Synthesis of I-3, 11-3-bis-(methylthio)biflavones from the corresponding bichalcones: a new application of the I_2-Me_2SO-H_2SO_4 reagent system

Jawaid Iqbal,[a,*] Anamika Gupta,[a] and Khwaja Ishratullah[b]

[a]*Organic Chemistry Section, Department of Chemistry, Aligarh Muslim University, Aligarh-202002, India*
[b]*Organic Chemistry Division-II, Indian Institute of Chemical Technology, Hyderabad-500007, India*
E-mail: Jawaid.Iqbal0@lycos.com

Abstract
The synthesis is described of I-3, II-3-bis-(methylthio)-I-4', II-4', I-5, II-5, I-7, II-7-hexamethoxy-[1-3', II-8]-biflavone (**2**) and I-3, II-3-bis-(methylthio)-I-4', II-4', I-5, II-5, I-7, II-7-hexamethoxy-[I-3', II-6]-biflavone (**4**), in one step from bichalcones **1** and **3**, respectively, using the I_2–Me_2SO–H_2SO_4 reagent system.

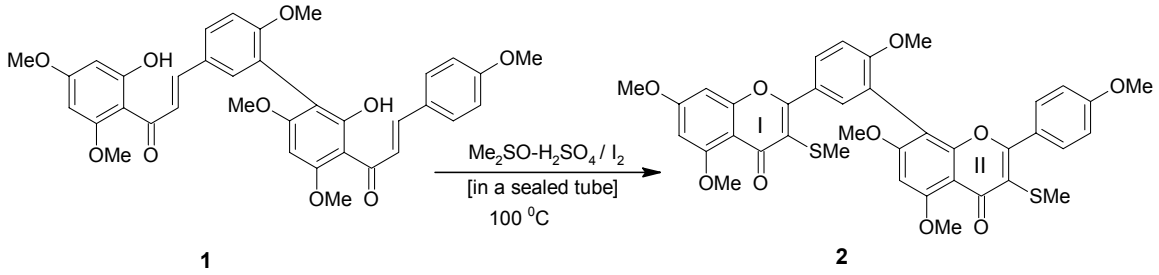
Keywords: Biflavonoid, bichalcone, bis-(methylthio)biflavone, dimethyl sulfoxide

Introduction

The oxidation–reduction cycle,[1] that sets in when dimethyl sulfoxide is reduced to dimethyl sulfide in the presence of a catalytic amount of halogen, has found potential synthetic applications.[1–4] Furukawa *et al*.[1] have used the halogen–dimethyl sulfoxide–sulfuric acid system as an oxidizing reagent for active aldehydes and ketones. Previous reports from our laboratory described its applications in the high-yield dehydrogenation of the 2,3-dihydropyrone ring of various flavanoid systems[2,3] and in a one-step synthesis of 3-iodoflavones from 2'-hydroxychalcones.[4] Furukawa's report indicated that in the oxidation of some active methylene ketones with this reagent system, the diketone oxidation product was accompanied by substantial amount of α-methylthio-ketone, when the reaction was carried under sealed tube conditions, *i.e*., when the *in situ*- generated dimethyl sulfide was allowed to react with the initially formed α-iodoketone.[1] Within the context of our work aimed at the synthesis and determination of absolute stereochemistry of biflavanoids, we studied the reaction of some 2',2'''-dihydroxybichalcones with I_2–Me_2SO–H_2SO_4 under sealed-tube conditions, and now report a new application of this reagent system in the synthesis of the hitherto unknown I-3, II-3-bis-(methylthio)biflavone.

Results and Discussion

2',2'''-Dihydroxy-4,4',4'',4''',6',6'''-hexamethoxy-[3,3''']-bichalcone **(1)** was first heated at 100°C for *ca*. 15 min. with dimethyl sulfoxide and a small amount of sulfuric acid, then a catalytic amount of iodine was added, and the mixture was heated in a sealed tube at 100°C for 2h. The major product, obtained in 63% yields after workup and chromatographic purification, was characterized as I-3, II-3-bis-(methylthio)-I-4', II-4', I-5, II-5, I-7, II-7-hexamethoxy-[I-3', II-8]-biflavone **(2)**, m.p. 198°C, from its UV, ^{1}H- and ^{13}C- NMR. and mass spectra (Scheme 1).

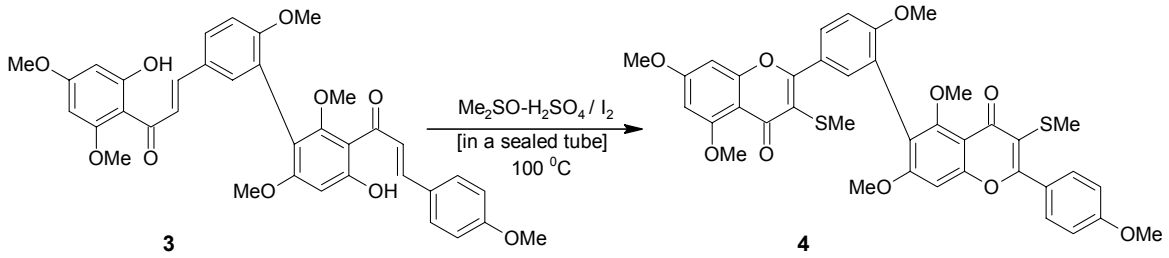


1 2

Scheme 1

The ^{1}H- NMR spectrum of **2** indicated the intact presence of all the aromatic ring protons and the absence of α- and β- protons of bichalcone. Further, two singlets at δ 2.91 and 2.94 each integrating for three protons indicated the presence of two methylthio (CH_3-S-) groups at I-C-3 and II-C-3. The ^{13}C- NMR spectral data are also in complete accord with the assigned structure. The mass spectrum shows the molecular ion peak at *m/z* 714 (40%), and retro- Diels-Alder fragments at m/z 537, 357, 223, 181 and 178 as required by structure **2**

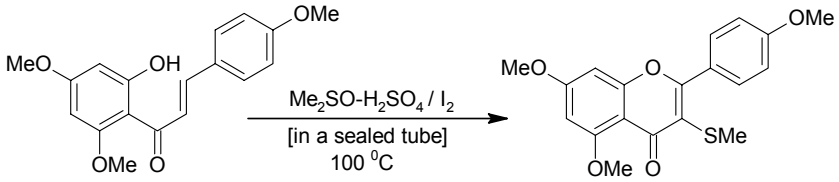
The formation of bis-(methylthio)biflavone from bichalcone appears to be general. When this reaction was extended with 2',2'''-dihydroxy-4,4',4'',4''',6',6'''- hexamethoxy-[3,5''']-bichalcone (**3**) under similar condition, it completed in 1.5 h, and on usual workup and purification afforded I-3, II-3-bis-(methylthio)-I-4',II-4',I-5,II-5,I-7,II-7-hexamethoxy-[I-3',II-6]-biflavone (**4**), in 60% yield (Scheme 2). The observed spectral data, UV, ^{1}H- and ^{13}C-NMR are compatible with the assigned structure.



3 4

Scheme 2

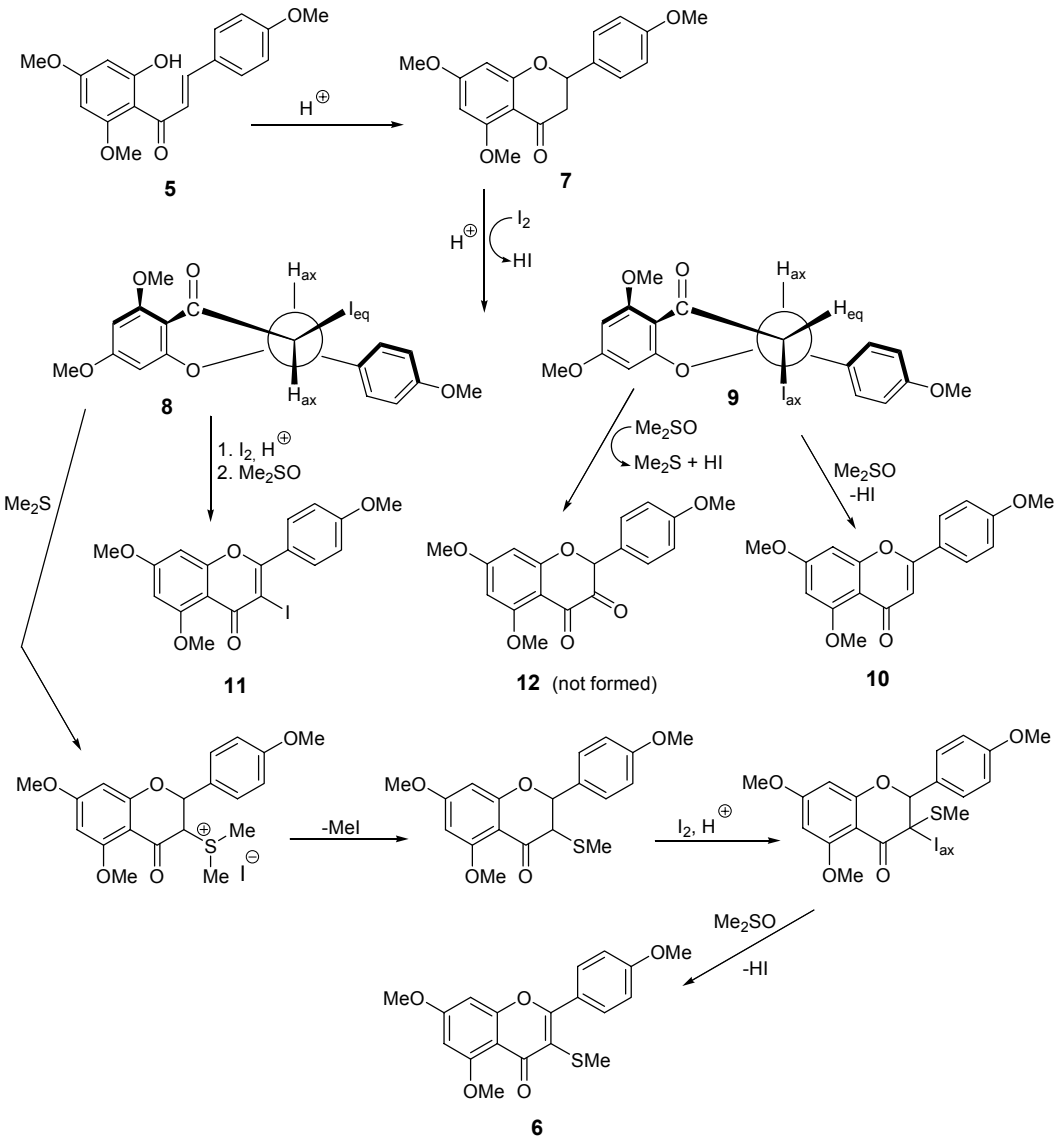
Further extension with 2'-hydroxy-4,4',6'-trimethoxychalcone (**5**), yielded 3-methylthio-5,7,4'-trimethoxyflavone (**6**), m.p. 150°C, as major product, characterized from its UV, NMR and mass spectra.



Scheme 3

This, a one step transformation of bis-(2'-hydroxy)bichalcone to bis-(methylthio)biflavone with iodine–dimethyl sulfoxide–sulfuric acid reagent system is interesting both from mechanistic and synthetic viewpoints. Introduction of a sulfur- containing substituent α- to a carbonyl group is often a key step in organic synthesis.[5] Although recent advances have removed some of the difficulties associated with the method of sulfenylation of aldehydes and ketones,[6] the convenience and mildness of this method may provide further improvement. In this context it may be mentioned that 3-sulfinylchromone was synthesized by base-induced acylation of sulfinyl ketone.[7]

A reasonable mechanism for these reactions is that shown in Scheme 4. The starting chalcone isomerises[4] in the presence of conc. sulfuric acid to the corresponding flavanone **7**, which undergoes iodination at C-3 to give isomeric 3-iodoflavanones.[2–4] In the light of our previous experiments[2-4], we argue that the C-3- iodination of flavanone produces two isomeric 3-iodoflavanones, **8** and **9**. In the present conditions **8** is formed predominantly and has an unfavorable conformation for *trans*- diaxial dehydrohalogenation. The differential predominance of the isomeric 3-iodoflavanones **8** or **9**, starting from chalcone or flavanone, respectively, have been observed and discussed in our previous reports[3,4] and is probably related with kinetic *versus* thermodynamic control: however, the way in which the chalcone–flavanone equilibrium affects this differential formation of 3-iodoflavanones is yet unclear. The major product, methylthioflavone was accompanied by a very small amount of the corresponding flavone **10** and 3-iodoflavone **11.** However, the formation of flavonol **12,** which could have resulted from an oxidation–reduction cycle**,**[1] was not observed in the experiments described.



Scheme 4

Experimental Section

General Procedures. M.p.s were taken on a Kofler block and are uncorrected, ^{1}H-NMR spectra were recorded on Varian A-60D and JEOL 4H-100 instruments and ^{13}C-NMR spectra with JEOL FX-100 spectrometer with Me_4Si as internal standard. Mass spectra were obtained on a JEOL-OSIG mass spectrometer at 75 eV. Commercial iodine was used without further purification. Dimethyl sulfoxide was dried by distillation from calcium hydride under reduced pressure.

Reaction of 2',2'''-dihydroxy-4,4',4'',4''',6',6'''-hexamethoxy[3,3''']-bichalcone (1) with I_2–Me_2SO–H_2SO_4 reagent system. A mixture of **1 (**630 mg, 1.0 mmol) and sulfuric acid (60 mg, 0.6 mmol) in Me_2SO (5 ml) was first heated at 100°C for *ca*. 15 min., then cooled to room temperature. After adding iodine (50 mg, 0.2 mmol), the mixture was further heated in a sealed tube at 100°C for ~ 2h. It was then poured into ice-water and the precipitate was filtered, washed with water and dried to give a solid which was chromatographed on silica gel (25 gm). Elution with chloroform–n-hexane (60:40) gave (450 mg, 63%) of I-3, II-3-bis-(methylthio)-I-4', II-4', I-5, II-5, I-7, II-7- hexamethoxy [I-3',II-8]biflavone (**2**), m.p. 198°C (Found: C, 63.7; H, 4.8; $C_{38}H_{34}O_{10}S_2$ requires: C, 63.8; H, 4.7%); λ_{max} (MeOH) 264, 341 nm; ^{1}H-NMR: δ_H ($CDC1_3$): 2.91 (3H, s, -S-CH_3), 2.94 (3H, s, -S-CH_3), 3.75 (6H, s, OMe-I-7,II-7), 3.82 (3H, s, OMe-II-4'),3.87 (3H,s,OMe-I-4'),3.92 (3H,s,OMe-I-5), 4.07 (3H, s, OMe-II-5), 6.32 (1H, d, J=2.5 Hz, H-I-6), 6.47 (1H, d, J=2.5 Hz, H-I-8), 6.63 (1H, s, H-II-6), 6.76 (2H, d, J=8.5 Hz, H-II-3', 5'), 7.11 (1H, s, H-I-5'), 7.38 (2H, d, J=8.5 Hz, H-II-2',6'), 7.89 (1H, dd, $J_{1=}$2.5 Hz, $J_{2=}$8.5 Hz, H-I-6'), 7.81 (1H, s, H-I-2'); ^{13}C-NMR: δ_C ($CDCI_3$) 23.1, 23.4 (-S-CH_3), 55.6 (I, II-4' OMe), 56.O (I, II-7-OMe), 56.2, 56.4 (I, II-5-OMe), 92.7 (I-C-8), 95.4 (II-C-6), 98.0 (I-C-6), 103.1, 103.9, 104.0, 104.2 (I, II-C-3, II-C-8, I, II-C-10), 111.4 (II-C-3', 5'), 114.5 (I-C-5'), 121.2, 122.6 (I-C-3', I, II-C-1'), 127.8 (I-C-2',6[1]), 128.3 (II-C-2'), 130.8 (II-C-6'), 153.5 (II-C-9), 157.7 (I-C-9), 160.4, 161.1, 161.4 (I, II-C-5, I-C-4', II-C-7), 162.7 (II-C-4'), 163.5 (I, II-C-2), 165.6 (I-C-7), 181.9, 182.2 (I, II-C-4); m/z 714 (40, M^+), 668, 537, 534, 491, 483, 357, 181, (100), 178, (Found M^+, 714.8161, Calcd. for $C_{38}H_{34}O_{10}S_2$: M_r, 714.8166).

Reaction of 2',2'''-dihydroxy-4,4',4'',4''',6',6''-hexamethoxy-[3, 5''']-bichalcone (3) with I_2–Me_2SO–H_2SO_4 reagent system. Reaction as above, using **3** (630 mg, 1.0 mmol), H_2SO_4 (50 mg, 0.5 mmol) and I_2 (50 mg, 0.2 mmol) in 4.5 ml of Me_2SO at 100°C for ~ 1.5 h, gave, after usual work-up and chromatographic purification (silica gel), (400 mg, 60%) of I-3, II-3-bis (methylthio)-I-4',II-4[1], I-5, II-5, I-7, II-7-hexamethoxy[1-3', II-6]-biflavone (**4**), crystallized from acetone–methanol, m.p. 233ºC. (Found: C, 63.2; H, 4.9; $C_{38}H_{34}O_{10}S_2$ requires: C, 63.8; H, 4.7%); λ_{max} (MeOH) 263, 343 nm; ^{1}H-NMR: δ_H ($CDCI_3$) 2.90 (3H, s, -S-CH_3), 2.92 (3H, s, -S-CH_3), 3.61, 3.86,3.87, 3.88, 3.91, 3.92 (3H each, s, OMe -II-5', II-4', II-7, I-7, I-4', I-5), 6.33 (1H, d, J=2.5 Hz, H-I-6), 6.56 (1H, d, J=2.5 Hz, H-I-8), 6.79 (1H, s, H-II-8), 7.03 (2H, d, J=8.7 Hz, H-II-3' ,5'), 7.08 (1H, d, J=8.7 Hz, H-I-5'), 7.61 (2H, d, J=8.7 Hz, H-II-2', 6'), 7.80 (1H, d, J=2.5 Hz, H-I-2'), 7.86 (1H, dd, $J_{1=}$2.5 Hz, $J_{2=}$8.7 Hz, H-I-6'); ^{13}C-NMR: δ_C ($CDCI_3$) 23.3, 23.6 (-S-CH_3), 55.6 (I, II-4'-OMe), 56.1 (I, II-7-OMe), 56.3, 56.5 (I, II-5-OMe), 93.8, 94.4 (I, II-C -8), 95.4 (I-C-6), 102.9, 103.2, 103.9, 104.1, 104.3 (I, II-C-3, II-C-6, I, II-C-10), 114.1 (II-C-3', 5'), 115.9 (I-C-5'), 121.1 (I-C-3'), 122.4 (I, II-C-1'), 127.2, 128.3, 130.6 (I, II-C -2', 6'), 157.6 (I, II-C-9), 159.1 (II-C-5), 160.4, 161.1, 161.5 (I, II -C-4', I-C-5), 163.1, 163.7, 164.1 (I, II-C-7, 2), 181.7, 181.9 (I, II-C-4); m/z 714 (31, M^+), 537, 536, 534, 491, 483, 477, 357, 181 (100), 135, (Found M^+, 714.8159, Calcd. For $C_{38}H_{34}O_{10}S_2$: M_r, 714.8166).

Reaction of 2'-hydroxy-4, 4', 6'-trimethoxychalcone (5) with I_2–Me_2SO–H_2SO_4 reagent system. The reaction, according to the above procedure, using **5 (**470 mg, 1.5 mmol), H_2SO_4 (40 mg, 0.4 mmol) and I_2 (50 mg, 0.2 mmol) in 4 ml of Me_2SO at 100ºC for 1.5h, gave, after the

usual work-up and chromatographic purification (silica gel), (350 mg, 65%) of 3-methylthio-5,7,4'-trimethoxyflavone (**6**), m.p. 150°C, as major product; λ_{max} (MeOH) 262, 341 nm; ^{1}H-NMR: δ_H ($CDCI_3$) 2.89 (3H, s, -S-CH_3), 3.90 (3H, s, OMe-4'), 3.97 (6H, s, OMe-5, 7), 6.46 (1H, s, H-6), 6.65 (1H, s, H-8), 7.06 (2H, d, J=8.6 Hz, H-3',5'), 8.04 (2H, d, J=8.6 Hz, H-2', 6'); ^{13}C-NMR: δ_C ($CDCl_3$) 22.6 (-S-CH_3), 55.8, 56.2, 56.5, (5, 7, 4'-OMe), 94.1 (C-6), 98.6 (C-8), 103.6 (C-3), 109.1 (C-10), 121.2 (C-3', 5'), 127.9 (C-1'), 130.1 (C-2', 6'), 157.1 (C-9), 161.1,161.3 (C-2,5), 161.9 (C-4'), 163.8 (C-7), 181.6 (C-4); m/z 358 (41, M^+), 331, 223, 181 (100), 178, 135 (Found M^+, 358.4155, Calcd. for $C_{19}H_{18}O_5S$: M_r, 358.4163).

References

1. Furukawa, N.; Akasaka, T; Aida, T; Oae, S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 372.
2. Fatma, W.; Iqbal, J.; Ismail, H.; Ishratullah, Kh.; Shaida, W.A.; Rahman, W. *Chem. Ind. (London)* **1979**, 315.
3. Fatma, W.; Iqbal, J.; Manchanda, V.; Shaida, W.A.; Rahman, W. *J. Chem. Research,* **1984** (S) 298; (M) 2656.
4. Iqbal, J.; Fatma, W.; Shaida, W.A.; Rahman, W., *J. Chem. Research* **1982**, (S) 92; (M) 1001.
5. Trost, B. M. *Acc. Chem. Res*. **1978**, *11*, 453.
6. House, H. *Modern Synthetic Reactions*, W.A. Benjamin, Menlo Park, California, 1972.
7. Von Strandtmann, M.; Klutchko, S.; Cohen, M. P.; Shavvel, J. *J. Heterocycl. Chem.* **1974**, *11*, 183.