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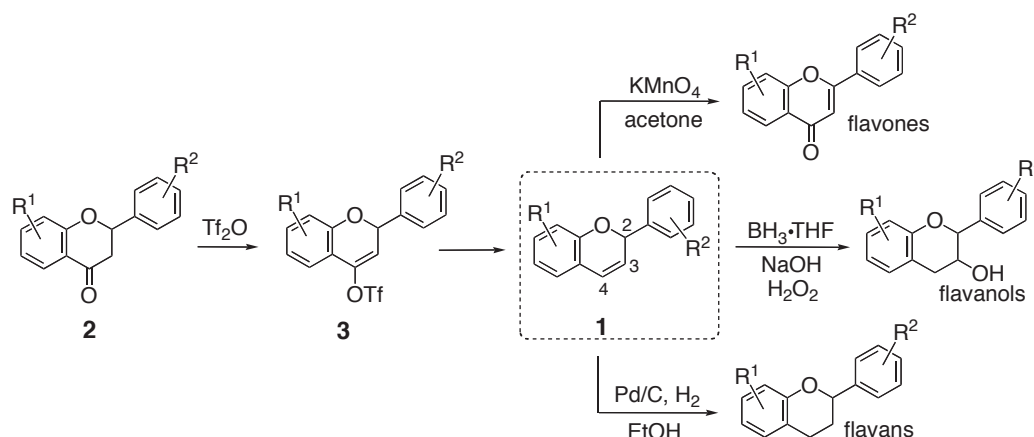
EFFICIENT TRANSFORMATION OF FLAV-3-ENES USING REDUCTIVE ELIMINATION OF FLAV-4-TRIFLATE

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Abstract – Flav-3-enes were prepared in excellent yields (up to 98%) by reductive elimination of flav-3-ene-4-triflates in the presence of palladium acetate, formic acid and tri-*n*-butylamine.

Flav-3-enes (3-phenyl-2*H*-1-benzopyrans) **1** are the useful intermediates of naturally occurring flavonoids such as flavones (2-phenyl-4*H*-1-benzopyran-4-ones),¹ flavans (2-phenyl-3,4-dihydro-2*H*-1-benzopyrans)² and flavanols (3-hydroxy-2-phenyl-3,4-dihydro-2*H*-1-benzopyrans),³ which have *anti*-allergic, *anti*-inflammatory,⁴ *anti*-microbial⁵ and *anti*-cancer⁶ activities (Scheme 1). It is therefore important to establish an effective synthetic methodology for the ring system **1**. Some synthetic methodologies have been reported previously for the synthesis of this ring system.⁷ In particular, the condensation of α , β -unsaturated carbonyl compounds with phenols under different reaction conditions represents a largely used and promising route.



Scheme 1. Transformations of flav-3-ene to several flavonoids

In addition, the methodology using NaBH_4 reduction of flavanone **2**, tosylation followed by dehydration of 4-tosylate is also efficient synthetic route.¹⁻³ The problem with these syntheses, however, relates to both their selectivity and their general applicability; moreover in some cases the overall yields are poor. We planned the new synthetic methodology using the conversion from **3** to vinyl triflate **2**, followed by the reductive elimination of **2** in the presence of palladium acetate, formic acid and tri-*n*-butylamine (Scheme 1).⁸ We describe in this paper the detail of our new and very simple synthetic methodology of **1** based on the reductive elimination of vinyl triflate **2**.

We attempted a conversion from ketones **2a-h** to vinyl triflates **3a-h** (Table 1). The reaction of the simplest ketone **2a** with triflic anhydride was carried out in CH_2Cl_2 in the presence of pyridine as a base at -78°C . The reaction successfully proceeded to afford the desired triflate **3a** in excellent yield (97%, entry 1). The reactions of several ketones **2b-h** having substituents on the phenyl group at 2-position or benzopyranone ring system, respectively, were also carried out under the same reaction conditions as those used for **2a**. As a result, all of the attempted reactions afforded the desired triflates **3b-h** in fairly good to excellent yields (88-98%, entries 2-8).

Next, the reductive eliminations of triflates **3a-h** were examined (Table 1). The reactions were carried out in the presence of formic acid, tri-*n*-butylamine, and three kinds of Pd catalysts such as $\text{Pd}(\text{OAc})_2\text{-dppf}$, $\text{Pd}(\text{OAc})_2\text{-2PPh}_3$, and $\text{Pd}(\text{PPh}_3)_4$ at 60°C . The reaction of **3a** using $\text{Pd}(\text{OAc})_2\text{-dppf}$ catalyst afforded the desired **1a** in an excellent isolated yield (95%) (entry 1). Although the use of $\text{Pd}(\text{OAc})_2\text{-2PPh}_3$ or $\text{Pd}(\text{PPh}_3)_4$ as a catalyst, respectively, also afforded satisfactory yields [$\text{Pd}(\text{OAc})_2\text{-2PPh}_3$: 85%, $\text{Pd}(\text{PPh}_3)_4$: 92%], they did not provide the catalytic activity of $\text{Pd}(\text{OAc})_2\text{-dppf}$. From the above results, it can be seen that $\text{Pd}(\text{OAc})_2\text{-dppf}$ is a better catalyst for the reductive elimination of triflate **3a**. The reactions of other substrates **2b-h** were also examined under the same reaction conditions as those used for **3a** (entries 2-8). The reactions successively proceeded to afford the desired **1b-h** in moderate to excellent yields, as shown in Table 1. Both the reactions using **3b** with a methoxy substituent or **3c** with a methyl substituent on the phenyl groups as an electron-donating group brought about a decrease in chemical yield with a complex mixture, although the reason for this decrease remains unclear (entries 2 and 3). It might be due to the steric and the electric factors of methyl or methoxy substituents. In addition, it might be due to the structural instability⁹ of **1b** and **1c**. On the other hand, substrates **3d** or **3h** with a chlorine substituent on the phenyl group as an electron-withdrawing group, respectively, gave chemoselectively **1d** (93%) and **1h** (92%), respectively without dechlorination that is observed under these reaction conditions (entries 4 and 8).

Table 1. Triflation of **2a-h** and reductive elimination of **3a-h**

Entry	Substrate ^a 2a-h	Time (h) ^b	Product 3a-h	Yield (%) ^c	Product ^d 1a-h	Yield (%) ^e
1		4		97		95
2		3		97		61
3		5		94		70
4		72		88		93
5		5		96		86
6		5		87		83
7		4		98		97
8		6		90		92

a. All reactions were carried out on a 2.0 mmol scale with TiF_2O (2.4 mmol) and pyridine (2.4 mmol) in CH_2Cl_2 under nitrogen atmosphere. *b.* Reaction time was determined by monitoring using TLC. *c.* Isolated yield after chromatography. *d.* All reactions were carried out on a 1.0 mmol scale in the presence of $\text{Pd}(\text{OAc})_2$ (2 mol%), dppf (4 mol%), HCO_2H (2.0 mmol) and Bu_3N (3.0 mmol) in dry-DMF under nitrogen atmosphere. *e.* Isolated yield after chromatography.

In conclusion, we have developed an efficient synthetic methodology for obtaining the flav-3-enes, which are useful intermediates for the synthesis of flavonoids. Thus the conversion from flavanones **2** to flav-3-enes **1** *via* triflates **3** was accomplished in total yields of 61-95% under very mild conditions. This new methodology can be extended to the preparation of still more flav-3-enes having various substituents. Further studies to examine the scope and limitations of our new synthetic methodology for the synthesis of flavonoids are now in progress.

EXPERIMENTAL

All reactions were carried out in anhydrous solvents and under nitrogen atmosphere. Flavanones were prepared from commercially available acetophenones and benzaldehydes according to well-known method. ^1H and ^{13}C NMR spectra were recorded at 270 MHz and 67.8 MHz on a JEOL JNM-EX 270 FT NMR SYSTEM in CDCl_3 using tetramethylsilane as an internal standard. TLC analyses were performed on commercial aluminum plates bearing a 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Wakogel 200 mesh) was used for column chromatography.

General procedure for synthesis of flav-3-ene-4-triflates 3a-h. Flavanone **2a** (2.0 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL) along with dry pyridine (2.4 mmol) under nitrogen. The solution was cooled at $-78\text{ }^\circ\text{C}$. 2.4 mmol of trifluoromethanesulfonic anhydride was slowly added. The resulting mixture was allowed to warm to $0\text{ }^\circ\text{C}$, stirred at $0\text{ }^\circ\text{C}$ for 1 h, then warmed to room temperature, and stirred until flavanone disappeared by monitoring using TLC. The reaction mixture was extracted with Et_2O and the extract was washed with H_2O , 1M aq. HCl and brine, and dried over MgSO_4 . The solvent was removed and the residue was isolated by silica gel column chromatography (hexane/EtOAc 4:1) to afford **3a**.

2-Phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyrane (3a). Light yellow oil, *R_f* 0.64 (4:1 hexane/EtOAc), ^1H NMR (CDCl_3): δ 5.81 (d, 1H, *J* = 3.8 Hz), 6.07 (d, 1H, *J* = 3.8 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 6.95 (t, 1H, *J* = 7.6 Hz), 7.21 (td, 1H, *J* = 8.0, 1.5 Hz), 7.29 (dd, 1H, *J* = 7.6, 1.5 Hz), 7.34-7.46 (m, 5H), ^{13}C NMR (CDCl_3): δ 76.3, 113.1, 116.4, 116.6, 121.6, 121.6, 127.1, 128.3, 128.9, 129.1, 131.8, 138.8, 143.1, 153.8.

3'-Methoxy-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3b). A Light yellow oil, *R_f* 0.59 (4:1 hexane/EtOAc), ^1H NMR (CDCl_3): δ 3.78 (s, 3H), 5.83 (d, 1H, *J* = 3.8 Hz), 6.08 (d, 1H, *J* = 3.6 Hz), 6.85 (d, 1H, *J* = 8.3 Hz), 6.89-7.04 (m, 3H), 7.22-7.34 (m, 3H), ^{13}C NMR (CDCl_3): δ 55.2, 77.1, 112.5, 113.0, 114.8, 116.4, 116.6, 119.3, 121.6, 121.7, 130.0, 131.8, 140.3, 143.2, 153.8, 160.0.

2',4'-Dimethyl-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3c). A light yellow oil, *R_f* 0.73 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 2.30 (s, 3H), 2.44 (s, 3H), 5.76 (d, 1H, *J* = 3.6 Hz), 6.29 (d, 1H, *J* = 3.6 Hz), 6.79 (dd, 1H, *J* = 8.3, 1.0 Hz), 6.80 (td, 1H, *J* = 7.6, 1.0 Hz), 7.00-7.05 (m, 2H), 7.21 (td, 1H, *J* = 7.6, 1.0 Hz), 7.27-7.33 (m, 2H), ¹³C NMR (CDCl₃): δ 19.1, 21.0, 74.9, 113.1, 116.5, 121.5, 121.6, 127.0, 128.0, 131.7, 132.0, 133.3, 136.3, 139.1, 143.4, 154.1.

3',4'-Dichloro-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3d). A light yellow oil, *R_f* 0.66 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 5.80 (d, 1H, *J* = 4.0 Hz), 6.07 (d, 1H, *J* = 4.0 Hz), 6.86 (d, 1H, *J* = 8.3 Hz), 7.00 (td, 1H, *J* = 7.6, 1.0 Hz), 7.29 (dd, 1H, *J* = 8.3, 2.2 Hz), 7.47 (d, 1H, *J* = 8.3 Hz), 7.55 (d, 1H, *J* = 2.2 Hz), ¹³C NMR (CDCl₃): δ 75.0, 116.2, 116.7, 121.9, 122.1, 126.3, 129.2, 131.0, 132.1, 133.1, 133.3, 138.9, 143.7, 153.4.

4'-Isopropyl-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3e). A light yellow oil, *R_f* 0.73 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 1.23 (d, 6H, *J* = 6.9 Hz), 2.90 (q, 1H, *J* = 6.9 Hz), 5.81 (d, 1H, *J* = 3.8 Hz), 6.60 (d, 1H, *J* = 3.8 Hz), 6.82 (dd, 1H, *J* = 8.1, 1.0 Hz), 6.94 (td, 1H, *J* = 7.6, 1.0 Hz), 7.21 (td, 1H, *J* = 7.8, 1.5 Hz), 7.24 (d, 2H, *J* = 8.3 Hz), 7.29 (dd, 1H, *J* = 7.8, 1.5 Hz), 7.37 (d, 2H, *J* = 8.3 Hz), ¹³C NMR (CDCl₃): δ 23.8, 33.9, 77.3, 113.2, 116.4, 116.6, 121.5, 121.6, 127.0, 127.3, 131.7, 136.2, 143.1, 150.0, 153.9.

7-Methyl-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3f). A light yellow oil, *R_f* 0.65 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 2.23 (s, 3H), 5.75 (d, 1H, *J* = 3.8 Hz), 6.04 (d, 1H, *J* = 3.8 Hz), 6.65 (s, 1H), 6.76 (d, 1H, *J* = 7.8 Hz), 7.16 (d, 1H, *J* = 7.8 Hz), 7.33-7.45 (m, 5H), ¹³C NMR (CDCl₃): δ 21.5, 77.3, 111.8, 113.8, 121.4, 127.1, 128.9, 129.0, 139.0, 142.7, 143.4, 153.8.

7-Methoxy-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3g). A light yellow oil, *R_f* 0.63 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 3.76 (s, 3H), 5.86 (d, 1H, *J* = 4.0 Hz), 6.03 (d, 1H, *J* = 3.8 Hz), 6.78-6.83 (m, 3H), 7.35-7.43 (m, 5H), ¹³C NMR (CDCl₃): δ 55.7, 77.1, 106.6, 113.9, 117.1, 117.4, 117.5, 127.1, 128.9, 129.1, 138.7, 143.2, 147.7, 154.3.

6-Chloro-7-methyl-2-phenyl-4-trifluoromethanesulfonyloxy-2H-1-benzopyran (3h). A light yellow oil, *R_f* 0.65 (7:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 2.29 (s, 3H), 5.83 (d, 1H, *J* = 4.0 Hz), 6.07 (d, 1H, *J* = 4.0 Hz), 6.72 (s, 1H), 7.23 (s, 1H), 7.37-7.41 (m, 5H); ¹³C NMR (CDCl₃): δ 20.3, 77.5, 113.0, 115.5, 119.0, 121.8, 127.0, 127.1, 129.0, 129.3, 138.5, 140.1, 142.2, 152.2.

General procedure for the synthesis of flav-3-enes (2-phenyl-2*H*-1-benzopyrans) 1a-h. To a mixture of **3a** (1.0 mmol) and tri-*n*-butylamine (3.0 mmol) in dry DMF (2.0 mL), formic acid (2.0 mmol) was added in the presence of palladium acetate (0.02 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.04 mmol) under nitrogen. The resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was extracted with Et₂O and the extract was washed with H₂O and brine, and dried over MgSO₄. The solvent was removed and the residue was isolated by silica gel column chromatography (hexane/EtOAc 10:1) to afford **1a**.

2-Phenyl-2*H*-1-benzopyran (1a).¹⁰ A light yellow oil, *R*_f 0.55 (4:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 5.79 (dd, 1H, *J* = 9.9, 3.5 Hz), 5.91 (dd, 1H, *J* = 3.3, 2.0 Hz), 6.53 (dd, 1H, *J* = 9.8, 1.4 Hz), 6.78 (d, 1H, *J* = 8.8 Hz), 6.86 (td, 1H, *J* = 8.0, 1.5 Hz), 7.29 (dd, 1H, *J* = 7.6, 1.5 Hz), 7.34-7.46 (m, 5H), ¹³C NMR (CDCl₃): δ 77.1, 116.0, 121.2, 121.3, 123.9, 124.8, 126.6, 127.0, 128.3, 128.6, 129.4, 140.8, 153.1, HRMS (EI): calcd for C₁₅H₁₂O: 208.0880; found: 208.0892.

3'-Methoxy-2-phenyl-2*H*-1-benzopyran (1b). A light yellow oil, *R*_f 0.42 (10:1 hexane/EtOAc); ¹H NMR (CDCl₃): δ 3.74 (s, 3H), 5.75 (dd, 1H, *J* = 9.7, 3.3 Hz), 5.85 (dd, 1H, *J* = 3.3, 2.0 Hz), 6.48 (dd, 1H, *J* = 9.7, 2.0 Hz), 6.77-7.28 (m, 8H), ¹³C NMR (CDCl₃): δ 55.1, 76.9, 112.5, 113.7, 115.9, 119.2, 121.1, 121.2, 123.9, 124.7, 126.5, 129.4, 129.6, 142.4, 153.1, 159.8, HRMS (EI): calcd for C₁₆H₁₄O₂: 238.0994; found: 238.0994.

2',4'-Dimethyl-2-phenyl-2*H*-1-benzopyran (1c). A light yellow oil, *R*_f 0.55 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 1.22 (s, 3H), 1.25 (s, 3H), 5.79 (dd, 1H *J* = 9.9, 3.5 Hz), 5.88 (dd, 1H, *J* = 3.5, 1.7 Hz), 6.52 (dd, 1H, *J* = 9.7, 1.6 Hz), 6.77 (d, 1H, *J* = 7.9 Hz), 6.85 (td, 1H, *J* = 7.4, 1.2 Hz), 7.00 (dd, 1H, *J* = 7.4, 1.8 Hz), 7.09 (td, 1H, *J* = 7.9, 1.8 Hz), 7.21 (m, 3H), ¹³C NMR (CDCl₃): δ 23.9, 33.9, 77.1, 116.0, 116.6, 121.1, 121.3, 123.9, 125.0, 127.0, 127.1, 129.1, 131.7, 138.2, 149.1, 153.2, HRMS (EI): calcd for C₁₇H₁₅O: 235.1124; found: 235.1127.

3',4'-Dichloro-2-phenyl-2*H*-1-benzopyran (1d). A light yellow oil, *R*_f 0.49 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 5.69 (dd, 1H *J* = 9.7, 3.5 Hz), 5.80 (dd, 1H, *J* = 3.5, 1.5 Hz), 6.39 (dd, 1H, *J* = 9.7, 1.5 Hz), 6.77 (d, 1H, *J* = 7.9 Hz), 6.85 (td, 1H, *J* = 7.3, 1.2 Hz), 6.97 (dd, 1H, *J* = 7.4, 1.7 Hz), 7.09 (td, 1H, *J* = 7.8, 1.8 Hz), 7.23 (dd, 1H, *J* = 8.3, 1.9 Hz), 7.36 (d, 1H, *J* = 8.3 Hz), 7.50 (d, 1H, *J* = 1.2 Hz), ¹³C NMR (CDCl₃): δ 75.5, 116.0, 120.9, 121.5, 123.4, 124.7, 126.2, 126.7, 128.9, 129.7, 130.5, 132.2, 132.6, 140.9, 152.6, HRMS (EI): calcd for C₁₅H₁₀OC₂: 276.0109; found: 276.0110.

4'-Isopropyl-2-phenyl-2H-1-benzopyran (1e). A light yellow oil, *R_f* 0.58 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 1.20 (d, 6H, *J* = 6.9 Hz), 2.85 (q, 1H, *J* = 6.9 Hz), 5.71 (dd, 1H, *J* = 9.9, 3.3 Hz), 5.83 (d, 1H, *J* = 3.3 Hz), 6.45 (d, 1H, *J* = 8.1 Hz), 6.78 (td, 1H, *J* = 7.4, 1.2 Hz), 6.94 (dd, 1H, *J* = 7.3, 1.7 Hz), 7.04 (td, 1H, *J* = 7.6, 1.8 Hz), 7.18 (d, 2H, *J* = 8.1 Hz), 7.34 (d, 2H, *J* = 8.1 Hz), ¹³C NMR (CDCl₃): δ 23.9, 33.8, 77.0, 115.9, 121.0, 121.3, 123.8, 124.9, 126.5, 126.6, 127.1, 129.3, 138.2, 149.0, 153.2, HRMS (EI): calcd for C₁₈H₁₈O: 250.1358; found: 250.1360.

7-Methyl-2-phenyl-2H-1-benzopyran (1f). A light yellow oil, *R_f* 0.58 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 2.24 (s, 3H), 5.70 (dd, 1H, *J* = 9.9, 3.4 Hz), 5.86 (d, 1H, *J* = 3.4 Hz), 6.47 (d, 1H, *J* = 9.9 Hz), 6.61 (s, 1H), 6.65 (d, 1H, *J* = 7.5 Hz), 6.87 (d, 1H, *J* = 7.5 Hz), 7.28-7.44 (m, 5H), ¹³C NMR (CDCl₃): δ 21.4, 77.1, 116.6, 118.6, 121.8, 123.7, 123.8, 126.3, 127.0, 128.2, 128.6, 139.7, 141.0, 153.0, HRMS (EI): calcd for C₁₆H₁₄O: 222.1045; found: 222.1045.

7-Methoxy-2-phenyl-2H-1-benzopyran (1g). A light yellow oil, *R_f* 0.51 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 3.72 (s, 3H), 5.79-5.84 (m, 2H), 6.48 (dd, 1H, *J* = 10.7, 2.8 Hz), 6.57 (d, 1H, *J* = 2.8 Hz), 6.65 (dd, 1H, *J* = 8.7, 2.8 Hz), 6.72 (d, 1H, *J* = 8.7 Hz), 7.28-7.44 (m, 5H), ¹³C NMR (CDCl₃): δ 55.6, 76.9, 111.7, 114.5, 116.5, 122.0, 124.1, 125.8, 127.0, 128.2, 128.6, 140.7, 147.0, 154.0, HRMS (EI): calcd for C₁₆H₁₄O₂: 238.0994; found: 238.1002.

6-Chloro-7-methyl-2-phenyl-2H-1-benzopyran (1h). A light yellow oil, *R_f* 0.64 (10:1 hexane/EtOAc), ¹H NMR (CDCl₃): δ 2.27 (s, 3H), 5.80 (dd, 1H, *J* = 9.73, 3.46 Hz), 5.87 (dd, 1H, *J* = 3.5, 1.7 Hz), 6.46 (dd, 1H, *J* = 9.7, 1.7 Hz), 6.66 (s, 1H), 6.98 (s, 1H), 7.71-7.44 (m, 5H), ¹³C NMR (CDCl₃): δ 20.1, 77.1, 118.3, 120.4, 123.0, 125.0, 126.0, 126.4, 127.0, 128.5, 128.7, 137.0, 140.4, 151.4, HRMS (EI): calcd for C₁₆H₁₃OCl: 256.0655; found: 256.0655.

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