

Note

Reactivity pattern of *in situ* generated tetraethylammonium superoxide with some flavonoids

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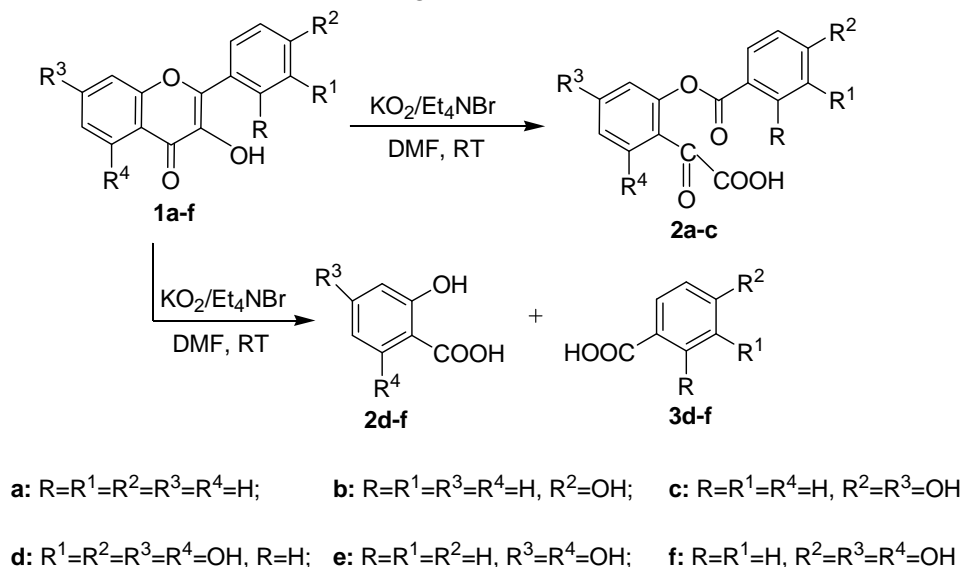
A number of flavonoids have been allowed to react under the mild reaction conditions of tetraethylammonium superoxide in dry dimethylformamide at room temperature. As an outcome, 3-hydroxyflavones **1a-c** undergo oxidative ring cleavage to afford 2-benzoyloxyphenylglyoxylic acids **2a-c**, whereas the substrates **1d-f** result in the formation of acids **2d-f** along with **3d-f**.

Keywords: Tetraethylammonium superoxide, phase transfer catalyst, flavonoids, hydrophobic conditions

Flavonoids constitute an important class of naturally occurring phenolic compounds ubiquitously distributed in the plant kingdom^{1,2}. They are essential components of the human diet and exhibit potent antioxidant activity due to their ability to scavenge free radicals³⁻⁶. Due to the efficient scavenging activity of natural and synthetic flavonoids, the study of the reactivity pattern of superoxide ion, $\text{O}_2^{\bullet-}$, with phenolic compounds is valuable for a clearer understanding of

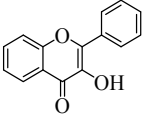
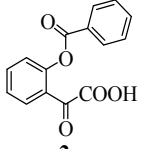
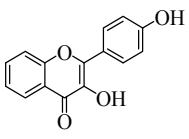
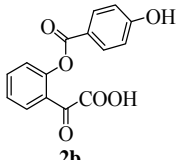
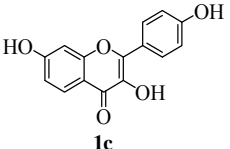
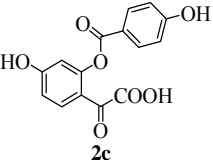
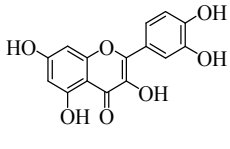
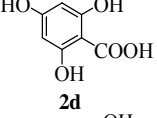
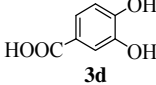
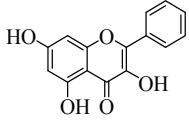
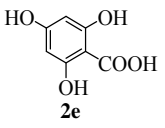

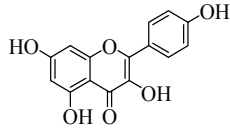
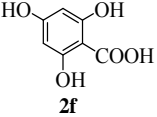
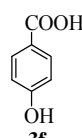
the biological mechanism⁷⁻¹⁴. Superoxide ion is of much current interest due to its biological implications and as a species of relatively unexplored chemical reactivity¹⁵⁻¹⁷. In view of the above, and as a part of the ongoing program on superoxide research¹⁸⁻²¹, the reaction of tetraethylammonium superoxide (Et_4NO_2) with some flavonoids has been undertaken. The substrates, 3-hydroxyflavone **1a**, 3,4'-dihydroxyflavone **1b**, 3,4',7-trihydroxyflavone **1c**, 3,3',4',5,7-pentahydroxyflavone (quercetin) **1d**, 3,5,7-trihydroxyflavone (galangin) **1e** and 3,4',5,7-tetrahydroxyflavone (kaemferol) **1f**, were made to react with Et_4NO_2 , generated *in situ* by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide in DMF at RT under inert atmosphere (**Scheme I**).

The reaction of Et_4NO_2 with 3-hydroxyflavones **1a-c** results in an oxidative ring opening to provide 2-benzoyloxyphenyl-glyoxylic acids **2a-c**, whereas the substrates **1d-f** undergo oxidative ring rupture to yield the acids **2d-f** along with **3d-f**. The results of the investigation are given in **Table I**. The reactions were conducted by employing a 4.0-fold molar excess of KO_2 and 2.0-fold molar excess of Et_4NBr with respect to the substrate **1**. After completion, the reaction mixture was quenched and worked-up to afford the products, which showed physical and spectroscopic data consistent with their structures.



Scheme I

Table I— Reaction of in situ generated Et₄NO₂ with different flavonoids **1a-f**

Substrate 1	Product (s) 2	Reaction Time (hr)	Yield* (%)
 1a	 2a	10	83
 1b	 2b	11.5	72
 1c	 2c	14	51
 1d	 2d	18	21
	 3d		17
 1e	 2e	16.5	27
	 3e		24
 1f	 2f	15	22
	 3f		19

*Isolated mass yield based on **1**.**Experimental Section**

Melting points were measured in open capillaries and are uncorrected. IR spectra were recorded on a Jasco FTIR-5300 spectrometer. NMR spectra were run on a Jeol FX-90Q FT-NMR spectrometer and the chemical shifts are expressed in δ (ppm), relative to

TMS as internal standard. Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, Germany and were used as received. Dry DMF from Aldrich, USA was stored over molecular sieves (4Å) prior to use. The substrates **1a** and **1e** were Aldrich products, whereas **1d** and **1f** were pro-

cured from Sigma. The other substrates **1b** and **1c** were prepared by literature method⁸.

General procedure for the reaction of *in situ* generated Et₄NO₂ with flavonoids **1a-f**:

Potassium superoxide (0.568 g, 0.008 mole) and Et₄NBr (0.64 g, 0.004 mole) were weighed under nitrogen atmosphere using atmosbag and were transferred into a two-necked round bottom flask containing dry DMF (25 mL) and fitted with a magnetic stirrer, a dropping funnel, an inlet nitrogen bubbler and a Liebig condenser provided with a calcium chloride guard tube. The reaction mixture was stirred magnetically for ~15 min and to it was then admitted the substrate **1** (0.002 mole). The stirring was continued for 10-18 hr at RT. After the reaction was over as concluded from the TLC, the mixture was successively treated with saturated aq. NaCl (25 mL) and saturated aq. NaHCO₃ (15 mL). It was then extracted with diethyl ether (3 × 20 mL). Aqueous layer was acidified with hydrochloric acid and extracted with diethyl ether (3 × 30 mL). The organic extract was dried over anhyd. Na₂SO₄, filtered and concentrated to yield the product(s). The mixture of the acidic products **2d/3d**, **2e/3e** and **2f/3f** were separated by column chromatography (silica gel) using petroleum ether-ethyl acetate (8.5:1.5) as eluant. All the products were purified by recrystallization and identified on the basis of their physico-chemical and spectral data.

Physical and spectral data of the products:

2a: m.p. 148°C (Lit.¹¹ 149°C); IR (KBr): 3240, 1718, 1695, 1678 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 7.32-7.64 (m, 7H, ArH), 8.10 (m, 2H, ArH), 11.1 (s, 1H, COOH). Anal. C₁₅H₁₀O₅ (Mol. wt. 270) Calcd. C, 66.66; H, 3.71. Found C, 66.52; H, 3.63%.

2b: m.p. 153°C (Lit.¹¹ 155°C). IR (KBr): 3300, 1715, 1698, 1678 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 4.91 (s, 1H, OH), 6.80 (d, 2H, ArH), 7.42-7.96 (m, 6H, ArH), 11.0 (s, 1H, COOH). Anal. C₁₅H₁₀O₆ (Mol. wt. 286) Calcd. C, 62.93; H, 3.49. Found C, 62.85; H, 3.51%.

2c: m.p. 151°C (Lit.¹¹ 152°C); IR (KBr): 3350, 1673, 1645 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 5.0 (s, 2H, OH), 6.88 (d, 2H, ArH), 7.34-7.98 (m, 5H, ArH), 11.0 (s, 1H, COOH). Anal. C₁₅H₁₀O₇ (Mol. wt. 302) Calcd. C, 66.17; H, 3.67. Found C, 66.21; H, 3.59%.

2d/2e/2f: m.p. 186°C (Lit.²² 188°C); IR (KBr): 3450-2400, 1659, 1630, 1456, 1413, 1210, 1190,

840 cm⁻¹; ¹H NMR: δ 5.1 (s, 3H, OH), 5.92 (s, 2H, ArH), 11.0 (s, 1H, COOH). Anal. C₇H₆O₅ (Mol. wt. 170) Calcd. C, 49.41; H, 3.52. Found C, 49.35; H, 3.48%.

3d: m.p. 200-02°C (Lit.²² 199°C); IR (KBr): 3300-2450, 1676, 1602, 1443, 1297, 1192, 1120 cm⁻¹; ¹H NMR (DMSO-*d*₆ + CDCl₃): δ 5.0 (s, 2H, OH), 6.80 (d, 1H, ArH), 7.42-7.56 (m, 2H, ArH), 11.08 (s, 1H, COOH). Anal. C₇H₆O₄ (Mol. wt. 154) Calcd. C, 54.54; H, 3.89. Found C, 54.49; H, 3.83%.

3e: m.p. 121°C (Lit.²² 122°C); IR (KBr): 3100-2450, 1690, 1580, 1455, 1424, 1325, 1294, 936, 705 cm⁻¹; ¹H NMR (CDCl₃): δ 7.16-8.36 (m, 5H, ArH), 12.16 (s, 1H, COOH). Anal. C₇H₆O₂ (Mol. wt. 122) Calcd. C, 69.85; H, 4.91. Found C, 69.83; H, 4.88%.

3f: m.p. 212°C (Lit.²² 213-14°C); IR (KBr): 3500-2200, 1675, 1595, 1320, 1295, 1245, 1169, 855, 619 cm⁻¹; ¹H NMR (DMSO-*d*₆ + CDCl₃): δ 5.0 (s, 1H, OH), 6.92 (d, 2H, ArH), 8.0 (d, 2H, ArH), 11.0 (s, 1H, COOH). Anal. C₇H₆O₃ (Mol. wt. 138) Calcd. C, 60.86; H, 4.34. Found C, 60.84; H, 4.31%.

Acknowledgement

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References

- 1 Seyoum A, Asres K & El-Fiky K, *Phytochemistry*, 67, **2006**, 2058.
- 2 Cotellet, N, *Curr Top Med Chem*, 1, **2001**, 569.
- 3 Jovanovic S V, Steenken S, Tosic M, Marjanovic B & Simic M, *J Am Chem Soc*, 116, **1994**, 4846.
- 4 Griffiths L A, in *Flavonoids: Advances in Research*, edited by J B Harbone and T J Mabry, (Chapman and Hall, London), **1982**, pp 681-718.
- 5 Bors W, Heller W, Michel C & Saran M, in *Methods in Enzymology*, Vol 186 (Academic Press, New York), **1990**, pp 343-355.
- 6 Havsteen B H, *Pharmacol Therap*, 96, **2002**, 67.
- 7 Matsuura T, *Tetrahedron*, 33, **1977**, 2869.
- 8 Nishinaga A, Tojo T, Tomita H & Matsuura T, *J Chem Soc, Perkin Trans 1*, **1979**, 2511.
- 9 Nishinaga A, Numada N & Maruyama K, *Tetrahedron Lett*, 30, **1989**, 2257.
- 10 Cotellet N, Bernier J L, Henichart J P, Catteau J P, Gaydec E & Wallet J C, *Free Radicals Biol Med*, 13, **1992**, 211.
- 11 El-Sukkary M M A & Speier G, *J Chem Soc, Chem Commun*, **1981**, 745.
- 12 Kano K, Mabuchi T, Uno B, Esaka Y, Tanaka T & Iinuma M, *J Chem Soc, Chem Commun*, **1994**, 593.
- 13 Tournaire C, Hocquaux M, Beck I, Oliveros E & Maurette M-T, *Tetrahedron*, 50, **1994**, 9303.

- 14 Bodini M E, Copia G, Tapia R, Leighton F & Herrera L, *Polyhedron*, 18, **1999**, 2233.
- 15 Afanasev I B, *Superoxide Ion: Chemistry and Biological Implications*, Vols 1 and 2 (CRC Press, Boca Raton), **1991**.
- 16 Riley D P, *Chem Rev*, 99, **1999**, 2573.
- 17 Sawyer D T & Valentine J S, *Acc Chem Res*, 14, **1981**, 29.
- 18 Singh S & Singh K N, *Synth Commun*, 35, **2005**, 2597.
- 19 Singh S, Verma M & Singh K N, *Synth Commun*, 34, **2004**, 4471.
- 20 Singh K N & Kumar R, *Indian J Chem*, 44B, **2005**, 381.
- 21 Shukla A K, Verma M & Singh K N, *Indian J Chem*, 43B, **2004**, 1748.
- 22 *Dictionary of Organic Compounds*, 4th Edn, Vols 1, 2, 3 and 5 (Eyre and Spottiswoode Publishers Ltd, London), **1965**, p 344, 1056, 1652 and 3134.