Synthesis of I-3, 11-3-bis-(methylthio)biflavones from the corresponding bichalcones: a new application of the I$_2$-Me$_2$SO-H$_2$SO$_4$ reagent system

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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-[I-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$_2$SO–H$_2$SO$_4$ 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 \(\alpha\)-methylthio-ketone, when the reaction was carried under sealed tube conditions, \textit{i.e.}, when the \textit{in situ}- generated dimethyl sulfide was allowed to react with the initially formed \(\alpha\)-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$_2$SO–H$_2$SO$_4$ 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, 1H- and 13C- NMR. and mass spectra (Scheme 1).

![Scheme 1](image1)

The 1H- 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 (CH₃-S-) groups at I-C-3 and II-C-3. The 13C- 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, 1H- and 13C-NMR are compatible with the assigned structure.

![Scheme 2](image2)
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. Although recent advances have removed some of the difficulties associated with the method of sulfonylation of aldehydes and ketones, 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.

A reasonable mechanism for these reactions is that shown in Scheme 4. The starting chalcone isomerises in the presence of conc. sulfuric acid to the corresponding flavanone 7, which undergoes iodination at C-3 to give isomeric 3-iodoflavanones. In the light of our previous experiments, 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 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, 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$_4$Si 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 I₂–Me₂SO–H₂SO₄ reagent system. A mixture of 1 (630 mg, 1.0 mmol) and sulfuric acid (60 mg, 0.6 mmol) in Me₂SO (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; C₃₈H₃₄O₁₀S₂ requires: C, 63.8; H, 4.7%); λ_max (MeOH) 264, 341 nm; ¹H-NMR: δ_H (CDCl₃): 2.91 (3H, s, -S-CH₃), 2.94 (3H, s, -S-CH₃), 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-3', 5'), 7.89 (1H, dd, J₁=2.5 Hz, J₂=8.5 Hz, H-I-6'), 7.81 (1H, s, H-I-2'); ¹³C-NMR: δ_C (CDCl₃) 23.1, 23.4 (-S-CH₃), 55.6 (I, II-4'-OMe), 56.0 (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'), 128.3 (II-C-2', 6'), 130.8 (II-C-6'), 135.3 (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⁺, 714.8166).

Reaction of 2',2'''-dihydroxy-4,4',4'',4''',6',6'''-hexamethoxy-[3, 5''']-bichalcone (3) with I₂–Me₂SO–H₂SO₄ reagent system. Reaction as above, using 3 (630 mg, 1.0 mmol), H₂SO₄ (50 mg, 0.5 mmol) and I₂ (50 mg, 0.2 mmol) in 4 ml of Me₂SO 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', I-5, II-5, I-7, II-7-hexamethoxy [I-3',II-6]-biflavone (4), crystallized from acetone–methanol, m.p. 233°C. (Found: C, 63.2; H, 4.9; C₃₈H₃₄O₁₀S₂ requires: C, 63.8; H, 4.7%); λ_max (MeOH) 263, 343 nm; ¹H-NMR: δ_H (CDCl₃) 2.90 (3H, s, -S-CH₃), 2.92 (3H, s, -S-CH₃), 3.61, 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, J₁=2.5 Hz, J₂=8.7 Hz, H-I-6'); ¹³C-NMR: δ_C (CDCl₃) 23.3, 23.6 (-S-CH₃), 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⁺), 668, 537, 534, 491, 483, 477, 357, 181, (100), 178, (Found M⁺, 714.8166).

Reaction of 2'-hydroxy-4, 4', 6'-trimethoxychalcone (5) with I₂–Me₂SO–H₂SO₄ reagent system. The reaction, according to the above procedure, using 5 (470 mg, 1.5 mmol), H₂SO₄ (40 mg, 0.4 mmol) and I₂ (50 mg, 0.2 mmol) in 4 ml of Me₂SO at 100°C 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; \( \lambda_{\text{max}} \) (MeOH) 262, 341 nm; \(^1\)H-NMR: \( \delta_H \) (CDCl\(_3\)) 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: \( \delta_C \) (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\(_5\)S: Mr, 358.4163).

References