Facile Deoxygenation of Hydroxylated Flavonoids by Palladium-Catalysed Reduction of its Triflate Derivatives

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Dedicated to Professor András Lipták on the occasion of his 70th birthday

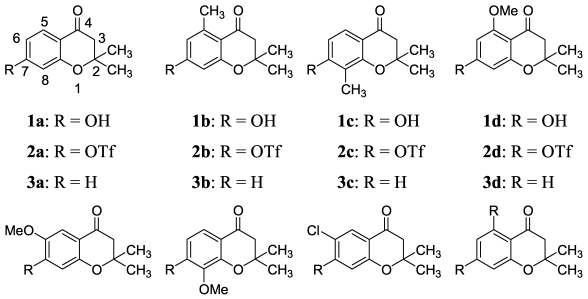
An efficient procedure to deoxygenate hydroxy substituted flavonoids, isoflavonoids and related compounds *via* their trifluoromethanesulfonates is presented. Their reduction with formic acid in the presence of a catalytic amount of palladium acetate, triethylamine and 1,3-bis(diphenylphosphanyl)propane (dppp) in DMF results in their *des*-hydroxy derivatives without affecting other functional groups.

Key words: Flavonoids, Reduction, Palladium(II) Acetate

Flavonoids and isoflavonoids possessing a 2- and 3-aryl substituted 1-benzopyran skeleton with various levels of saturation and oxidation, respectively, belong to the class of naturally occuring *O*-heterocyclic compounds [1] with wide range of biological importance due to their significant antioxidant [2], hepatoprotective [3], antifungal [4], antibacterical [5] and antiviral [6] activities.

Although, there are numerous independent methods available for the preparation of these natural products and the procedures of synthetic importance have been reviewed extensively [1, 7, 8], these conditions are mostly suitable for direct synthesis of their 7-hydroxy- or 5,7-dihydroxy derivatives and hence synthetic accessibility of their *des*-7-hydroxy derivatives is strongly limited. To overcome this problem several methods such as catalytic hydrogenation of *O*-aryl-N,N-dialkylisoureas by Pd/C [9], desulfurization of S-aryl-N,N-dialkyl thiocarbamates (prepared by Newman-Kwart rearrangement of *O*-aryl-N,N-dialkyl thiocarbamates) by Raney nickel [10] and reduction of *O*-aryl (or methyl)-*p*-toluenesulfonates by $NaBH_4$–$NiCl_2$ [11] or Raney nickel [12] have been recently introduced by Patonay *et al.* [13] in this field using 2,2-dimethyl-7-hydroxychromanone (**1a**) as the substrate.

Efficient procedures for the deoxygenation of simple phenols have been reported *via* their trifluoromethanesulfonates (triflates) by hydrogenolysis under heterogeneous conditions (Pd/C) [14] and Ni(0)- [15] or Pd(0)-catalyzed [16, 17] reduction under homogeneous conditions. As a continuation of our research program aiming at the application of Pd(0)-catalyzed transformation for the synthesis of *O*-heterocyclic compounds [18 – 20], it seemed promising to study also the deoxygenation of hydroxybenzopyranoid triflates by Pd(0)-catalyzed reduction.



1a: R = OH **1b**: R = OH **1c**: R = OH **1d**: R = OH
2a: R = OTf **2b**: R = OTf **2c**: R = OTf **2d**: R = OTf
3a: R = H **3b**: R = H **3c**: R = H **3d**: R = H

1e: R = OH **1f**: R = OH **1g**: R = OH **1h**: R = OH
2e: R = OTf **2f**: R = OTf **2g**: R = OTf **2h**: R = OTf
3e: R = H **3f**: R = H **3g**: R = H **3h**: R = H

Scheme 1.

In order to compare our results with those published by Patonay *et al.* [13], 2,2-dimethyl-7-hydroxychromanone (**1a**) and its derivatives **1b – h** were chosen as model compounds (Scheme 1) whose corresponding triflates **2a – h** were prepared in high yields (85 – 94%) by treatment with trifluoromethanesulfonic anhydride in the presence of triethylamine in dichloromethane at −15 °C. When the reaction of 2,2-dimethyl-chromanon-7-yl triflate (**2a**) with 1 equiv-

Table 1. Compounds **3a – h** prepared.

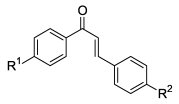
Sub-strate	Product	Time [min]	Yield[a] [%]	M. p. [°C]	Lit. m. p. [°C]	Lit. yield[b] [%]
2a	**3a**	50	93	88.5 – 89	89 – 90 [13]	80
2b	**3b**	25	90	68 – 69	96.5 [21]	82
2c	**3c**	30	91	oil	oil [22]	80
2d	**3d**	70	95	124 – 125	118 – 119 [23]	83
2e	**3e**	30	92	75 – 76	71 – 72 [23]	80
2f	**3f**	20	91	132 – 133	126 – 127 [23]	78
2g	**3g**	15	70.4	oil	oil [24]	41
2h	**3h**	30	75	88 – 89	89 – 90 [13]	70

[a] Isolated yields; [b] ref. [13].

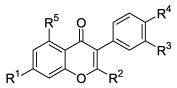
Table 2. Compounds **4c – 11c** prepared.

Sub-strate	Product	Time [min]	Yield[a] [%]	M. p. [°C]	Lit. m. p. [°C]
4b	**4c**	60	83	57 – 58	60 – 62 [25]
5b	**5c**	90	83	56 – 57	60 – 62 [25]
6b	**6c**	60	85	96 – 97	97 [26]
7b	**7c**	30	90	134 – 135	133 – 134 [27]
8b	**8c**	60	93	108 – 109	86 – 87 [28]
9b	**9c**	60	90	150 – 151	154 – 156 [29]
10b	**10c**	30	94	75 – 76	75 – 78 [30]
11b	**11c**	90	79	66 – 67	64 – 65 [31]

[a] Isolated yields.

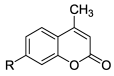


4a: R^1 = OH, R^2 = H **5a**: R^1 = H, R^2 = OH **6a**: R = OH
4b: R^1 = OTf, R^2 = H **5b**: R^1 = H, R^2 = OTf **6b**: R = OTf
4c: R^1 = R^2 = H **6c**: R = H

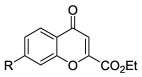


7a: R^1 = OH, R^2 = R^3 = R^4 = R^5 = H **8a**: R^1 = OH, R^2 = Me, R^3 = R^4 = H, R^5 = OH
7b: R^1 = OTf, R^2 = R^3 = R^4 = R^5 = H **8b**: R^1 = OTf, R^2 = Me, R^3 = R^4 = H, R^5 = OH
7c: R^1 = R^2 = R^3 = R^4 = R^5 = H **8c**: R^1 = R^3 = R^4 = H, R^2 = Me, R^5 = OH

9a: R^1 = OH, R^2 = H, R^3 + R^4 = -OCH_2O-, R^5 = H
9b: R^1 = OTf, R^2 = H, R^3 + R^4 = -OCH_2O-, R^5 = H
9c: R^1 = R^2 = H, R^3 = R^4 = -OCH_2O-, R^5 = H



10a: R = OH
10b: R = OTf
10c: R = H



11a: R = OH
11b: R = OTf
11c: R = H

Scheme 2.

alent of formic acid as a reducing agent was conducted in *N*,*N*-dimethyl formamide (DMF) at 60 °C in the presence of palladium(II) acetate (2.2 mol-%) and triphenylphosphane (PPh_3) (4.2 mol-%) according to the method described by Cacchi *et al.* [17], quantitative formation of 2,2-dimethylchromanone (**1c**) was observed within 15 minutes. As shown in Table 1, the other related derivatives **2b – g** reacted readily to afford the corresponding reduction products **3b – g**, respectively, in excellent yields (70 – 95%). Ditriflate **2h** required the use of twice the amounts of the reagents to convert efficiently into **3a**. It is noteworthy that chloro and carbonyl groups are completely unaffected under these conditions and the yields have been found to be comparable with those published by Patonay *et al.* [13] but our procedure is significantly milder and simpler. Moreover, it has been also recognized that triflates **2a** and **2g** were less reactive towards the catalytic system using PPh_3 instead of dppp. In both cases, hydrolysis of triflates **2a, g** to **1a, g**, respectively, could also be observed besides their deoxygenation (**2a** → **3a**, **2g** → **3g**). In order to determine the scope and limitation of this deoxygenation procedure the transformation of the chalcones **4b** and **5b**, the flavone **6b**, the isoflavones **7b – 9b**, the coumarin **10b** and chromone derivatives **11b** was also studied (Scheme 2). The reduction of these compounds took place very smoothly to give the desired deoxygenated derivatives **4c – 11c**, respectively, in good yields (79 – 94%) and no byproducts could be detected (TLC) in any cases (Table 2).

In conclusion, these results have clearly indicated that the palladium(II) acetate/1,3-bis(diphenylphosphanyl)propane (dppp)/formic acid/triethylamine system in DMF is an efficient agent for deoxygenation of hydroxysubstituted flavonoids, isoflavonoids and related compounds *via* their trifluoromethanesulfonates.

Experimental Section

Melting points were determined on a Büchi 535 apparatus and are not corrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 NMR spectrometer in $CDCl_3$ with TMS as internal standard. EI-MS (70 eV) spectra were obtained with a VG TRIO-2 instrument. TLC was performed on Merck Kieselgel 60 F_{254} pre-coated aluminium plates. Elemental analyses (C, H) were conducted using Carlo Erba 1106 EA instrument. 7-Hydroxyflavone (**6a**) was purchased from Sigma-Aldrich. The preparation of the following derivatives was described earlier: **1a** [22], **1b** [32], **1c** [22], **1d** [13], **1e** [33], **1f** [13], **1g** [34], **1h** [35], **4a**, **5a** [36], **7a**, **8a**, **9a** [37], **10a** [38], **11a** [39].

*Aryl triflates. General procedure: 2,2-Dimethyl-7-(trifluoromethylsulfonyloxy)chromanone (***2a***)*

To a solution of 7-hydroxy-2,2-dimethylchromanone [22] (2.40 g, 12.50 mmol) in 20 ml of dichloromethane and

3 ml of triethylamine at −15 °C was slowly added trifluoromethanesulfonic anhydride (2.15 ml, 3.70 g, 13.10 mmol). The mixture was stirred at this temperature for 5 minutes and then was allowed to warm to 23 °C and stirred until no starting material could be detected by TLC (30 minutes). The mixture was washed with conc. $NaHCO_3$ solution (2 × 30 ml) and conc. NaCl solution, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography [silica gel, elution with *n*-hexane : ethyl acetate (3:1)] to afford **2a** as white crystals (3.80 g, 94%); m. p. 29 – 30 °C. – ^{1}H NMR: $\delta = 1.45$ (s, 6H, 2-H), 2.75 (s, 2H, 3-H), 6.90 (m, 2H, 6-H, 8-H), 7.95 (d, $J = 9.28$ Hz, 1H, 5-H). – MS: m/e (%) = 324 (M^+, 8), 309 (22), 269 (12), 176 (19), 149 (19), 107 (39), 79 (32), 69 (100). – $C_{12}H_{11}F_3O_5S$ (324.29): calcd. C 44.45, H 3.42; found C 44.40, H 3.49.

The compounds **2b – h** and **4b – 11b** were prepared in an analogous manner.

*7-Trifluoromethylsulfonyloxy-2,2,5-trimethylchromanone (**2b**)*

(20 min, yield: 93%, oil). – ^{1}H NMR: $\delta = 1.45$ (s, 6H, 2,2-CH_3), 2.65 (s, 3H, 5-CH_3), 2.75 (s, 2H, 3-H), 6.65 (d, $J = 2.80$ Hz, 1H, 6-H or 8-H), 6.75 (d, $J = 2.80$ Hz, 1H, 6-H or 8-H). – MS: m/e (%) = 338 (M^+, 26), 323 (10), 283 (16), 121 (25), 93 (11), 69 (100). – $C_{13}H_{13}F_3O_5S$ (338.30): calcd. C 46.15, H 3.87; found C 46.91, H 3.81.

*7-Trifluoromethylsulfonyloxy-2,2,8-trimethylchromanone (**2c**)*

(10 min, yield: 90%, white crystals, m. p. 53 – 54 °C). – ^{1}H NMR: $\delta = 1.50$ (s, 6H, 2,2-CH_3), 2.25 (s, 3H, 8-CH_3), 2.75 (s, 2H, 3-H), 6.90 (d, $J = 9.13$ Hz, 1H, 5-H or 6-H), 7.80 (d, $J = 9.10$ Hz, 1H, 5-H or 6-H). – MS: m/e (%) = 338 (M^+, 20), 323 (51), 283 (22), 190 (25), 149 (29), 93 (11), 69 (100). – $C_{13}H_{13}F_3O_5S$ (338.30): calcd. C 46.15, H 3.87; found C 46.31, H 3.60.

*2,2-Dimethyl-5-methoxy-7-(trifluoromethylsulfonyloxy)-chromanone (**2d**)*

(10 min, yield: 93%, oil). – ^{1}H NMR: $\delta = 1.45$ (s, 6H, 2,2-CH_3), 2.70 (s, 2H, 3-H), 3.90 (s, 3H, 5-OMe), 6.35 (d, $J = 2.17$ Hz, 1H, 6-H or 8-H), 6.50 (d, $J = 2.15$ Hz, 1H, 6-H or 8-H). – MS: m/e (%) = 354 (M^+, 11), 339 (10), 299 (39), 206 (7), 138 (10), 83 (8), 69 (100). – $C_{13}H_{13}F_3O_6S$ (354.30): calcd. C 44.07, H 3.69; found C 44.25, H 3.62.

*2,2-Dimethyl-6-methoxy-7-(trifluoromethylsulfonyloxy)-chromanone (**2e**)*

(10 min, yield: 89%, white crystals, m. p. 87 – 88 °C). – ^{1}H NMR: $\delta = 1.45$ (s, 6H, 2,2-CH_3), 2.75 (s, 2H, 3-H), 3.90 (s, 3H, 6-OMe), 6.90 (s, 1H, 8-H), 7.45 (s, 1H, 5-H). – MS: m/e (%) = 354 (M^+, 8), 339 (15), 299 (8), 206 (5), 165 (6), 138 (32), 69 (100). – $C_{13}H_{13}F_3O_6S$ (354.30): calcd. C 44.07, H 3.69; found C 44.50, H 3.59.

*2,2-Dimethyl-8-methoxy-7-(trifluoromethylsulfonyloxy)-chromanone (**2f**)*

(15 min, yield: 88%, oil). – ^{1}H NMR: $\delta = 1.55$ (s, 6H, 2,2-CH_3), 2.80 (s, 2H, 3-H), 4.05 (s, 3H, 8-OMe), 6.85 (d, $J = 8.80$ Hz, 1H, 6-H), 7.65 (d, $J = 8.80$ Hz, 1H, 5-H). – MS: m/e (%) = 354 (M^+, 30), 339 (41), 299 (31), 206 (25), 107 (100), 109 (28), 69 (100). – $C_{13}H_{13}F_3O_6S$ (354.30): calcd. C 44.07, H 3.69; found C 44.32, H 3.70.

*6-Chloro-2,2-dimethyl-7-(trifluoromethylsulfonyloxy)chromanone (**2g**)*

(30 min, yield: 92%, white crystals, m. p. 58 – 58.5 °C). – ^{1}H NMR: $\delta = 1.45$ (s, 6H, 2,2-CH_3), 2.75 (s, 2H, 3-H), 7.00 (s, 1H, 8-H), 8.00 (s, 1H, 5-H). – MS: m/e (%) = 358 (M^+, 6), 343 (12), 303 (6), 210 (10), 141 (12), 113 (9), 69 (100). – $C_{12}H_{10}ClF_3O_5S$ (358.72): calcd. C 40.17, H 2.80; found C 40.30, H 2.95.

*5,7-Bis(trifluoromethylsulfonyloxy)-2,2-dimethylchromanone (**2h**)*

(30 min, yield: 85%, white crystals, m. p. 123 – 124 °C). – ^{1}H NMR: $\delta = 1.51$ (s, 6H, 2,2-CH_3), 2.80 (s, 2H, 3-H), 6.73 – 6.74 (d, $J = 2.20$ Hz, 1H, 6-H or 8-H), 6.97 – 6.99 (d, $J = 2.29$ Hz, 1H, 6-H or 8-H). – $C_{13}H_{10}F_6O_8S_2$ (472.26): calcd. C 33.06, H 2.11; found C 33.21, H 2.16.

*4'-(Trifluoromethylsulfonyloxy)chalcone (**4b**)*

(20 min, yield: 94%, white crystals, m. p. 96 – 97 °C). – ^{1}H NMR: $\delta = 7.14 - 7.55$ (m, 6H, aromatic-H, α-CH), 7.60 – 7.75 (m, 2H, aromatic-H), 7.80 – 8.15 (m, 3H, aromatic-H, β-CH). – MS: m/e (%) = 356 (M^+, 42), 253 (76), 131 (100), 69 (72). – $C_{16}H_{11}F_3O_4S$ (356.32): calcd. C 53.93, H 3.11; found C 53.90, H 3.18.

*4-(Trifluoromethylsulfonyloxy)chalcone (**5b**)*

(15 min, yield: 95%, white crystals, m. p. 60 – 61 °C). – ^{1}H NMR: $\delta = 7.35$ (d, $J = 8.72$ Hz, 2H, aromatic-H), 7.50 (d, $J = 5.99$ Hz, 2H, aromatic-H), 7.56 – 7.66 (m, 5H, aromatic-H, α- and β-CH), 8.03 (dd, $J_1 = 1.37$ Hz, $J_2 = 8.71$ Hz, 2H, aromatic-H). – MS: m/e (%) = 356 (M^+, 25), 223 (66), 131 (77), 105 (100), 69 (82). – $C_{16}H_{11}F_3O_4S$ (356.32): calcd. C 53.93, H 3.11; found C 53.19, H 3.08.

*7-(Trifluoromethylsulfonyloxy)flavone (**6b**)*

(30 min, yield: 78%, white crystals, m. p. 137 – 138 °C). – ^{1}H NMR: $\delta = 6.87$ (s, 1H, 3-H), 7.35 (dd, $J_1 = 2.25$ Hz, $J_2 =$

8.82 Hz, 1H, 6-H), 7.51 – 7.59 (m, 4H, aromatic-H), 7.91 – 7.96 (m, 2H, aromatic-H), 8.35 (d, $J = 8.80$ Hz, 1H, 5-H). – MS: m/e (%) = 370 (M^+, 80), 273 (57), 268 (54), 237 (100), 135 (55), 69 (75). – $C_{16}H_9F_3O_5S$ (370.30): calcd. C 51.89, H 2.74; found C 51.01, H 2.79.

*7-(Trifluoromethylsulfonyloxy)isoflavone (**7b**)*

(45 min, yield: 89%, white crystals, m. p. 146 – 147 °C). – ^{1}H NMR: $\delta = 7.26 - 7.57$ (m, 7H, aromatic-H), 8.06 (s, 1H, 2-H), 8.43 (d, $J = 8.84$ Hz, 1H, 5-H). – MS: m/e (%) = 370 (M^+, 52), 273 (72), 268 (88), 237 (72), 135 (82), 69 (100). – $C_{16}H_9F_3O_5S$ (370.30): calcd. C 51.89, H 2.74; found C 52.01, H 2.86.

*5-Hydroxy-2-methyl-7-(trifluoromethylsulfonyloxy)-isoflavone (**8b**)*

(30 min, yield: 68%, white crystals, m. p. 128 – 129 °C). – ^{1}H NMR: $\delta = 2.30$ (s, 3H, CH_3), 7.02 (s, 1H, 8-H), 7.35 – 7.44 (m, 6H, aromatic-H), 13.14 (s, 1H, 5-OH). – MS: m/e (%) = 400 (M^+, 32), 331 (44), 303 (63), 284 (58), 267 (88), 151 (77), 69 (100). – $C_{17}H_{11}F_3O_6S$ (400.33): calcd. C 51.00, H 2.76; found C 51.17, H 2.85.

*3',4'-Methylenedioxy-7-(trifluoromethylsulfonyloxy)-isoflavone (**9b**)*

(30 min, yield: 73%, white crystals, m. p. 174 – 175 °C). – ^{1}H NMR: $\delta = 6.01$ (s, 2H, $-OCH_2O-$), 6.89 (d, $J = 8.01$ Hz, 1H, 5'-H), 6.98 (dd, $J_1 = 1.66$ Hz, $J_2 = 8.01$ Hz, 1H, 6'-H), 7.08 (d, $J = 1.66$ Hz, 1H, 2'-H), 7.35 (dd, $J_1 = 2.32$ Hz, $J_2 = 8.83$ Hz, 1H, 6-H), 7.46 (d, $J = 2.32$ Hz, 1H, 8-H), 8.02 (s, 1H, 2-H), 8.42 (d, $J = 8.83$ Hz, 1H, 5-H). – MS: m/e (%) = 414 (M^+, 38), 281 (88), 268 (75), 252 (72), 146 (51), 69 (100). – $C_{17}H_9F_3O_7S$ (414.32): calcd. C 49.28, H 2.18; found C 49.57 H 2.23.

*4-Methyl-7-(trifluoromethylsulfonyloxy)coumarin (**10b**)*

(30 min, yield: 91%, white crystals, m. p. 83 – 84 °C). – ^{1}H NMR: $\delta = 2.47$ (d, $J = 1.18$ Hz, 3H, 4-CH_3), 6.36 – 6.38 (q, $J = 1.18$ Hz, 1H, 3-H), 7.22 (d, $J = 2.45$ Hz, 1H, 8-H), 7.29 (dd, $J_1 = 2.45$ Hz, $J_2 = 8.60$ Hz, 1H, 6-H), 7.70 (d, $J = 8.60$ Hz, 1H, 5-H). – MS: m/e (%) = 308 (M^+, 46), 239 (40), 175 (74), 69 (100). – $C_{11}H_7F_3O_5S$ (308.23): calcd. C 42.86, H 2.29; found C 42.57, H 2.25.

*Ethyl 7-(trifluoromethylsulfonyloxy)chromone-2-carboxylate (**11b**)*

(30 min, yield: 66%, white crystals, m. p. 127 – 128 °C). – ^{1}H NMR: $\delta = 1.45$ (t, $J = 7.14$ Hz, 3H, ethyl-CH_3), 4.49 (q, $J = 7.14$ Hz, 2H, ethyl-CH_2), 7.16 (s, 1H, 3-H), 7.37 (dd, $J_1 = 2.34$ Hz, $J_2 = 8.87$ Hz, 1H, 6-H), 7.65 (d, $J = 2.34$ Hz, 1H, 8-H), 8.31 (d, $J = 8.87$ Hz, 1H, 5-H). – MS: m/e (%) = 336 (M^+, 20), 297 (62), 268 (82), 233 (54), 69 (100). – $C_{13}H_9F_3O_7S$ (366.27): calcd. C 42.63, H 2.47; found C 42.17, H 2.50.

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