Pergamon

Tetrahedron Letters 43 (2002) 5563–5567

TETRAHEDRON LETTERS

Selective halogenation of flavanones

Paolo Bovicelli,[a,*] Roberta Bernini,[b,*] Roberto Antonioletti[a] and Enrico Mincione[b]

[a]*Istituto di Chimica Biomolecolare del CNR, Sezione di Roma, Dipartimento di Chimica, Università "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy*

[b]*Dipartimento A.B.A.C., Università degli Studi della Tuscia, V. S. Camillo de Lellis, 01100 Viterbo, Italy*

Received 22 May 2002; revised 11 June 2002; accepted 13 June 2002

Abstract—A mild, efficient and regioselective method for the selective halogenation of flavonoids is presented. Halogenated flavanones and flavones are considered potential benzodiazepine receptor ligands and with DMD/NaX or oxone/acetone/water/NaX systems they can be synthesised in preparative amounts.

Flavonoids (phenylbenzopyrones) are present in all vascular plants, both free and bound to sugars. They are credited with a number of biological properties, the most usual of them being anti-oxidant, anti-inflammatory and anti-viral ones.[1] In a recent paper, the effects of two flavonoids, viz., apigenin and chrysin, on the central nervous system have been considered. In a previous paper, Medina,[2] pursuing his studies on safer BDZ-receptor ligands, described a series of flavonoids possessing anxiolytic activity and low sedative or myorelaxant effects. Among the most active compounds, a number of halogenated flavones have been reported; in particular, 6-bromoflavone and 6-bromo-3′-nitroflavone showed activities close to or higher than that of diazepam. In order to show these activities, the presence of electro-donating or withdrawing substituents on the aromatic ring of the flavonoids seems to be essential,[3] but derivatives thereof may present a lower affinity toward benzodiazepine receptors. This is indeed what happens in the case of 6,8-dibromochrysin which is as active as chrysin itself, while the bromination of flavone leads to a compound endowed with an enhanced binding affinity and anxiolytic properties.

In the literature, several methods for halogenating aromatic compounds are reported. Direct bromination, e.g. with elemental bromine,[4] is a highly polluting method which, in addition, involves serious difficulties connected with the handling of a highly corrosive agent. Other methods, including NBS-amberlyst,[5] metal-oxo-catalysed $KBr–H_2O_2$,[6] and $KBr–NaBO_3$,[7] suffer from harsh conditions or require complex or laborious work-up. Recently, a method which makes use of LiBr and CAN has been reported,[8] which however only allows monohalogenation of electron-rich aromatic compounds.

The interest in halogenation of flavonoid compounds is witnessed by recent papers one of which reports on an enzymatic halogenation.[9] Although yields are very low, the reaction seems to bear some interest due to the potential bioactivity of the obtained products. Although several halogenated flavanones and flavones are present in nature, to our knowledge no other report about enzymatic halogenations of these compounds seems to have appeared. It is also worth noting that information on the biological activity of halogenated flavonoids is scant due to the difficulty of obtaining the starting materials.

In the last few years we have been searching for an efficient and selective halogenation of activated aromatic compounds by using dimethyldioxirane (DMD), both in isolated form and generated in situ, as an oxidant of halide anions. The reaction proved to be subject to acid catalysis and thus it can be performed either in halohydric media or in acid in the presence of halide ions. We found recently that DMD generated in situ is indeed very efficient, the decomposition of the oxone being sufficient for providing the acid medium required for the catalysis.

In order to assess the bio-activity of various halogenated flavonoids, we submitted to halogenation a number of naturally occurring compounds. We also tried to make the halogenation selective by modulating the attack of the halogenating species in order to allow both investigation of the activity of flavonoids having

* Corresponding authors.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01117-6

different degrees of halogenation and the determination of the effect on the activity of the position of the halogen atom in the molecule.

In this paper we report on preliminary studies directed to the synthesis of a number of new compounds to be tested with respect to their anxiolytic, sedative, myorelaxant, antiviral and anti-oxidant activity and to their suitability as intermediates for the preparation of long-chain alkyl derivatives (for improving their bio-availability) and of polyisoprenyl ones (for obtaining bio-active compounds).

Our recently described method[10] for the halogenation of simple aromatics was found to be compatible also with complex and sensitive compounds such as flavanones. In a typical procedure, DMD was added to a mixture of substrate, acetone, sodium bromide (or chloride) and sulphuric acid. The amount of DMD added determined the degree of halogenation, the most activated positions of the substrate being attacked sequentially.

Although the preparation of the DMD solution in acetone is an easy and safe operation, this step can be avoided by in situ generation of the oxidant. In this case, to a mixture of substrate, sodium bromide (or chloride), and oxone in acetone the appropriate amount of water was added. An acid catalyst is unnecessary.

By this method, flavanone **1a** was chlorinated and brominated at position C-6, activated by the *para* ethereal oxygen of the fused heterocyclic ring, which proved to be the most reactive one (Table 1). Worth noting is the observed regioselectivity since, in principle, also position C-8 should be able to react, being activated by the *ortho* ethereal oxygen of the fused heterocyclic ring. The carbonyl group of the pyranone ring, being *meta* to both positions, exerts the same deactivating effect on both C-6 and C-8. This result confirms the existence of a *para* effect in this reaction already observed by us in the case of the halogenation of anisole. Position C-6 proved to be highly reactive even if a methoxy substituent was present in the phenyl ring C: indeed, only the 6,3′-dihalogenated product formed upon bromination of **1b** (Scheme 1).

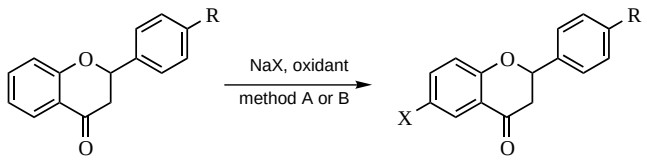
In the case of more activated substrates the reaction was faster and the regioselectivity difficult to control: regioselective processes could thus be obtained only by carefully adjusting the reaction conditions. Table 2 shows the conditions used for the halogenation of 5-methoxyflavanone (Scheme 2), both positions C-6 and C-8 of which appeared equally activated toward an electrophilic attack: as a matter of fact, with an acetone/water ratio of 5:1, the 8-bromo derivative formed preferentially, while in 1:1 acetone/water the 6,8-dibromo-5-methoxyflavanone was obtained along with a demethylated side product (6,8-dibromo-5-hydroxyflavanone) probably originating from the incursion of an undesired process. In any case, the yield of dibromo compounds was quantitative. By contrast, the chlorination reactions required harsher conditions and thus afforded the mono- and dichloro derivatives in somewhat lower yields.

7-Methoxyflavanone behaves similarly, but shows a higher selectivity: both the 6-bromo and the 6,8-dibromo derivatives were indeed obtained in almost quantitative yields. Chlorination was again less selective, the 6,8-dichloro derivative being always formed in almost quantitative yields under all conditions adopted. Worth noting is the excellent result obtained for the chlorination of 7-methoxyflavanone by using method B (Scheme 3 and Table 3).

Table 1. Halogenation of flavanone and 4′-methoxyflavanone[11]

Entry	Substrate	X	Substrate/reagents ratio	Acetone/H_2O volume ratio	T (°C)	t (h)	Product	Yield%
1	**1a**	Br	1/1/4[a]	1/1	25	3	6-Br	97
2	**1b**	Br	1/1/4[a]	1/1	25	0.3	3′,6-Br	74
3	**1a**	Cl	1/1/20[a]	1/1	25	1	6-Cl	85
4	**1b**	Cl	1/4/20[a]	1/1	25	0.3	3′,6-Cl	55
5	**1a**	Cl	1/4/20[b]		25	0.5	6-Cl	85
6	**1b**	Cl	1/4/20[b]		25	0.3	3′,6-Cl	58

[a] Method A: substrate/oxone/Nax molar ratio.
[b] Method B: substrate/DMD/HCl molar ratio.



1a R=H
1b R=OCH_3

2a R=H
2b R=OCH_3

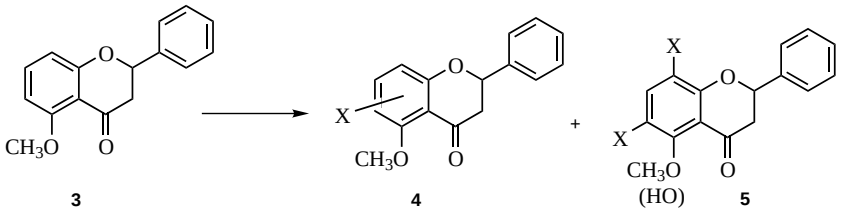
Method A: a solution of substrate, oxone and NaBr in acetone was treated with water
Method B: a solution of substrate and HCl in acetone was treated with a DMD solution in acetone

Scheme 1. Halogenation of flavanone and 4′-methoxyflavanone.

Table 2. Halogenation of 5-methoxyflavanone[11]

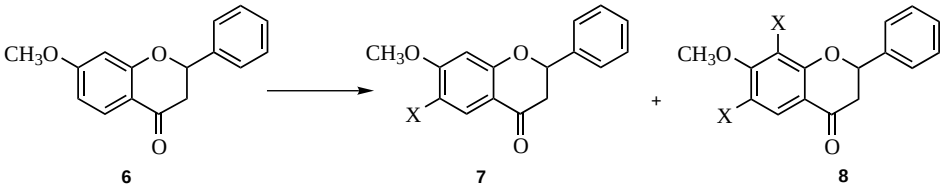
Entry	Substrate	X	Substrate/reagents ratio	Acetone/H_2O volume ratio	T (°C)	t (min)	Product	Yield%
1	**3**	Br	1/1/2[a]	5/1	25	30	6-Br	19
							8-Br	79
2	**3**	Br	1/1/4[a]	1/1	25	15	5-OCH_3-6,8-Br	58
							5-OH-6,8-Br	36
3	**3**	Cl	1/1/4[a]	5/1	25	120	8-Cl	59
							6,8-Cl	16
4	**3**	Cl	1/3/20[a]	1/1	25	15	6,8-Cl	98
5	**3**	Cl	1/3/20[b]		−20	15	6,8-Cl	96

[a] Method A: substrate/oxone/Nax molar ratio.
[b] Method B: substrate/DMD/HCl molar ratio.



Method A: a solution of substrate, oxone and NaBr in acetone was treated with water
Method B: a solution of substrate and HCl in acetone was treated with a DMD solution in acetone

Scheme 2. Halogenation of 5-methoxyflavanone.



Method A: a solution of substrate, oxone and NaBr in acetone was treated with water
Method B: a solution of substrate and HCl in acetone was treated with a DMD solution in acetone

Scheme 3. Halogenation of 7-methoxyflavanone.

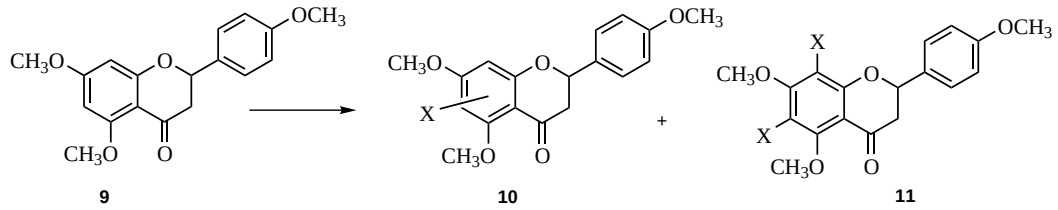
Table 3. Halogenation of 7-methoxyflavanone[11]

Entry	Substrate	X	Substrate/reagents ratio	Acetone/H_2O volume ratio	T (°C)	t (h)	Product	Yield%
1	**6**	Br	1/10[a]	1/1	25	0.3	6-Br	97
2	**6**	Br	4/20[a]	1/1	25	0.5	6,8-Br	>98
3	**6**	Cl	1/4[a]	1/1	25	6	6-Cl	38
							6,8-Cl	30
4	**6**	Cl	4/20[a]	1/1	25	0.5	6,8-Cl	>98
5	**6**	Cl	4/20[b]		25	0.5	6,8-Cl	>98

[a] Method A: substrate/oxone/Nax molar ratio.
[b] Method B: substrate/DMD/HCl molar ratio.

In the case of 7-methoxyflavanone the electrophilic attack was orientated preferentially toward the C-6 position, despite the steric hindrance brought about by the 7-substituent. The results obtained are in favour of a larger *ortho* activating effect by the ethereal cycloaliphatic oxygen compared with that of the methoxy group, the effect being more pronounced in the case of the bromination than in that of the chlorination. These observations were confirmed by the results obtained in the halogenation of very activated compounds: indeed, bromination of naringenin trimethyl ether afforded both the 8-bromo and the 6,8-dibromo derivatives in almost quantitative yield, while either a mixture of 6-chloro and 8-chloro compounds or the 6,8-dichloro compound was formed depending on the experimental conditions (Scheme 4 and Table 4).

These preliminary results stimulate further investigations aimed at assessing the potentialities of the halogenation reaction for the synthesis of both biologically active substances and intermediates useful for the elaboration of more complex derivatives.



Method A: a solution of substrate, oxone and NaBr in acetone was treated with water
Method B: a solution of substrate and HCl in acetone was treated with a DMD solution in acetone

Scheme 4. Halogenation of naringenin trimethyl ether.

Table 4. Halogenation of naringenin trimethyl ether[11]

Entry	Substrate	X	Substrate/reagents ratio	Acetone/H_2O volume ratio	T (°C)	t (min)	Product	Yield%
1	**9**	Br	1/1/2[a]	5/1	25	45	8-Br	>98
2	**9**	Br	1/1/4[a]	1/1	25	45	6,8-Br	>98
3	**9**	Cl	1/1/4[a]	1/1	25	60	6-Cl	30
							8-Cl	65
4	**9**	Cl	1/3/10[b]	1/1	−20	60	6,8-Cl	96

[a] Method A: substrate/oxone/Nax molar ratio.
[b] Method B: substrate/DMD/HCl molar ratio.

References

1. Zanoli, P.; Avallone, R.; Baraldi, M. *Fitoterapia* **2000**, *71*, S117–S123.
2. Medina, J. H.; Vioila, H.; Wolfman, C.; Marder, M.; Wasowski, C.; Calvo, D.; Paladini, A. C. *Neurochem. Res.* **1997**, *22*, 419–425.
3. Sternbach, L. H. *Prog. Drug Res.* **1978**, *44*, 1340–1344.
4. De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976; Chapter 5.
5. Goldberg, Y.; Alper, H. *J. Mol. Cat.* **1994**, *88*, 377.
6. (a) Clague, M. H.; Butler, A. *J. Am. Chem. Soc.* **1995**, *117*, 3475; (b) Hanson, J. R.; Harpel, S. R.; Medina, I. C.; Rose, D. *J. Chem. Res.* **1997**, 432.
7. Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083–2086.
8. Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941–6942.
9. Yaipakdee, P.; Robertson, L. W. *Phytochemistry* **2001**, *57*, 341–347.
10. Bovicelli, P.; Mincione, E.; Antonioletti, R.; Bernini, R.; Colombari, M. *Synth. Commun.* **2001**, *31*, 2955–2963.
11. All products were obtained as oils and isolated by flash chromatography, when possible, and afforded spectral data and CH analysis consistent with the structures proposed. ^{13}C NMR data allowed the identification of correct structures on the basis of NMR studies reported in the literature for flavonoids carrying methoxy groups on the A-ring (Panichpol, K.; waterman, P. G. *Phytochemistry* **1978**, *17*, 1363 and references cited therein). A methoxy substituent on an aromatic system lies in the plane of the ring. In this conformation there is the maximum overlap between the lone pair of the oxygen and the π-orbitals of the aromatic ring. The methyl carbon is then shielded by the conjugated electrons and chemical shifts occur between 55.0 and 56.5 ppm. When the methoxy group is between bulky substituents, this conformation is disfavoured, the oxygen is not fully conjugated with the aromatic ring and the methoxy carbon deshielded to 59.5–63.6 ppm. Significant NMR data of relevant compounds: **6-bromoflavanone**: ^1H NMR δ 6.95 (1H, d, $J=8.8$ Hz, H-8); 7.57 (1H, dd, $J=2.5$, 8.8 Hz, H-7); 8.02 (1H, d, $J=2.5$ Hz, H-5). ^{13}C NMR δ 114.3 (C-Br), 120.2 (C-8), 122.1 (C-10), 129.5 (C-5), 138.2 (C-7), 160.4 (C-9). **6-chloroflavanone**: ^1H NMR δ 6.98 (1H, d, $J=8.7$ Hz, H-8); 7.42 (1H, dd, $J=2.8$, 9.7 Hz, H-7); 7.87 (1H, d, $J=2.9$ Hz, H-5). ^{13}C NMR δ 119.8 (C-8), 121.7 (C-10), 126.1 (C-5), 135.9 (C-7), 127.2 (C-Cl), 159.9 (C-9). **3′,6-dibromo-4′-methoxyflavanone**: ^1H NMR δ 6.92 (1H, d, $J=8.6$ Hz, H-5′); 6.93 (1H, d, $J=9$ Hz, H-8); 7.34 (1H, dd, $J=2.2$, 8.6 Hz); 7.56 (1H, dd, $J=2.5$, 9 Hz, H-7); 7.67 (1H, d, $J=2.2$ Hz, H-2′); 8.01 (1H, d, $J=2.5$ Hz, H-5). ^{13}C NMR δ 56.3 (CH_3O), 114.2 and 114.4 (C-Br), 122.1 (C-10), 156.1 (C-4′); 160.4 (C-9). **3′,6-dichloro-4′-methoxyflavanone**: ^1H NMR δ 6.95 (1H, d, $J=8.6$ Hz, H-5′); 6.97 (1H, d, $J=9$ Hz, H-8); 7.30 (1H, dd, $J=2.2$, 8.6 Hz, H-6′); 7.41 (1H, dd, $J=2.9$, 8.7 Hz, H-7); 7.52 (1H, d, $J=2.2$ Hz, H-2′); 7.56 (1H, dd, $J=2.5$, 9 Hz, H-7); 7.86 (1H, d, $J=2.9$ Hz, H-5). ^{13}C NMR δ 56.2 (CH_3O), 116.6 and 127.2 (C-Cl), 121.7 (C-10), 155.3 (C-4′); 161.0 (C-9). **8-bromo-5-methoxyflavanone**: ^1H NMR δ 6.47 (1H, d, $J=8.9$ Hz, H-6); 7.62 (1H, d, $J=8.9$ Hz, H-7). ^{13}C NMR δ 56.3 (CH_3O), 102.4 (C-Br), 105.2 (C-6), 112.4 (C-10), 138.8 (C-7), 158.7 (C-9) 160.0 (C-5). **6,8-dibromo-5-methoxyflavanone**: ^1H NMR δ 7.93 (1H, s, H-7). ^{13}C NMR δ 61.8 (CH_3O), 100.0 (C-Br), 102.0 (C-Br), 110.7 (C-10), 141.3 (C-7), 156.7 (C-9), 158.1 (C-5). **8-chloro-5-methoxy-flavanone**: ^1H NMR δ 6.50 (1H, d, $J=9.0$ Hz, H-6), 7.48 (1H, d, $J=9.0$ Hz, H-7). ^{13}C NMR δ 56.7 (CH_3O), 117.5 (C-Cl). **6,8-dichloro-5-methoxy-flavanone**: ^1H NMR δ 7.59 (1H, s, H-7). ^{13}C NMR δ 117.0 (C-Cl), 118.7 (C-Cl), 121.6 (C-10), 135.7 (C-7), 154.9 and 156.5 (C-5 and C-9). **6-bromo-7-methoxyflavanone**: ^1H NMR δ 6.52 (1H, s, H-8); 8.08 (1H, s, H-5). ^{13}C NMR δ 56.7 (CH_3O), 100.6 (C-8), 105.4 (C-10), 115.5 (C-Br), 129.0 (C-5), 161.7 and 162.5 (C-7 and C-9).

6-chloro-7-methoxyflavanone: ^{1}H NMR δ 6.53 (1H, s, H-8); 7.90 (1H, s, H-5). ^{13}C NMR δ 56.5 (CH_3O), 100.7 (C-8), 114.7 (C-10), 117.5 (C-Cl), 128.8 (C-5), 160.9 and 161.9 (C-7 and C-9). **6,8-dibromo-7-methoxyflavanone**: ^{1}H NMR δ 8.09 (1H, s, H-5). ^{13}C NMR δ 60.8 (CH_3O), 108.4 and 110.7 (C-Br), 128.9 (C-5), 158.6 and 160.3 (C-7 and C-9). **6,8-dichloro-7-methoxyflavanone**: ^{1}H NMR δ 7.88 (1H, s, H-5). ^{13}C NMR δ 60.9 (CH_3O), 118.2 and 119.0 (C-Cl), 129.1 (C-5), 157.1 and 158.4 (C-7 and C-9). **8-bromo-4′,5,7-trimethoxyflavanone**: ^{1}H NMR 6.13 (1H, s, H-8). ^{13}C NMR δ 55.3, 56.2 and 56.4 (CH_3O), 89.3 (C-6), 91.6 (C-10), 106.7 (C-Br), 159.7, 160.0, 161.5 and 161.8 (C-5, C-7, C-9 and C-4′). **6-chloro-4′,5,7-trimethoxyflavanone** and **8-chloro-4′,5,7-trimethoxyflavanone**, characterised in mixture by ^{1}H NMR in which signals at δ 6.14 (8-Br) and 6.37 (6-Br) are present in 2:1 ratio. **6,8-dichloro-4′,5,7-trimethoxyflavanone**: ^{1}H NMR in the aromatic region only the AB system of ring C is present: 6.93 (2H, d, $J=8.8$ Hz, H-3′ and H-5′); 7.39 (2H, d, $J=8.6$ Hz, H-2′ and H-6′). ^{13}C NMR δ 55.3 and 60.9, 61.8 (CH_3O), 113.4 and 117.6 (C-Cl), 156.0, 157.4, 158.5, 160.0 (C-4′, C-5, C-7 and C-9).