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Study on the Synthesis of Some New Biflavonoids. VIII. A New Synthesis of C_3-Linked Biflavones, Bithioflavones and Bithiochromones

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STUDY ON THE SYNTHESIS OF SOME NEW BIFLAVONOIDS. Ⅷ. A NEW SYNTHESIS OF C_3–LINKED BIFLAVONES, BITHIOFLAVONES AND BITHIOCHROMONES

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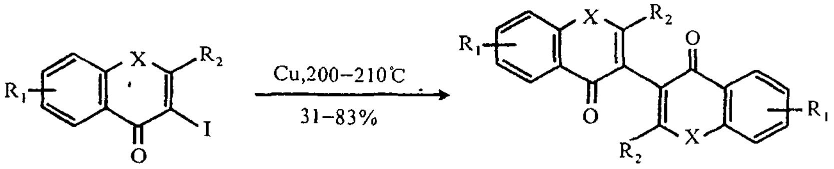
Abstract: Reactions of the 3–iodo derivatives of flavones, thioflavones and thiochromones with finely divided copper at 200–210℃ gave the title compounds respectively. Thus a new way to these compounds was provided.

3,3″–Biflavonoids are an interesting class of compounds. Their synthesis has received considerable attention since the 1950s. Chamaejasmine[2], a natural 3,3″–biflavanone, was first isolated from *Stellera chamaejasme* L. in 1979. Following that, seven other chamaejasmine–type biflavanones[3–6] were also isolated from the same plant. Subsquent research[7] showed that some of the natural 3,3′–biflavanones exhibit antitumour activity. The discovery of the natural 3,3″–biflavanones and their potential therapeutic properties further added great impetus to this research field. Although many attempts have been made to synthesize 3,3″–biflavonoids, in most cases[8–14], the reactions failed or gave poor yields. Recently, an approach[15–16] to these compounds was developed in our laboratory, which involved a 1,4–bis (2–hydroxy –4,6–di– methoxy phenyl) butane–1,4– dione as the key intermediate. By this route, two 3,3″–biflavones have been prepared and one of them was hydrogenated to give the corresponding 3,3″–biflavanone[17], a chamaejasmine–like molecule.

However, as a synthetic strategy, the most straightforward approach to 3,3″–biflavonoids seemed to be the coupling of flavonoids which were readily available. Therefore, several potential routes to 3,3″–biflavanones starting from flavanones were explored[18]. A 3,3″–biflavanone can be regarded as a complex butane–1,4–dione. So we attempted to extend some methods for the preparation of butane–1,4–diones to the synthesis of 3,3″–biflavanones. Considering that the C–ring of a flavanone is readily cleaved by strong acid or base, we tried to steer clear of reactions requiring vigorous conditions. Our first synthetic plan was based on that used for the synthesis of 2,2′–bicyclohexanone[19]. 4′,7–Dimethoxyflavanone and 4′,5,7– trimethoxy– flavanone were treated with nickle peroxide respectively. Disappointedly, only the corresponding flavones, as oxidated products, were obtained in low yields. Then the 3–bromo and 3–chloro derivatives[20] of 4′,5,7– trimethoxy flavone were reacted with nickle(0) respectively, analogous to the procedure for the preparation of butane–1,4–diones[21]. However, the reactions failed to generate the desired 3,3″–biflavanone, producing instead only the 4′,5,7– trimethoxyflavanone in both cases. The 3–bromo –4′,5,7–trimethoxyflavanone were also treated with $Fe(CO)_5$ under the same condition[22] used for the conversion of phenacyl bromide into 1,4–diphenylbutane–1,4–dione. Unexpectedly, 4′,7– dimethoxy–5–hydroxyflavone was obtained in good yield. In view of the above failure, we turned our attention to the synthesis of 3,3″–biflavones, key intermediates of 3,3″–biflavanones.

C_3–linked bithioflavones and bithiochromones are the analogues of 3,3″–biflavones. They consist of a new and hitherto unknown class of compounds. Studies on their biological activity and reactivity may lead to some significant results. So their synthesis has also attracted our interest.



1 2

1,2	X	R_1	R_2	1,2	X	R_1	R_2
a	O	H	C_6H_5	**e**	S	6–Me	Me
b	O	H	4′–$MeOC_6H_4$	**f**	S	H	C_6H_5
c	O	7–MeO	4′–$MeOC_6H_4$	**g**	S	6–Me	C_6H_5
d	S	H	Me				

Table 3,3″–Biflavones, 3,3″–Bithioflavones and 3,3′–Bithiochromones

Product	Yield (%)	mp(℃) (solvent)	Molecular Fomular[a]	Elemental Analyses Calcd.	Found
2a	81	287–288	$C_{30}H_{18}O_4$	C: 81.44	81.31
		(MeOH)	(442.5)	H: 4.10	4.01
2b	71	240–242	$C_{32}H_{22}O_6$	C: 76.48	76.62
		(CH_2Cl_2 / MeOH)	(502.5)	H: 4.41	4.38
2c	86	234–236	$C_{34}H_{26}O_8$	C: 72.59	72.84
		(CH_2Cl_2 / MeOH)	(562.6)	H: 4.66	4.59
2d	31	230–231	$C_{20}H_{14}O_2S_2$	C: 68.55	68.43
		(MeOH)	(350.5)	H: 4.03	3.82
2e	33	289–291	$C_{22}H_{18}O_2S_2$	C: 69.81	69.75
		(MeOH)	(378.5)	H: 4.79	4.60
2f	83	322(dec.)	$C_{30}H_{18}O_2S_2$	C: 75.92	75.62
		(CH_2Cl_2 / MeOH)	(474.6)	H: 3.80	3.63
2g	80	305–306	$C_{32}H_{22}O_2S_2$	C: 76.46	76.38
		(CH_2Cl_2 / MeOH)	(502.7)	H: 4.41	4.31

Recently, a series of 3–iodo derivatives of flavones, thioflavones and thiochromones have been synthesized by reaction of the corresponding flavones, thioflavones and thiochromones with I_2–CAN system[23]. Because all these compounds are highly conjugated molecules, they can be regarded as aryl iodides. Therefore the Ullmann reaction seems to be an appropriate method of choice for coupling the 3–iodo derivatives to their C_3–linked dimers.

Herein the 3–iodo derivatives(**1a–g**) of flavones, thioflavones and thiochromones were heated with finely divided copper at 200–210℃ under Ar. The results are listed in the Table.

As shown in the Table, the coupling of 3–iodoflavones and 3–iodothioflavones under the Ullmann reaction condition proceeded smoothly to give 3,3″–biflavones and 3,3″–bithioflavones respectively in good yields. In the case of 3–iodothiochromones,the yields of 3,3″–bithiochromones were low, possibly due to their sublimation at the reaction temperature . The structures of all these synthetic compounds were confirmede by their spectral data.

In summary, we have provided a general and efficient approach to 3,3″–biflavones, 3,3″–bithioflavones and 3,3′–bithiochromones. We view the generality and efficiency of the coupling approach as a harbinger of future applications for construction of C_3–$C_{3''}$(or C_3–$C_{3'}$) linkage between flavonoids and their analogues.

Experimental

All reagents and equipment were thoroughly dried prior to use.

Melting points were measured with a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on Nicolet 170 SX FT–IR spectrometer..^{1}H–NMR spectra were recorded on a Bruker Ac–80 or FT–80 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained on a ZAB–HS instrument using a FAB source. Microanalysis were performed by using a MOD–1106 elemental analyzer.

Synthesis of 3,3″–biflavones, 3,3″–bithioflavones and 3,3′–bithiochromones

General procedure

A mixture of a substrate (0.4 mmol) and finely divided copper (2.4 mmol) was heated under Ar at 200–210℃ for 7 h. The reaction mixture was extracted repeatedly with CH_2Cl_2 and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel using hexane / EtOAc (9:1–3:2) as eluants to afford the product.

2a: IR: 1647, 1635, 1615, 1465, 1370,1218, 1057, 756, 697 cm^{-1}..^{1}H–NMR: δ 7.05–7.85(16H, m, ArH), 8.25–8.45(2H, m, 5–H, 5″–H). MS: m / z 443(MH$^+$)

2b: IR: 1634, 1610, 1507, 1466, 1368, 1254, 1176, 761 cm^{-1}..^{1}H–NMR: δ 3.76(6H, s, OMe × 2), 6.72(4H, dd, J = 2.1,8.9Hz, 3′–H, 3‴–H, 5′–H, 5‴–H), 7.23(4H, dd, J = 2.1, 8.9Hz, 2′–H, 2‴–H, 6′–H, 6‴–H), 7.28–7.80(6H, m, ArH), 8.27(2H, dd, J = 1.5, 9.0Hz, 5–H, 5″–H). MS: m / z 503(MH$^+$).

2c: IR: 1612, 1542, 1503, 1440, 1346, 1253, 1174, 834 cm^{-1}..^{1}H–NMR: δ 3.77(6H, s, OMe× 2), 3.89(6H, s, OMe × 2), 6.72(4H, d, J = 8.9Hz, 3′–H, 3‴–H, 5′–H, 5‴–H), 6.83(2H, d, J = 2.3Hz, 8–H, 8″–H), 6.97(2H, dd, J = 2.3, 8.8Hz, 6–H, 6″–H), 7.20(4H, d, J=8.9Hz, 2′–H, 2‴–H, 6′–H, 6‴–H), 8.18(2H, d, J=8.8Hz, 5–H, 5″–H). MS: m / z 351(MH$^+$).

2d: IR: 1615, 1586, 1539, 1320, 745, 686, 640 cm^{-1}..^{1}H–NMR: δ 2.27(6H, s, Me × 2), 7.35–7.85(6H, m, ArH), 8.40–8.60(2H, m, 5–H, 5′–H). MS: m / z 351(MH$^+$).

2e: IR: 1615, 1594, 1534, 1472, 1329, 1292, 1099, 804 cm^{-1}..^{1}H–NMR: δ 2.22(6H, s, Me × 2), 2.44(6H, s, ArMe × 2), 7.42(4H, s, 7–H, 7′–H, 8–H, 8′–H), 8.27(2H, s, 5–H, 5′–H). MS: m / z 379(MH$^+$).

2f: IR: 1609, 1587, 1536, 1439, 1324, 906, 794, 697 cm^{-1}..^{1}H–NMR: δ 6.77(4H, dd, J=1.7, 8.0Hz, 2′–H, 2‴–H, 6′–H, 6‴–H), 6.90–7.25(6H, m, ArH), 7.35–7.60(6H, m, ArH), 8.35–8.65(2H, m, 5–H, 5″–H). MS: m / z 475(MH$^+$).

2g: IR: 1616, 1594, 1539, 1475, 1405, 1336, 1294, 911, 751, 730, 702 cm^{-1}..^{1}H–NMR: δ 2.46(6H, s, Me× 2), 6.78(4H, dd, J=1.7, 8.0Hz, 2′–H, 2‴–H, 6′–H, 6‴–H), 6.85–7.45(10H, m, ArH), 8.39(2H, d, J=0.6Hz,5–H, 5″–H). MS: m / z 405(MH$^+$).

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