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Epoxidation of chromones and flavonoids in ionic liquids

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Abstract—A convenient and efficient procedure for the epoxidation of chromone, isoflavone, and chalcone derivatives using 1-butyl-3-methyl imidazolium tetrafluoroborate [bmim]BF_4 as solvent and alkaline hydrogen peroxide as oxidant is described. All reactions proceed in good yields and faster than in conventional solvents. No evidence of formation of compounds derived from the opening of the epoxide ring was attained.

1. Introduction

Natural products having a chromonic and flavonoidic structure (chalcones and isoflavones) exhibit important biological properties such as antiviral, cardioprotective, antioxidant, hepatoprotective, antitumoral and antiflammatory activities.[1] Their corresponding epoxides are postulated as biosynthetic intermediates of some natural compounds. Chalcone and isoflavone epoxides are useful building blocks in flavonoid chemistry.[2] A nucleophilic oxidant such as alkaline hydrogen peroxide has been suggested to be the reagent of choice for the direct preparation of these compounds (Weitz–Scheffer epoxidation).[3] Recently, the epoxidation of chalcones and isoflavones by using dimethyldioxirane (DMD), an electrophilic oxidant,[4] has been reported. However, long reaction times (up to 140 h) and a large excess of the reagent (up to 15 equiv.) are required.[5]

Because of the role of chiral epoxides as useful intermediates in the synthesis of natural products and drug molecules,[6] the asymmetric epoxidation of α,β-unsaturated ketones has also been widely investigated in the last few years. An asymmetric Weitz–Scheffer epoxidation of isoflavones mediated by optically active cinchonine catalysts has been reported,[7] as well as the use of the Jacobsen's Mn(III)salen catalyst in the presence of DMD as the source of the oxygen atom.[8] Chalcones have been subjected to asymmetric epoxidation by using a variety of polymer-bound chiral supports.[9–11] All these reactions have been performed in conventional solvents (acetone, toluene, tetrahydrofuran) as well as under phase-transfer conditions.[12–14]

Our interest in the functionalization of natural molecules by benign oxidative methodologies and in the preparation of fine-chemicals as well as bioactive compounds[15] prompted us to investigate the development of an epoxidation protocol for chromenes and flavonoids under environmentally friendly conditions. Particularly, we focused our attention on the use of room temperature ionic liquids. They are considered very promising and attractive substitutes for volatile organic solvents and are widely used in the Green Chemistry area.[16] In fact, having a negligible vapour pressure, their loss into the environment by evaporation is minimal; this property may offer environmental advantages in industrial processes. Ionic liquids possess several other attractive properties including a high flash point, thermal stability, immiscibility with some organic solvents, and capacity to dissolve a wide range of organic, inorganic and organometallic compounds. Cations usually present in room temperature ionic liquids are: tetraalkylammonium, tetraalkylphosphonium, trialkylsulfonium, *N*-alkylpyridinium and 1,3-dialkylimidazolium. Anions are generally polyatomic inorganic species (Fig. 1). They have been employed in a variety of organic reactions such as hydrogenation,[17] olefin dimerization and oligomerization,[18] Heck reactions,[19] hydroformylation,[20] alkoxycarbonylation,[21] and allylic substitution.[22] To the best of our knowledge, however, very little has been done in the oxidation area,[23] in particular in the epoxidation of natural compounds. Recently, the epoxidation of simple cyclohexenone derivatives by alkaline hydrogen peroxide in ionic liquids has been reported.[24]

Keywords: Epoxidation; Chromones; Flavonoids; Chalcones; Isoflavones; Ionic liquids; [bmim]BF_4.
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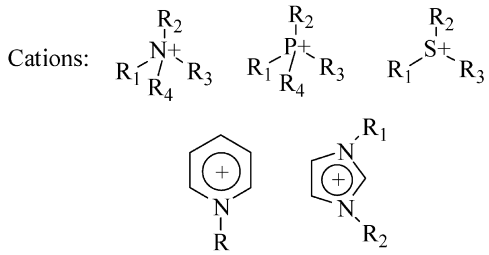


Figure 1. Common cations and anions in room temperature ionic liquids.

We report here that satisfactory results in the epoxidation of the enone moiety of natural compounds such as chromone, chalcone, and isoflavone derivatives can be obtained by hydrogen peroxide in 1-butyl-3-methyl imidazolium tetrafluoroborate, [bmim]BF_4 (Fig. 2).

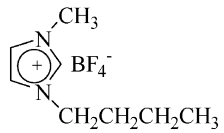


Figure 2. 1-Butyl-3-methyl imidazolium tetrafluoroborate [bmim]BF_4.

2. Results and discussion

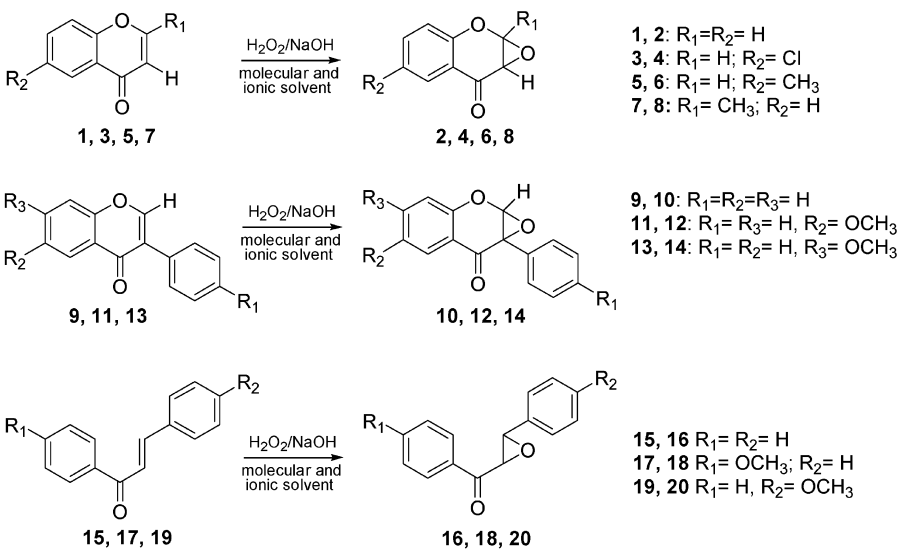
For our initial investigation, the epoxidation of chromone **1** with alkaline hydrogen peroxide was selected as a model reaction. For comparison, reactions were carried out in acetone and [bmim]BF_4. After 2 h, the epoxide derivative **2** was obtained in only 40% yield in acetone and in >98% yield in the ionic liquid (Scheme 1, Table 1, entries 1 and 2). In agreement with the formation of the epoxide ring,[3b] its ^{1}H NMR spectrum shows two doublets at 3.70 and 5.72 ppm (J=2.9 Hz). This structural assignment is further supported by ^{13}C NMR data and GC–MS fragmentation (M^+=162). No evidence of formation of products derived from the opening of the epoxide ring was attained.

Table 1. Epoxidation of chromones **1**, **3**, **5**, **7**, isoflavones **9**, **11**, **13**, and chalcones **15**, **17**, **19** with H_2O_2/NaOH[a] in conventional solvents (dichloromethane or acetone) and [bmim]BF_4

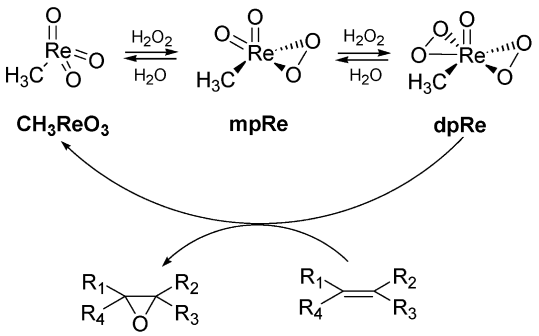
Entry	Substrate	Conditions[a]	Epoxide	Conversion (%)[b]	Yield (%)[b]
1	**1**	CH_3COCH_3, 0 °C, 2 h	**2**	40	>98
2	**1**	[bmim]BF_4, 0 °C, 2 h	**2**	>98	>98
3	**3**	CH_2Cl_2, 0 °C, 2 h	**4**	5	>98
4	**3**	[bmim]BF_4, 0 °C, 2 h	**4**	62	>98
5	**5**	CH_2Cl_2, 0 °C, 2 h	**6**	6	>98
6	**5**	[bmim]BF_4, 0 °C, 2 h	**6**	52	>98
7	**7**	CH_3COCH_3, 0 °C, 2 h	**8**	5[c]	>98[c]
8	**7**	[bmim]BF_4, 0 °C, 2 h	**8**	65[c]	>98[c]
9	**9**	CH_3COCH_3, rt, 2 h	**10**	20	>98
10	**9**	[bmim]BF_4, rt, 2 h	**10**	98	>98
11	**11**	CH_3COCH_3, rt, 2 h	**12**	20	>98
12	**11**	[bmim]BF_4, rt, 2 h	**12**	98	>98
13	**13**	CH_3COCH_3, rt, 2 h	**14**	12	>98
14	**13**	[bmim]BF_4, rt, 2 h	**14**	82	>98
15	**15**	CH_3COCH_3, rt, 0.5 h	**16**	5	>98
16	**15**	[bmim]BF_4, rt, 0.5 h	**16**	98	>98
17	**17**	CH_3COCH_3, rt, 0.5 h	**18**	7	>98
18	**17**	[bmim]BF_4, rt, 0.5 h	**18**	98	>98
19	**19**	CH_3COCH_3, rt, 0.5 h	**20**	5	>98
20	**19**	[bmim]BF_4, rt, 0.5 h	**20**	95	>98

[a] 3 equiv. of H_2O_2 (35% solution in water) and 2 equiv. of NaOH.
[b] Conversions and yields were determined after chromatographic purification of reaction mixtures.
[c] Conversions and yields were determined by ^{1}H NMR analysis of crude reaction mixtures.

Most probably, under our conditions, a nucleophilic mechanism is operating in the oxidation of the α,β-unsaturated fragment. Therefore, for the sake of comparison, we also tested the reactivity of methyltrioxorhenium/hydrogen peroxide in [bmim]BF_4. In fact, the active peroxodicomplexe **dpRe**, generated from methyltrioxorhenium during the reaction course (Scheme 2), has been reported to show some nucleophilic character.[25]



Scheme 1. Epoxidation of chromones **1**, **3**, **5**, **7**, isoflavones **9**, **11**, **13** and chalcones **15**, **17**, **19**.



Scheme 2. Epoxidation of alkenes by the H_2O_2/CH_3ReO_3 catalytic system.

Nevertheless, though the desired epoxide derivative was formed as almost the only product, a very low conversion of the substrate was observed (10–15%), even charging a large excess of the oxidation system (10% of methyltrioxorhenium and up to 12 equiv. of hydrogen peroxide).

Our reaction conditions (H_2O_2/NaOH in [bmim]BF_4 at 0 °C or rt) were next extended to other chromone derivatives such as 6-chlorochromone **3**, 6-methylchromone **5**, 2-methylchromone **7** and to some natural flavonoids such as isoflavone **9**, 6-methoxyisoflavone **11**, 7-methoxyisoflavone **13**, chalcone **15**, 4′-methoxychalcone **17**, and 4-methoxychalcone **19** (Scheme 2). In every case, the use of [bmim]BF_4 resulted to be superior to that of molecular solvents: the corresponding epoxides were isolated in significantly higher yields in all the comparisons (Table 1, compare entries 4, 6, 8, 10, 12, 14, 16, 18, and 20 with entries 3, 5, 7, 9, 11, 13, 15, 17, and 19). In addition, faster reaction times were always observed. Chromone epoxides **4**, **6**, and **8** were obtained in satisfactory yields in 2 h. The new cromone products **4** and **6** were fully characterized by ^{1}H NMR, ^{13}C NMR, IR spectra and GC–MS while **8** was found to be unstable.[3b] After usual work-up with diethyl ether, the reaction mixture could not be purified by chromatography without decomposition of the epoxide. However, ^{1}H NMR analysis of the crude reaction mixture (singlet at 3.64 ppm) confirmed the presence of the epoxide ring[3b] as well as also the GC–MS fragmentation. Isoflavone epoxides **10**, **12**, **14** and chalcone epoxides **16**, **18** and **20** were obtained in satisfactory yields. All products were fully characterized by NMR, IR, and GC–MS (Section 4).

3. Conclusions

We have developed a simple and efficient procedure for the epoxidation of natural compounds containing the α,β-enone moiety in [bmim]BF_4. The method merits attention due to the simplicity of the experimental procedure, the reduced waste production and the high yields in short reaction time.

4. Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. Chromones **1**, **3**, **5**, **7** and chalcones **15**, **17**, **19** are commercially available (Aldrich) and were used as purchased. Isoflavones **9**, **11** and **13** were synthesized according to literature.[26] Acetone and dichloromethane, ACS reagent grade solvents, were redistilled and dried according to standard procedures. Preparation of [bmim]BF_4 was carried out according to Ref. 27. Thin layer chromatography was carried out using Merck platen Kieselgel 60 F254. Reaction products were purified by flash chromatography by using Merck silica gel 60, 230–400 (eluents: hexane/ethyl acetate, 9:1 or 8:2). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using NaCl paltes. NMR spectra were recorded on a Bruker (200 MHz) spectrometer and are reported in δ values. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. Elementary analyses were performed by a Carlo Erba 1106 Analyser.

4.1. General procedure for the oxidation of chromone and flavonoid derivatives with H_2O_2/NaOH in [bmim]BF_4

The substrate (1.0 mmol) was solubilized in [bmim]BF_4 (1 mL). Then, hydrogen peroxide (35% aqueous solution, 3.0 mmol) and NaOH power (2.0 mmol) were added. Reactions were monitored by thin layer chromatography and by gas-chromatography. Products were extracted with diethyl ether, the organic layer was evaporated under vacuum and the mixture was purified by flash-chromatography.

4.1.1. Chromone epoxide (1). Yellow solid, mp 64–66 °C (lit.[3b] 65–66 °C). Found: C, 66.65; H, 3.73; O, 29.62. $C_9H_6O_3$ requires C, 66.67; H, 3.73; O, 29.60%; ν_{max} (KBr): 3052, 1682; δ_H ($CDCl_3$, 200 MHz): 7.87 (1H, dd, J_1=7.9 Hz, J_2=1.8 Hz, Ph), 7.59–7.50 (1H, m, Ph), 7.18–7.02 (2H, m, Ph), 5.72 (1H, d, J=2.9 Hz, –COC*H*OCH–), 3.70 (1H, d, J=2.9 Hz, –COCHOC*H*–); δ_C ($CDCl_3$, 50 MHz): 188.1, 155.4, 136.3, 127.1, 123.4, 119.8, 118.0, 77.2, 55.3; *m*/*z* (EI) 162 (M^+, 51.1%).

4.1.2. 6-Chloro chromone epoxide (4). Yellow solid, mp 92–94 °C. Found: C, 54.98; H, 2.57; O, 24.40; Cl, 18.05. $C_9H_5O_3Cl$ requires C, 54.99; H, 2.56; O, 24.42; Cl, 18.03%; ν_{max} (KBr): 3049, 1691; δ_H ($CDCl_3$, 200 MHz): 7.85 (1H, d, J=2.6 Hz, Ph), 7.53–7.46 (1H, m, Ph), 7.03 (1H, d, J=8.8 Hz, Ph), 5.68 (1H, d, J=2.8 Hz, –COC*H*OCH–), 3.71 (1H, d, J=2.4 Hz, –COCHOC*H*–), δ_C ($CDCl_3$, 50 MHz): 186.9, 153.8, 136.1, 129.0, 125.6, 120.2, 119.7, 77.4, 55.0; *m*/*z* (EI) 198 (M^++2, 17.0%).

4.1.3. 6-Methyl chromone epoxide (6). Yellow solid, mp 80–82 °C. Found: C, 68.21; H, 4.56; O, 27.23. $C_{10}H_8O_3$ requires C, 68.19; H, 4.57, O, 27.24%; ν_{max} (KBr): 3055, 1679; δ_H ($CDCl_3$, 200 MHz): 7.67 (1H, d, J=1.6 Hz, Ph), 7.38–7.33 (1H, m, Ph), 6.95 (1H, d, J=8.4 Hz, Ph), 5.64 (1H, d, J=2.4 Hz, –COC*H*OCH–), 3.67 (1H, d, J=2.5 Hz, –COCHOC*H*–), 2.31 (3H, s, *Me*); δ_C ($CDCl_3$, 50 MHz): 188.3, 153.5, 138.1, 133.0, 126.7, 119.4, 117.7, 77.2, 55.3, 20.4; *m*/*z* (EI) 177 (M^+, 6.7%).

4.1.4. Isoflavone (9). White solid, mp 129–131 °C (lit.[26] 131–132 °C). Found: C, 81.10; H, 4.53; O, 14.37. $C_{15}H_{10}O_2$ requires C, 81.07; H, 4.53; O, 14.40%; ν_{max} (KBr): 1675, 1638, 1567, 1465; δ_H ($CDCl_3$, 200 MHz): 8.30 (1H, dd, J_1=7.9 Hz, J_2=1.6 Hz, Ph); 7.99 (1H, s, =C*H*), 7.70–7.36 (8H, m, Ph); δ_C ($CDCl_3$, 50 MHz): 176.1, 156.1,

153.0, 136.0, 133.7, 133.5, 131.7, 128.8, 128.4, 128.1, 127.7, 127.1, 126.3, 125.1, 117.9; *m/z* (EI) 222 (M^+, 49.8%).

4.1.5. Isoflavone epoxide (10). Colourless oil. Found: C, 75.60; H, 4.24; O, 20.16. $C_{15}H_{10}O_3$ requires C, 75.62; H, 4.23; O, 20.15%; ν_{max} (KBr): 3043, 1683; δ_H ($CDCl_3$, 200 MHz): 8.01 (1H, dd, J_1=7.9 Hz, J_2=1.7 Hz, Ph), 7.64–7.38 (6H, m, Ph), 7.23–7.08 (2H, m, Ph), 5.51 (1H, s, –OC*H*O); δ_C ($CDCl_3$, 50 MHz): 187.4, 155.0, 136.1, 130.4, 129.0, 128.4, 128.3, 127.7, 127.1, 127.0, 123.3, 120.0, 117.8, 82.9, 63.0; *m/z* (EI) 238 (M^+, 1.0%).

4.1.6. 6-Methoxyisoflavone (11). Yellow solid, mp 137–139 °C. Found: C, 76.21; H, 4.78; O, 19.01. $C_{16}H_{12}O_3$ requires C, 76.18; H, 4.79; O, 19.03%; ν_{max} (KBr): 1670, 1640, 1440; δ_H ($CDCl_3$, 200 MHz): 7.99 (1H, s, =C*H*), 7.65 (1H, d, *J*=3.0 Hz, Ph), 7.57 (2H, dd, *J*=8.2 Hz, Ph), 7.47–7.39 (4H, m, Ph), 7.25 (1H, dd, J_1=9.1 Hz, J_2=3.2 Hz, Ph), 3.89 (3H, s, O*Me*); δ_C ($CDCl_3$, 50 MHz): 175.9, 157.0, 152.9, 151.0, 132.0, 128.9, 128.7, 128.6, 128.4, 128.1, 125.2, 124.5, 123.6, 119.4, 105.4, 55.7; *m/z* (EI) 252 (M^+, 80.7%).

4.1.7. 6-Methoxyisoflavone epoxide (12). Colourless oil. Found: C, 71.60; H, 4.50; O, 23.90. $C_{16}H_{12}O_4$ requires C, 71.63; H, 4.51; O, 23.86%; ν_{max} (KBr) 3020, 1670;?δ_H ($CDCl_3$, 200 MHz): 7.44–7.38 (7H, m, Ph), 7.03 (1H, d, *J*=9.1 Hz, Ph), 5.48 (1H, s, –OC*H*O), 3.81 (3H, s, O*Me*); δ_C ($CDCl_3$, 50 MHz): 187.4, 155.4, 149.4, 130.6, 128.9, 128.7, 128.3, 127.2, 126.1, 125.0, 120.6, 119.1, 108.2, 82.9, 62.8, 55.8; *m/z* (EI) 268 (M^+, 1.7%).

4.1.8. 7-Methoxyisoflavone (13). White solid, mp 140–142 °C. Found: C, 76.15; H, 4.79; O, 19.06. $C_{16}H_{12}O_3$ requires C, 76.18; H, 4.79; O, 19.03%; ν_{max} (KBr): 1680, 1634, 1441; δ_H ($CDCl_3$, 200 MHz): 8.20 (1H, d, *J*=8.9 Hz, Ph), 7.92 (1H, s, =C*H*); 7.56–7.52 (2H, m, Ph), 7.46–7.35 (3H, m, Ph), 6.98 (1H, dd, J_1=8.9 Hz, J_2=2.4 Hz, Ph), 6.84 (1H, d, *J*=2.36 Hz), 3.89 (3H, s, O*Me*); δ_C ($CDCl_3$, 50 MHz): 190.5, 175.5, 164.0, 157.9, 152.5, 131.9, 128.9, 128.7, 128.4, 128.0, 127.8, 125.2, 118.4, 114.5, 100.1, 55.8; *m/z* (EI) 252 (M^+, 69.8%).

4.1.9. 7-Methoxyisoflavone epoxide (14). White solid, mp 121–123 °C (lit.[3b] 123–124 °C). Found: C, 71.62; H, 4.50; O, 23.88. $C_{16}H_{12}O_4$ requires C, 71.63; H, 4.51; O, 23.86%; ν_{max} (KBr) 3005, 1689; δ_H ($CDCl_3$, 200 MHz): 7.94 (1H, d, *J*=8.8 Hz, Ph), 7.48–7.37 (5H, m, Ph), 6.74 (1H, dd, *J*=11.2 Hz, Ph), 6.53 (1H, d, *J*=2.3 Hz, Ph), 5.47 (1H, s, –OC*H*O), 3.86 (3H, s, O*Me*); δ_C ($CDCl_3$, 50 MHz): 186.0, 166.1, 157.1, 130.7, 129.4, 128.9, 128.7, 128.4, 128.3, 127.1, 113.5, 111.6, 101.0, 83.2, 62.3, 55.7; *m/z* (EI) 268 (M^+, 2.5%).

4.1.10. Chalcone epoxide (16). White solid, mp 88–90 °C (lit.[5a] 88–89 °C).

4.1.11. 4′-Methoxychalcone epoxide (18). White solid, mp 74–76 °C (lit.[5a] 75–76 °C).

4.1.12. 4-Methoxychalcone epoxide (20). White solid, mp 82–84 °C (lit.[5a] 82–83 °C).

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