed in Table 1.

The choice of base was crucial for the regioselective deprotection of isoflavone **4**. Employing PhSH (1.2 equiv) as the thiol and NMP (*N*-methyl pyrolidinone) as the solvent at 0 °C, the presence of DBU (0.35 equiv) or K_2CO_3 (0.35 equiv) produced the desired 7-OH product **5** in 52 and 67% isolated yields, respectively, after the disappearance of the starting **4**. The over-deprotected diols were detected as byproducts (entries 1 and 2). When 2,6-lutidine was used as a base (0.35 equiv), the reaction hardly took place at 0 °C. Upon raising the temperature to 25 °C, the reaction proceeded, albeit sluggishly, producing **5** in 35% yield with 57% of **4** being recovered after 24 h (entry 3). Imidazole was found to be ideal for the present purpose and (0.35 equiv) prompted the reaction to be complete within 4.5 h, generating the desired **5** in an excellent 90% yield (entry 4). Phenylthiohexanoate was isolated in a comparable yield, which supports the transesterification mechanism.[12b] Therefore, the effect of bases in this reaction is well correlated to their basicity: 2,6-lutidine ($pK_a = 6.7$)[14] < imidazole ($pK_a = 7.1$)[14] < DBU ($pK_a = 24.13$[15] or 23.9[16]), which determines the effectiveness for the initial generation of PhS^- for transesterification. Expectedly, temperature, solvent, and the amount of imidazole had remarkable effects on the selective deprotection reaction using the combination of PhSH and imidazole (entries 5−9). Thus, the reaction at 25 °C finished within 2 h, generating **5** in 87% yield, while at −25 °C, the reaction proceeded very slowly (cf. entries 4−6). The reactions in THF or CH_2Cl_2 solvent were very sluggish (entries 8−9). Reducing the amount of the imidazole by one-half (from 0.35 to 0.18 equiv) more than doubled the time required to bring the reaction to completion (cf. entries 5 and 7).

To investigate the scope and limitation of the present protocol for selective 7-*O*-deprotection of flavonoid esters, chrysin (flavone) esters (**6a**−**c**), daidzein (isoflavone) esters (**8a**,**b**), quercetin (flavonol) esters (**10a**,**b**), peracylated isoflavone glycoside **12**, and chromone hexanoate **14** were subjected to the above optimized conditions (1.2 equiv of PhSH, 0.35 equiv of imidazole, NMP, rt). The reactions were monitored by TLC and stopped after the disappearance of the starting flavonoid esters (Figure 1). Chrysin esters (**6a**−**c**) and daidzein esters (**8a**,**b**), which bear only two acyloxy groups, gave the corresponding 7-OH products (**7a**−**c** and **9a**,**b**) in excellent yields (90−96%). Acetate and benzoate, in addition to hexanoate, were well deprotected regioselectively, albeit requiring different reaction times (Bz > hexanoyl ≥ Ac) to bring the reaction to completion. Remarkably, the 7-*O*-acyl group, from the other four, on quercetin esters (**10a**,**b**) was well distinguished by the present transesterification conditions, affording the 7-*O*-monodeprotected **11a**,**b** in satisfactory yields (81 and 84%, respectively), while an inseparable mixture containing two diols, as shown by ^{1}H NMR, was isolated in about 10% yield. For isoflavone glycoside **12**, the 7-*O*-hexanoate was selectively cleaved over the neighboring 8-*O*-hexanoate as well as the three *O*-benzoate on the sugar moiety, providing **13** in 80% yield. Thus, further modifications on the 7-OH of this isoflavonoid glycoside become straightforward such as methylation and sulfonation that are common ways of

(11) Shin, J.-S.; Kim, K.-S.; Kim, M.-B.; Jeong, J.-H.; Kim, B.-K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 869.
(12) (a) Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem.* **1999**, *64*, 8027. (b) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 2541.
(13) Li, M.; Han, X.-W.; Yu, B. *Tetrahedron Lett.* **2002**, *43*, 9467.
(14) Reich, H. J.; Rigby, J. H. *Handbook of Reagents for Organic Synthesis: Acidic and Basic Reagents*; John Wiley & Son: Chichester, UK, 1999.
(15) Kaljurand, I.; Rodima, T.; Leito, I.; Koppel, I. A.; Schwesinger, R. *J. Org. Chem.* **2000**, *66*, 6202.
(16) Leffek, K.; Przuszynski, P.; Thanapaalasingham, K. *Can. J. Chem.* **1989**, *67*, 590.

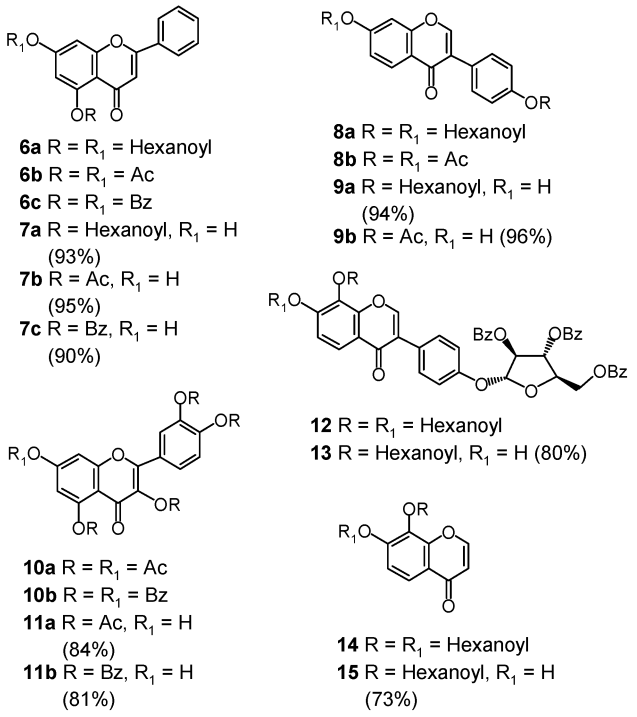
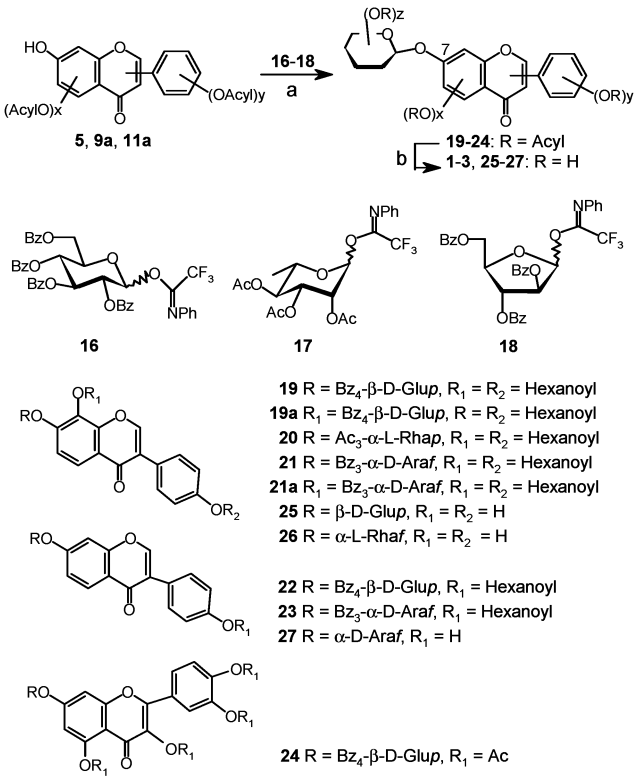


FIGURE 1. Regioselective deprotection of the 7-*O*-acyl Groups of flavonoids. Enclosed in the parentheses are isolated yields for the corresponding 7-*O*-deprotection products. Reagents and conditions: PhSH (1.2 equiv), imidazole (0.35 equiv), NMP, rt.

natural decoration of flavonoids.[2] Finally, subjection of chromone hexanoates **14**, which bear only two hexanoates but *are in fact not flavonoids*, to the above standardized conditions afforded the 7-*O*-monodeprotected **15** in a lower yield of 73%. These results demonstrate that the present protocol is ideal for the regioselective deprotection of the 7-*O*-acyl groups of the peracylated flavones, isoflavones, and flavonols, which possess the conjugated ABC ring system.

With this efficient method in hand to regioselectively free the 7-OH of flavonoid esters, we set out to effect the 7-*O*-glycosidic coupling. Compared to aliphatic hydroxyls, phenolic hydroxyls are weaker nucleophiles and thus usually require activation, in the presence of a hindered organic base[17] or via the formation of a stannyl ether[18] or a butyl ether,[19] to effect the coupling with glycosyl donors under the promotion of Lewis acids. Joyfully, we disclosed that our newly developed glycosyl trifluoroacetimidates,[20] under the promotion of $BF_3{\cdot}Et_2O$ (0.3 equiv), served as effective donors for the glycosylation of the 7-OH of flavonoid esters. The results for the coupling reactions between flavonoid derivatives (**5**, **9a**, and **11a**) and glycosyl trifluoroacetimidates (**16**−**18**) are depicted in Scheme 2 and Table 2.

SCHEME 2. Synthesis of Flavonoid 7-*O*-Glycosides[a]



[a] Reagents and conditions: (a) **16**−**18** (2.5 equiv), $BF_3{\cdot}OEt_2$ (0.3 equiv), 4Å MS, CH_2Cl_2, rt, overnight. (b) K_2CO_3, MeOH-THF (1:1), 40°C; or NaOMe, MeOH− $CHCl_3$, 6°C.

TABLE 2. Synthesis of Flavonoid 7-*O*-Glycosides

entry	acceptor	donor	glycosidation product (yield)[a]	deprotection product (yield)[a,b]
1	**5**	**16**	**19** (64%)[c]	**25** (100%)
2	**5**	**17**	**20** (72%)	**26** (100%)
3	**5**	**18**	**21** (64%)[c]	**1** (64%)
4[d]	**9a**	**16**	**22** (90%)	**2** (100%)
5[d]	**9a**	**18**	**23** (75%)	**27** (68%)
6	**11a**	**16**	**24** (82%)	**3** (50%)

[a] Isolated yields. [b] Compounds **25**−**27** are artificial flavonoid glycosides. [c] Compounds **19a** and **21a** were isolated in ∼15% yields. [d] Reaction was carried out in the absence of 4 Å MS.

Glycosylation of 4′,8-dihexanoxy-7-hydroxy isoflavone **5** with perbenzoylated D-glucopyranosyl-, peracetylated L-rhamnopyranosyl-, and perbenzoylated D-arabinofuranosyl-(*N*-phenyl)trifluoroacetimidate (**16**−**18**, 2.5 equiv) provided the corresponding coupling products (**19**−**21**) in 64−72% yields (Table 2, entries 1−3). An unexpected 8→7 acyl migration took place during the glycosylation, as evidenced by the isolation of the 8-*O*-glycosides **19a** and **21a** (∼15% yield). Acyl migration from a hydroxyl of stronger acidity to a hydroxyl of weaker acidity under basic conditions is known.[21] However, a reverse migration

(17) (a) Yamaguchi, M.; Horiguchi, A.; Fukuda, A.; Minami, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1079. (b) Oyama, K.-I.; Kondo, T. *Synlett* **1999**, 1627. (c) Lee, Y. S.; Rho, E. S.; Min, Y. K.; Kim, B. T.; Kim, K. H. *J. Carbohydr. Chem.* **2001**, *20*, 503.

(18) Clerici, F.; Gelmi, M. L.; Mottadelli, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 985.

(19) (a) Jensen, K. J.; Meldal, M.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2119. (b) Vargas-Berenguel, A.; Meldal, M.; Paulsen, H.; Jensen, K. J.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3287.

(20) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099.

(21) (a) Jurd, L.; Rolle, L. A. *J. Am. Chem. Soc.* **1958**, *80*, 5527. (b) Simpson, T. H.; Wright, R. S. *J. Org. Chem.* **1961**, *26*, 4686. (c) Vermes, B.; Farkas, L.; Nógrádi, M. In *Topics in Flavonoid Chemistry and Biochemistry*; Farkas, L., Gábor, M., Kállay, F., Eds.: Akademiai: Budapest; Elsevier: Amsterdam, 1975; pp 162−170. (d) Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2176.

under acidic conditions on flavonoids has not been reported. The coupling of 4′-hexanoxy-7-hydroxy isoflavone **9a** with trifluoroacetimidates **16** and **18** hardly proceeded under similar conditions for the coupling of **5**; however, the reaction took place readily in the absence of the 4 Å molecular sieves (entries 4−5), giving the desired products (**22** and **23**) in good to excellent yields. Coupling of the quercetin derivative **11a** with **18** met with no problem, affording **24** in 82% yield. All the glycosidic linkages generated were confirmed by ^{1}H NMR analysis to be 1,2-trans configurations due to the neighboring participation of the donors in the glycosylation.

Final removal of the acyl groups to elaborate the flavonoid glycosides was effected under the action of K_2CO_3 in MeOH−THF (1:1) (Table 2). For isoflavone glycosides, especially the furanosides (i.e., **21** and **23**), the basic conditions were found to cause the partial cleavage of the sugar moieties, leading to the lower yields of **1** and **27** (Table 2, entries 3 and 5). Caution was especially taken in treating flavanol derivatives with a free 3-OH (i.e., **24**→**3**); an inert atmosphere was found to be essential to prevent the plausible oxygenation of the resulting flavonol glycosides under basic conditions.[22]

In summary, the combination of PhSH and imidazole in NMP was found to be ideal for the highly regioselective deprotection of the 7-*O*-acyl groups of the peracylated flavones, isoflavones, and flavonols. Glycosylation of the resulting 7-OH of the flavonoid derivatives with glycosyl trifluoroacetimidates gave satisfactory yields of the coupling products under the promotion of $BF_3{\cdot}Et_2O$. Cautious removal of the acyl protecting groups under basic conditions afforded the desired 7-*O*-flavonoid glycosides.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and references for all known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Rajananda, V.; Brown, S. B. *Tetrahedron Lett.* **1981**, *22*, 4331. (b) Balogh-Hergovich, É.; Speier, G. *J. Org. Chem.* **2001**, *66*, 7974.