Pergamon

Tetrahedron Letters 42 (2001) 5401–5404

TETRAHEDRON LETTERS

A new and efficient Baeyer–Villiger rearrangement of flavanone derivatives by the methyltrioxorhenium/H_2O_2 catalytic system

Roberta Bernini,[a,*] Enrico Mincione,[a] Manuela Cortese,[a] Giovanni Aliotta,[b] Anna Oliva[b] and Raffaele Saladino[a,*]

[a]*Dipartimento A.B.A.C., Università della Tuscia, Via S. Camillo de Lellis, 01100 Viterbo, Italy*
[b]*Dipartimento di Scienze della Vita, II[a] Università di Napoli, Via Vivaldi 43, 81100 Caserta, Italy*

Received 10 May 2001; accepted 6 June 2001

Abstract—The catalytic Baeyer–Villiger rearrangement of flavanones is described by the use of the homogeneous methyltrioxorhenium (MTO)/H_2O_2 system. In these experimental conditions 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-ones and previously not reported *para*-quinone derivatives have been obtained in mild experimental conditions from acceptable to good yields.

Flavonoids are polyphenolic compounds ubiquitous in plants foods (fruits, vegetables) and they are important components of the human diet.[1] In particular, flavanones (2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one derivatives) are prominent components of *Citrus* fruits and they are present in solid wastes and residues obtained during their industrial processing.[2] These compounds have been long recognized to possess hypolipidemic, antihypertensive, diuretic and anti-inflammatory activities,[3] as well as antioxidant,[4] antitumoral,[5] and antiproliferative properties.[6] Oxidative transformations of flavanones have been reported in the literature to synthesize new derivatives with high biological activity and low toxicity. Among them, much attention has been focused on the chemistry of the *C*-ring, including the conversion of flavanones into flavones,[7] and isoflavanone derivatives.[8] On the other hand, only few data are reported about methods of expanding the *C*-ring, with the exception of the synthesis of benzoxazepine derivatives by Schmidt rearrangement,[9] and benzodioxepin-2-one derivatives by Baeyer–Villiger rearrangement.[10] In the latter case a large excess of *meta*-chloroperbenzoic acid (*m*-CPBA), that cannot be stored in pure form because of the explosion hazards, are required. A catalytic Baeyer–Villiger rearrangement of flavanones, by use of transition metal compounds for the activation of the environmentally friendly hydrogen peroxide,[11] can be easily predicted as a target for a large scale industrial preparation of biologically important benzodiazepine analogues.[12] Methyltrioxorhenium (MTO)[13] is a useful catalyst for both electrophilic[14] and nucleophilic[15] oxidations with H_2O_2, including the oxidation of natural products such as nucleic acid and cardanol derivatives.[16] Herein we report the first described catalytic Baeyer–Villiger rearrangement of flavanones. The oxidizing system used was H_2O_2 in the presence of catalytic amounts of MTO. The benzodioxepin-2-one derivatives obtained were also tested for the inhibition of radish and wheat germination. Flavanone derivatives **1**–**5** (1 mmol) were allowed to react with H_2O_2 (2.0–6.0 mmol; 35% aq. solution) in acetic acid/methanol (ratio 9:1; 5 ml) in the presence of catalytic amounts of MTO (2 mol%) at 25–80°C.[17] In the absence of MTO less than 2% conversion of substrates takes place under otherwise identical conditions. Treatment of flavanone **1**, 5–methoxyflavanone **2**, and 7-methoxyflavanone **3**, afforded the corresponding 1,5-benzodioxepin-2-ones **6**–**8** in high yields and conversions (Scheme 1, Table 1).

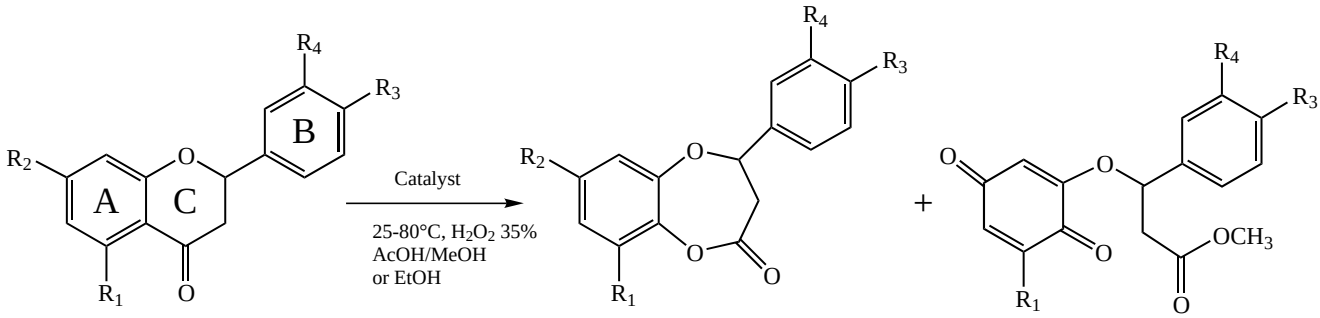
The presence of the methoxyl group on the C-5 or C-7 positions of the *A*-aromatic ring appear to improve both yields and conversions with respect to unsubstituted flavanone **1** (entries 2–3, Table 1).

Noteworthy, in the case of **3** a demethoxylation/acetylation process was also operative at the C-7 position. In compounds **6**–**8** the change in carbonyl functionality from ketone to lactone was reflected in a significant shift (ca. 50 cm^{-1}) of the IR carbonyl absorption band

Keywords: Baeyer–Villiger reactions; lactonisation; flavanones; flavonoids.

* Corresponding authors.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01005-X



1: $R_1=R_2=R_3=R_4=H$
2: $R_1=OCH_3$; $R_2=R_3=R_4=H$
3: $R_2=OCH_3$; $R_1=R_3=R_4=H$
4: $R_1=R_2=R_3=OCH_3$; $R_4=H$
5: $R_1=R_2=R_3=R_4=OCH_3$

6: $R_1=R_2=R_3=R_4=H$
7: $R_1=OCH_3$; $R_2=R_3=R_4=H$
8: $R_2=OCOCH_3$; $R_1=R_3=R_4=H$
11: $R_1=R_2=R_3=R_4=OCH_3$

9: $R_1=R_3=OCH_3$; $R_4=H$
10: $R_1= R_3=R_4=OCH_3$

Scheme 1.

Table 1.

Entry	Substrate	T (°C)	H_2O_2 (equiv.)	Product (s)	Yield (%)[a]	Conversion[a] (%)
1	**1**	80	6.0	6	63	75
2	**2**	25	2.0	7	>98	>98
3	**3**	80	6.0	8	95	>98
4	**2**	25	5.0	7	92	>98
5	**4**	80	6.0	9	>98	>98
6	**5**	25	2.0	10	93	>98
7	**5**	25	2.0	10 (11)	18 (64)	>98

[a] Conversions and yields calculated after purification of the reaction mixture.

to higher frequencies. Products **6**–**8** were assigned to be 1,5-benzodioxepin-5-ones rather than the isomeric 1,4-benzodioxepin-5-ones (not shown) by ^1H and ^{13}C NMR spectroscopy, in accord with data previously reported in the literature.[10,18,19] Adam and coworkers reported that in MTO mediated oxidation of phenols and methoxybenzenes[20] the actual oxidant was the η^2-diperoxo rhenium complex[21] without any participation of in situ freshly generated peracetic acid. On the basis of these data, it is reasonable to suggest that the MTO catalyzed Baeyer–Villiger rearrangement of flavanones **1**–**3** proceeds through the formation of an intermediate peroxometallacyclic species[11] for which spectroscopic evidences have been recovered in the case of cyclic ketones.[16] This hypothesis is further supported by a peracetic acid free control experiment in which 5-methoxyflavanone **2** (1 mmol) was treated with H_2O_2 (4.0 mmol; 35% aq. solution) in ethanol (5 ml) in the presence of MTO (2 mol%) and HBF_4 (1 ml; 54% diethyl ether solution) at 25°C to give **7** in good yield (Table 1, entry 4). When methylated naringenin **4** and hesperetin **5** were treated with the MTO/H_2O_2 system under similar experimental conditions the *para*-quinones **9** and **10** were obtained as the only recovered products in high yields (Scheme 1, Table 1, entries 5–6).[22] In accord with results previously described,[10] the first formed lactones might be opened at the *C*-ring via a solvolytic transesterification, to give the corresponding phenols (not recovered in our experimental conditions). These intermediates might be further oxidized with concomitant C-7 demethoxylation to **9** and **10**. The acidic character of MTO may be, at least in part, responsible for the ring-opening of the lactone moiety. For example, in MTO epoxidations of alkenes the oxiranyl ring is opened quite readily to the diol.[23] To avoid such detrimental side reaction pyridine and pyrazole have been proposed as Lewis acid buffers.[24] Thus, when the oxidation of **8** was performed in the presence of pyridinium acetate (ratio substrate:salt = 1:2), lactone **11** was recovered as the main product and the *para*-quinone **10** as by product (Table 1, entry 7). Compounds **1**–**10**, were evaluated for the inhibition of radish (*Raphanus sativus* L.) and wheat (*Triticum durum*) germination, by in vitro dose–response assays.[25] Compounds **5** and **9** were the most active on wheat germination with a ID_{50} (amount of compound that cause 50% inhibition) of 14 and 56 μM, respectively. Furthermore, **10** was active against radish germination at low concentration ($ID_{50}=3$ μM). This level of activities is comparable to many commercial herbicide, and concentrations greater than 1×10^{-4} M are considered beyond the range of interest for agronomic purposes.[26]

Supplementary material

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz spectrometer in $CDCl_3$ as the solvent.

All chemical shifts are reported in parts per million (ppm) against internal tetramethylsilane. Coupling constants J_{HH} were measured in Hz. IR spectra were recorded on a Perkin–Elmer Paragon 500 FT-IR spectrometer in $CHCl_3$ solution and positions are reported in cm^{-1}. Elemental analyses were performed by a Carlo Erba 1106 analyzer.

2,3-Dihydro-5,7-dimethoxy-2-(4′-methoxyphenyl)4H-1-Benzopyran-4-one (Methylated naringenin) (4). IR (ν_{max}): 3036, 2840, 1670, 1608, 1458, 1254. ^{1}H NMR: 7.27 (d, J=8.6 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 5.99 (dd, J=2.3, 9.3 Hz, 2H), 5.22 (dd, J=3.0, 12.9 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.69 (s, 3H), 2.77 (dd, J=12.9, 16.6 Hz, 2H). ^{13}C NMR: 190.3, 166.3, 165.2, 162.3, 159.9, 130.8, 127.7, 114.1, 105.7, 93.7, 93.0, 78.9, 55.9, 55.6, 55.3, 45.2. Anal. calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found C, 68.68; H, 5.71.

2,3-Dihydro-5,7-dimethoxy-2-(3′,4′-dimethoxyphenyl)4H-1-Benzopyran-4-one (Methylated hesperetin) (5). IR (ν_{max}): 3040, 2840, 1670, 1465, 1264. ^{1}H NMR: 6.99–6.84 (m, 3H), 6.10 (dd, J=2.2, 12.4 Hz, 1H), 5.32 (dd, J=3.0, 13.0 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 6H), 3.79 (s, 3H), 2.89 (dd, J=13.0, 16.5 Hz, 2H). ^{13}C NMR: 188.8, 165.6, 164.6, 161.9, 149.1, 148.9, 131.0, 118.5, 110.9, 109.2, 105.6, 93.5, 92.8, 78.8, 55.8, 55.7, 55.2, 45.3. Anal. calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.86; O, 27.87. Found C, 66.20; H, 5.86; O, 27.86

3,4-Dihydro-5-methoxy-4-phenyl-2H-1,5-Benzodioxepin-2-one (7). IR (ν_{max}): 3038, 2840, 1764, 1602, 1474, 1252. ^{1}H NMR: 7.36 (s, 5H), 7.06 (t, J=8.4 Hz, 1H), 6.79 (dd, J=1.3, 8.4 Hz, 1H), 6.61 (dd, J=1.3, 8.4 Hz, 1H), 5.69 (t, J=6.8 Hz, 1H), 3.87 (s, 3H), 3.11 (dd, J=1.1, 6.1 Hz, 2H). ^{13}C NMR: 167.0, 150.3, 146.1, 138.5, 135.2, 128.9, 128.8, 128.6, 126.1, 125.6, 115.8, 109.1, 83.5, 56.2, 38.3. Anal. calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; O, 23.68. Found C, 71.07; H, 5.22; O, 23.60.

3,4-Dihydro-7-acethoxy-4-phenyl-2H-1,5-Benzodioxepin-2-one (8). IR (ν_{max}): 3040, 2838, 1760, 1600, 1475, 1250. ^{1}H NMR: 7.55–7.24 (m, 8H), 6.14 (dd, J=5.0, 8.9 Hz, 1H), 2.90 (dd, J=8.9, 16.2 Hz, 2H), 2.08 (s, 3H). ^{13}C NMR: 169.9, 167.0, 149.9, 145.7, 145.0, 136.1, 128.8, 127.7, 126.1, 125.9, 120.6, 113.9, 111.3, 83.3, 38.4, 21.0. Anal. calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73; O, 26.82. Found C, 68.41; H, 4.73; O, 26.82.

***para*-Benzoquinone derivative (9).** IR (ν_{max}): 3034, 2840, 1786, 1668, 1613, 1461, 1254. ^{1}H NMR: 6.99 (d, J=2.2 Hz, 1H), 6.76 (d, J=2.2 Hz, 1H), 5.33 (d, J=1.9 Hz, 1H), 4.84 (d, J=1.9 Hz, 1H), 4.03 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.49 (s, 3H), 3.02 (dd, J=11.7, 17.2 Hz, 1H). ^{13}C NMR: 193.2, 175.4, 174.5, 164.6, 159.2, 128.8, 128.4, 113.5, 95.7, 93.9, 56.4, 55.8, 55.1, 51.5, 32.8. Anal. calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24; O, 32.34. Found C, 62.40; H, 5.24; O, 32.31.

***para*-Benzoquinone derivative (10)**. IR (ν_{max}): 3035, 2840, 1794, 1669, 1445, 1264. ^{1}H NMR: 6.75–6.55 (m, 3H), 5.36 (d, J=2.0 Hz, 1H), 4.86 (d, J=2.0 Hz, 1H), 4.03 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.51 (s, 3H), 3.04 (dd, 1H, J=12.0, 17.2 Hz). ^{13}C NMR: 193.2, 175.2, 174.6, 164.8, 148.7, 148.5, 126.1, 119.0, 111.0, 110.7, 95.9, 94.0, 56.3, 56.2, 55.8, 51.9, 32.7. Anal. calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36; O, 34.01. Found C, 60.61; H, 5.36; O, 34.0.

3,4-Dihydro-5,7-dimethoxy-4-(3′,4′-dimethoxyphenyl)2H-1,5-Benzodioxepin-2-one (11). IR (ν_{max}): 3040, 2850, 1760, 1604, 1475, 1250. ^{1}H NMR: 6.99–6.84 (m, 3H), 6.12 (dd, 2H, J=2.1, 12.0 Hz), 5.70 (t, J=6.8 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 6H), 3.76 (s, 3H), 3.12 (dd, J=1.7, 5.9 Hz, 2H); ^{13}C NMR: 168.3, 156.6, 151.4, 150.2, 148.1, 137.9, 121.8, 117.7, 107.7, 99.0, 97.6, 83.4, 56.3, 55.8, 55.62, 55.5, 38.2. Anal. calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59; O, 3.08. Found C, 63.30; H, 5.58; O, 3.04.

Acknowledgements

We are grateful to Consorzio I.N.C.A., Venice who has supported this research with a grant. A grant from MURST 5% is also acknowledged.

References

1. Singleton, V. L. *Adv. in Food Res.* **1981**, *27*, 149–242.
2. Satoru, K.; Yasuhiko, T.; Eriko, K.; Kazunori, P.; Masamochi, Y. *J. Agr. Food Chem.* **1999**, *47*, 3565–3571.
3. Galati, E. M.; Trovato, A.; Kirjavainen, S.; Forestieri, A. M.; Rossetto, A.; Monforte, M. T *Il Farmaco* **1996**, *51*, 219–221.
4. (a) Pietta, P. *J. Nat.Prod.* **2000**, *63*, 1035–1042; (b) Van Acker, F. A. A.; Hageman, J. A.; Haenen, G. R. M. M.; Van der Vijgh, W. J. F.; Bast, A.; Menge, W. M. P. B. *J. Med. Chem.* **2000**, *43*, 3752–3760.
5. Bracke, M. E.; Depypere, H. T.; Botemberg, T.; Van Mack, U. L. *J. Nat. Cancer. Inst.* **1999**, *91*, 354–358.
6. Le Bail, J. C.; Varnat, F.; Nicolas, J. C.; Habrioux, G. *Cancer Lett.* **1998**, *130*, 209–216.
7. (a) Prakash, O.; Pahuja, S.; Moriarty, R. M. *Synth. Commun.* **1990**, *20*, 1417–1422; (b) Khanna, M. S.; Singh, O. V.; Garg, C. P.; Kapoor, R. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2565–2568; (c) Bernini, R.; Mincione, E.; Sanetti, A.; Bovicelli, P.; Lupattelli, P. *Tetrahedron Lett.* **1997**, *38*, 4651–4654.
8. Kinoshita, T.; Ichinose, K.; Sankawa, U. *Tetrahedron Lett.* **1990**, *50*, 7355–7356.
9. Litkei, G.; Patonay, T. *Acta Chim. Hung.* **1983**, *114*, 47.
10. Gelebe, A. C.; Kaye, P. T.; Liddell, J. R. *Synth. Commun.* **1991**, *21*, 2263–2268.
11. Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198–1209.
12. Medina, J. H.; Viola, H.; Wolfman, C.; Marder, M.; Wasowski, C.; Calvo, D.; Paladini, A. C. *Neurochem. Res.* **1997**, *22*, 419–425.
13. Romao, C. C.; Kuhn, F. E.; Hermann, W. A. *Chem. Rev.* **1997**, *97*, 3197–3246 and references cited therein.

14. Hermann, W. A.; Fischer, R. W.; Rauch, M. U.; Scherer, W. *J. Mol. Cat.* **1994**, *86*, 243–266.
15. Hermann, W. A.; Fischer, R. W.; Correira, G. D. G. *J. Mol. Cat.* **1994**, *94*, 213.
16. (a) Saladino, R.; Neri, V.; Mincione, E.; Marini, S.; Coletta, M.; Fiorucci, C.; Filippone, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, *4*, 581–586; (b) Saladino, R.; Carlucci, P.; Danti, M. C.; Crestini, C.; Mincione, E. *Tetrahedron* **2000**, *56*, 10031–10037.
17. Flavanone **1** was purchased from Sigma–Aldrich. 5-Methoxyflavanone **2** and 7-methoxyflavanone **3** were furnished from Extrasynthese. Methylated naringenin **4** and hesperitin **5** have been prepared starting from naringenin and hesperetin by treatment with CH_3I in dry DMF at 25°C.
18. Structures of all new compounds were determined by FT-IR, mass spectrometry (EI), and ^1H ^{13}C NMR spectroscopy. All new compounds gave satisfactory (+/− 0.4% of the theoretical values) elemental analyses. Selected data for 3,4-dihydro-4-phenyl-1,5-Benzodioxepin-2-one **6**: Oil; IR (ν_{max}): 3038, 1770. 1602, 1474, 1252. ^1H NMR: 7.55–7.00 (m, 9H, ar-H), 5.71 (t, $J=6.9$, 1H, 4-H), 3.11 (dd, $J=1.8$, 6.0, 2H, 3-H). ^{13}C NMR: 167.2, 146.0, 138.5, 135.5, 128.8, 128.5, 126.0, 125.5, 115.7, 109.0, 83.2, 38.4.
19. Reddy, M. S.; Krupadanam, G. L. D.; Srimannarayana, G. *Org. Prep. Proced. Int.* **1989**, *21*, 221.
20. Adam, W.; Hermann, W. A.; Saha-Möller, C. R.; Shimizu, M. *J. Mol. Cat. A* **1995**, *97*, 15–20.
21. (a) Hermann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem.* **1991**, *103*, 1706; (b) Hermann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1638.
22. The presence of absorption proton signals in the typical region located δ 6.3 and 7.3 in the ^1H NMR spectra as well as the presence of new quaternary absorption carbon signal in the ^{13}C NMR spectra were diagnostic for the quinonoid structures.
23. (a) Al-Ajlouni, A. M.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 3969–3976; (b) Hermann, W. A.; Fischer, R. W.; Rauch, M. U. *J. Mol. Cat. A* **1994**, *86*, 243–266.
24. Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189–6190.
25. Analyses were performed as reported in literature: Weidenhamer, J. D.; Morton, T. C.; Romeo, J. T. *J. Chem. Ecol.* **1987**, *13*, 1481–1491.
26. Dayan, F. E.; Romagni, J. G.; Duke, S. O. *J. Chem. Ecol.* **2000**, *26*, 2079–2094.