An Expeditious Synthesis of Flavonols Promoted by Montmorillonite KSF Clay and Assisted by Microwave Irradiation under Solvent-Free Conditions

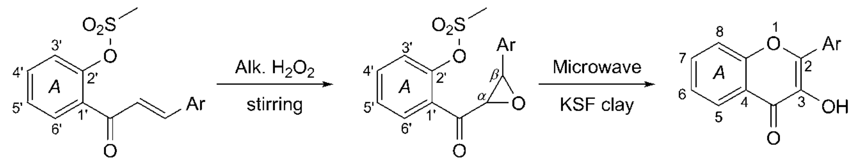
by **Mariappan Babu**, **Kasi Pitchumani**, and **Penugonda Ramesh***

Department of Natural Products Chemistry, School of Chemistry, Madurai Kamaraj University,
Madurai – 625021, Tamil Nadu, India
(phone: +91 452-2458471; e-mail: npc_ramesh@yahoo.com)

A simple, efficient, rapid, and ecofriendly synthesis of flavonols in >90% yield from 2′-(mesyloxy)epoxychalcones (=2-(3-aryl-2,3-epoxypropanoyl)phenyl methanesulfonates) promoted by montmorillonite KSF clay and assisted by microwave irradiation has been described.

Introduction. – Acidic clays contain both *Lewis* and *Brønsted* acid sites, so we anticipated that montmorillonite KSF clay in conjunction with microwave (MW) irradiation might bring about the conversion of epoxychalcones to flavonols under solvent-free conditions. With this objective of investigating the effect of acidic clays on epoxychalcones, we irradiated 2′-(mesyloxy)epoxychalcones (=2-(3-aryl-2,3-epoxypropanoyl)phenyl methanesulfonates; **2**) adsorbed on montmorillonite KSF clay using microwaves (*Scheme*). The results are compiled in the *Table.*

Scheme



1a Ar = Ph
1b Ar = 2-Cl–C_6H_4
1c Ar = 3-NO_2–C_6H_4
1d Ar = 4-MeO–C_6H_4
1e Ar = 4-Cl–C_6H_4
1f Ar = furan-2-yl
1g Ar = 1,3-benzodioxol-5-yl
1h Ar = 1*H*-indol-5-yl
1i Ar = 3,4-$(MeO)_2$–C_6H_3
1j Ar = 4-NO_2–C_6H_4

2a Ar = Ph
2b Ar = 2-Cl–C_6H_4
2c Ar = 3-NO_2–C_6H_4
2d Ar = 4-MeO–C_6H_4
2e Ar = 4-Cl–C_6H_4
2f Ar = furan-2-yl
2g Ar = 1,3-benzodioxol-5-yl
2h Ar = 1*H*-indol-5-yl
2i Ar = 3,4-$(MeO)_2$–C_6H_3
2j Ar = 4-NO_2–C_6H_4

3a Ar = Ph
3b Ar = 2-Cl–C_6H_4
3c Ar = 3-NO_2–C_6H_4
3d Ar = 4-MeO–C_6H_4
3e Ar = 4-Cl–C_6H_4
3f Ar = furan-2-yl
3g Ar = 1,3-benzodioxol-5-yl
3h Ar = 1*H*-indol-5-yl
3i Ar = 3,4-$(MeO)_2$–C_6H_3
3j Ar = 4-NO_2–C_6H_4

Results and Discussion. – Product **3a** of the MW irradiation of **2a**, adsorbed on montmorillonite KSF clay, has been identified as flavonol by its spectroscopic data. It provided negative test for sulfur and positive ferric test, indicating the presence of a chelated OH group. The UV spectrum of **3a** (λ_{max} (MeOH), 276, 321 nm) is

Table. *KSF Clay-Catalyzed Synthesis of Flavonols* **3** *under Microwave Irradiation*

Flavonols	Ar	Irradiation time [min]	Yield [%][a])
3a	C_6H_5	2.0	96
3b	2-Cl–C_6H_4	1.5	95
3c	3-NO_2–C_6H_4	2.5	90
3d	4-MeO–C_6H_4	2.5	91
3e	4-Cl–C_6H_4	1.5	95
3f	Furan-2-yl	2.0	92
3g	1,3-benzodioxol-5-yl	2.5	91
3h	1*H*-indol-5-yl	3.0	94
3i	3,4-$(MeO)_2$–C_6H_3	2.5	92
3j	4-NO_2–C_6H_4	3.0	93

[a]) Yield of the product after recrystallization.

reminiscent of flavones. Further, a bathochromic shift of 52 nm observed in band I upon addition of $AlCl_3$ to **3a** in MeOH (λ_{max} (MeOH + $AlCl_3$), 286, 374 nm) indicated the presence of a 3-OH group in the product [1]. That product **3a** was a flavonol and not a dihydroflavonol was inferred from the absence of a pair of *doublets* in the ^{1}H-NMR spectrum in the region of δ(H) 4.0–5.0 for H–C(2) and H–C(3) [2], and by the appearance of a downfield *singlet* at δ(H) 10.68, which exchanged with D_2O. The mass spectrum of **3a** displayed the molecular ion (M^+) at *m*/*z* 238 and the base peak at *m*/*z* 221 ($[M - OH]^+$), suggesting the presence of a OH group. The position of the OH group at C(3) is evident from *retro-Diels–Alder* [3] fragment-ion peaks at *m*/*z* 121 ($A_1 + H$) and 105 (B_2^+). Based on the above spectroscopic data, the MW-irradiation product **3a** has been characterized as flavonol, and its identity was further supported by ^{13}C-NMR spectral data, and by comparison of its melting point, spectroscopic data with those published in [4]. To evaluate the efficacy of this method, various *B*-ring-substituted 2′-(mesyloxy)chalcones, **3b**–**3j**, were prepared and subjected to clay-promoted MW irradiation (*Table*). In all cases, only flavonols are obtained as sole homogeneous products of irradiation in $> 90\%$ yield.

Conclusions. – Although flavonols are accessible by *Allan–Robinson* [5], *Algar–Flynn* [6], and *von Auwers* reactions [7], all these methods suffer from low yields. The present protocol offers a simple, efficient, and environmentally benign synthesis of flavonols under solvent-free condition. Furthermore, shorter reaction times, simple reaction conditions and workup, and attractive yields ($\geq 90\%$) without side-products render this method superior to earlier methods.

To the best of our knowledge, this is the first report on conversion of 2′-hydroxy-epoxychalcones to flavonols under solvent-free condition promoted by montmorillonite KSF clay in conjunction with microwave irradiation.

Experimental Part

General. All regents and solvents were purchased from commercial sources and purified before used. All reactions were monitored by TLC. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh).

M.p.: micro-melting-point apparatus; uncorrected. FT-IR Spectra: *JASCO-410* IR Spectrophotometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 300* MHz spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si, J in Hz. Elemental analysis: *Vario-EL-CHNS* elemental analyzer. All microwave irradiations were carried out in the cavity of a commercially available *CEM Discover* apparatus. All the products were identified by comparison of their spectra, melting points, and anal. data with those in the literature.

Synthesis of 2-(3-Arylacryloyl)phenyl Methanesulfonates **1a**–**1j**. *General Procedure.* To a suspension of chalcone (0.01 mol) in Et_3N (10 ml), methanesulfonyl chloride (MsCl; 0.05 mol) was added dropwise, and the mixture was warmed and kept overnight. The solid, that separated on adding ice-cold H_2O, was filtered, washed with cold H_2O, dried, and crystallized from aq. EtOH.

Data of 2-(3-Phenylprop-2-enoyl)phenyl methanesulfonate (**1a**). M.p. 144° (AcOEt/petroleum ether (PE)). Yield: 74%. IR: 1648 (CO), 1379 (asym. SO_2Me), 1155 (sym SO_2Me), 1541. ^{1}H-NMR: 3.60 (*s*, SO_2Me); 6.12 (*d*, $J = 13.8$, H_α); 6.54 (*d*, $J = 13.8$, H_β); 7.25–7.74 (*m*, 9 arom. H). ^{13}C-NMR: 38.1; 116.5; 117.4 (C(α)); 122.6; 123.1; 125.2; 127.7; 128.4; 136.3; 148.4 (C(β)); 156.9; 193.1 (CO). Anal. calc. for $C_{16}H_{14}O_4S$ (302.35): C 63.56, H 4.67; found: C 63.58, H 4.65.

Synthesis of 2-(3-Aryloxirane-2-carbonyl)phenyl Methanesulfonates **2a**–**2j**. *General Procedure.* To a stirred soln. of **1a**–**1j** (0.01 mol) in EtOH (30.0 ml) kept at 5°, 30% H_2O_2 soln. (0.05 mol) and aq. NaOH (5%, 0.05 mol) were added in succession, while maintaining the temp. of the mixture at 5°, and stirring was continued for 4 h. The solid that separated was filtered, washed with H_2O, dried, and crystallized from aq. EtOH.

Data of 2-[(3-Phenyloxirane-2-yl)carbonyl]phenyl Methanesulfonate (**2a**). Yellow needles. M.p. 123–124° (EtOH). Yield: 75%. IR: 1662 (CO), 1383 (asym. OSO_2), 1184 (sym OSO_2), 1261 (asym. COC), 1080 (sym. COC). ^{1}H-NMR: 3.62 (*s*, SO_2Me); 4.61 (*d*, $J = 2.7$, H_β); 4.85 (*d*, $J = 2.7$, H_α); 7.43–7.71 (*m*, 9 arom. H). ^{13}C-NMR: 37.5 (SO_2Me); 59.0; 67.5; 114.3; 122.0; 123.3; 124.7; 127.0; 128.5; 137.7; 157.8; 192.9 (CO). Anal. calc for $C_{16}H_{14}O_5S$ (318.34): C 60.37, H 4.43; found: C 60.38, H 4.41.

*Representative Procedure for the Synthesis of 2-Aryl-3-hydroxy-4*H*-chromen-4-ones* **3a**–**3j**. An intimate mixture of **2a**–**2j** and montmorillonite KSF clay in a 1:3 ratio (*w*/*w*) was charged in a microwave (MW) test tube placed in a MW cavity and irradiated with MWs at 120° (power, 200 W) for 2–3 min (*Table*). The course of the reaction was followed by TLC. After the disappearance of the starting material, the MW test tube was removed, cooled to r.t., and the residue was stirred with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried, and purified by passing through a small column of SiO_2. Evaporation of the solvent gave pure 2-aryl-3-hydroxy-4*H*-chromen-4-ones in > 90% yield.

*Data of 3-Hydroxy-2-phenyl-4*H*-chromen-4-one* (**3a**). Yield: 96%. M.p. 170° (aq. EtOH; [8]: 170–171°). IR: 3383 (OH), 1659 (CO), 1607, 1576, 1551 (C=C). ^{1}H-NMR: 7.25–7.73 (*m*, 9 arom. H); 10.68 (*s*, HO–C(3)). ^{13}C-NMR: 118.3; 122.0; 125.4; 127.6; 128.9; 130.5; 134.7; 135.8; 145.8; 156.2; 172.1 (CO). FAB-MS (pos.): 238.5 (37, M^+), 221.4 (100), 212.0 (28), 183.1 (34), 165.0 (37), 145.1 (24), 133.0 (32), 121.1 (39), 105.2 (69). Anal. calc. for $C_{15}H_{10}O_3$ (238.24): C 75.62, H 4.23; found: C 74.88, H 5.01.

*Data of 2-(2-Chlorophenyl)-3-hydroxy-4*H*-chromen-4-one* (**3b**). Yield: 95%. M.p. 178–179° (aq. EtOH; [8]: 178°). ^{1}H-NMR: 7.36–8.03 (*m*, 8 arom. H); 10.53 (*s*, HO–C(3)). ^{13}C-NMR: 116.1; 121.5; 123.4; 125.2; 126.7; 129.6; 130.3; 131.3; 132.6; 135.2; 136.5; 156.2; 160.2; 173.1 (CO). Anal. calc. for $C_{15}H_9ClO_3$ (272.68): C 66.07, H 3.33; found: C 65.98, H 3.38.

*Data of 3-Hydroxy-2-(3-nitrophenyl)-4*H*-chromen-4-one* (**3c**). Yield: 90%. M.p. 203–205° (aq. EtOH; [8]: 205–206°). ^{1}H-NMR: 7.70–8.12 (*m*, 8 arom. H); 10.70 (*s*, HO–C(3)). ^{13}C-NMR: 115.4; 120.0; 121.6; 123.1; 123.4; 129.5; 131.2; 134.0; 135.2; 136.5; 146.9; 147.8; 156.2; 172.6 (CO). Anal. calc. for $C_{15}H_9NO_5$ (283.24): C 63.61, H 3.20; found: C 63.65, H 3.22.

*Data of 3-Hydroxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one* (**3d**). Yield: 91%. M.p. 196–197° (aq. EtOH; [8]: 197–199°). ^{1}H-NMR: 3.83 (*s*, MeO); 6.90–8.06 (*m*, 8 arom. H); 10.60 (*s*, HO–C(3)). ^{13}C-NMR: 57.3 (MeO); 114.2; 115.4; 122.0; 122.8; 125.2; 128.6; 135.2; 137.5; 146.6; 156.2; 159.8; 171.8 (CO). Anal. calc. for $C_{16}H_{12}O_4$ (268.26): C 71.64, H 4.51; found: C 71.62, H 4.54.

*Data of 2-(4-Chlorophenyl)-3-hydroxy-4*H*-chromen-4-one* (**3e**). Yield: 95%. M.p. 197–198° (MeOH; [8]: 198–200°). ^{1}H-NMR: 7.36–8.10 (*m*, 8 arom. H); 10.53 (*s*, HO–C(3)). ^{13}C-NMR: 115.6; 121.5; 123.3; 125.9; 127.8; 128.1; 130.2; 135.3; 136.9; 145.6; 157.1; 158.9; 171.8 (CO). Anal. calc. for $C_{15}H_9ClO_3$ (272.68): C 66.07, H 3.33; found: C 66.11, H 3.35.

*Data of 3-Hydroxy-2-(furan-2-yl)-4*H*-chromen-4-one* (**3f**). Yield: 92%. M.p. 172–174° (aq. EtOH; [8]: 171–172°). ^{1}H-NMR: 7.61–8.22 (*m*, 7 arom. H); 10.73 (*s*, HO–C(3)). ^{13}C-NMR: 110.0 (C(3′)); 112.7; 116.1; 121.6; 133.5; 134.9; 135.6; 143.7; 146.6; 147.4; 154.2; 156.8; 173.2 (CO). Anal. calc. for $C_{13}H_8O_4$ (228.20): C 68.42, H 3.53; found: C 68.40, H 3.51.

*Data of 2-(1,3-Benzodioxol-5-yl)-3-hydroxy-4*H*-chromen-4-one* (**3g**). Yield: 91%. M.p. 210–211° (aq. EtOH; [8]: 214–215°). ^{1}H-NMR: 6.07 (*s*, O–CH$_2$–O); 6.82 (*d*, $J = 2$, H–C(2′)); 6.94 (*d*, $J = 9$, H–C(5′)); 7.21 (*dd*, $J = 9.0$, 2.1, H–C(6′)); 7.75–8.04 (*m*, 4 arom. H); 10.81 (*s*, HO–C(3)). ^{13}C-NMR: 107.9 (OCH$_2$O); 108.4; 116.1; 121.1; 123.6; 124.1; 135.2; 136.5; 146.9; 148.0; 156.6; 172.3 (CO). Anal. calc. for $C_{16}H_{10}O_5$ (282.25): C 68.09, H 3.57; found: C 68.04, H 3.58.

*Data of 3-Hydroxy-2-(1*H*-indol-5-yl)-4*H*-chromen-4-one* (**3h**). Yield: 94%. Dark brown oil. ^{1}H-NMR: 6.92–8.03 (*m*, 9 arom. H); 10.61 (*s*, HO–C(3)); 11.43 (*s*, NH). ^{13}C-NMR: 114.0; 115.6; 118.8; 121.8; 123.8; 124.8; 126.0; 130.7; 135.5; 136.5; 136.7; 156.4; 160.3; 171.7 (CO). Anal. calc. for $C_{17}H_{11}NO_3$ (277.27): C 73.64, H 4.00; found: C 73.61, H 4.03.

*2-(3,4-Dimethoxyphenyl)-3-hydroxy-4*H*-chromen-4-one* (**3i**). Yield: 92%. M.p. 197–198° (aq. EtOH; [8]: 201–202°). ^{1}H-NMR: 3.86 (*s*, MeO–C(3′), MeO–C(4′)); 6.94–8.12 (*m*, 7 arom. H); 10.64 (*s*, HO–C(3)). ^{13}C-NMR: 56.7 (MeO); 111.5; 116.2; 121.4; 122.6; 123.4; 126.5; 134.6; 137.2; 148.9; 149.4; 156.4; 172.9 (CO). Anal. calc. for $C_{17}H_{14}O_5$ (298.29): C 68.45, H 4.73; found: C 68.41, H 4.70.

*3-Hydroxy-2-(4-nitrophenyl)-4*H*-chromen-4-one* (**3j**). Yield: 93%. M.p. 294–296° (aq. EtOH; [8]: 295–297°). ^{1}H-NMR: 7.45–8.22 (*m*, 8 arom. H); 10.58 (*s*, HO–C(3)). ^{13}C-NMR: 115.8; 121.3; 123.4; 123.8; 125.2; 127.6; 129.7; 131.3; 136.4; 142.0; 156.6; 172.9 (CO). Anal. calc. for $C_{15}H_9NO_5$ (283.24): C 63.61, H 3.20; found: C 63.60, H 3.22.

The authors thank School of Chemistry for providing FT-NMR recordings (under DST-IRHPA Programme), and one of the authors is grateful to UGC for UGC–Meritorious fellowship.

REFERENCES

[1] T. J. Mabry, K. R. Markham, M. B. Thomas, ‘Systematic Identification of Flavonoids’, Springer-Verlag, 1970.
[2] J. B. Harbone, ‘The Flavonoids: Advances in Research’, Eds. T. J. Mabry, H. Mabry, Chapman and Hall, London, 1975, p. 262.
[3] J. B. Harbone, ‘The Flavonoids: Advances in Research’, Eds. T. J. Mabry, H. Mabry, Chapman and Hall, London, 1975.
[4] A. Fougerousse, E. Gonzalez, R. Brouillard, *J. Org. Chem.* **2000**, *65*, 583; J. Grassmann, S. Hippeli, ‘Organic Reactions’, John Wiley & Sons, Hoboken, 1999, p. 54.
[5] J. Allan, R. Robinson, *J. Chem. Soc., Trans.* **1924**, *125*, 2192.
[6] J. Algar, J. P. Flynn, *Proc. Roy. Irish. Acad.* **1934**, *42B*, 1.
[7] T. H. Minton, H. Stephen, *J. Chem. Soc., Trans.* **1922**, *121*, 1598; E. M. Philbin, W. I. A. O’Sullvan, T. S. Wheeler, *J. Chem. Soc.* **1954**, *245*, 4174.
[8] A. Fougerousse, E. Gonzalez, R. Brouillard, *J. Org. Chem.* **2000**, *65*, 583; J. Grassmann, S. Hippeli, ‘Organic Reactions’, John Wiley & Sons, Hoboken, 1999, p. 54.

Received July 1, 2012