DEHYDROGENATION BY IODINE-DIMETHYLSULFOXIDE SYSTEM: A GENERAL ROUTE TO SUSBTITUTED CHROMONES AND THIOCHROMONES[☆]

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Abstract: The generality of the titled procedure for the convenient and easy preparation of flavones, 3-substituted flavones, chromones, 2-substituted chromones and their thio analogues is demonstrated.

INTRODUCTION

4*H*-1-Benzopyran-4-ones (chromones) and their 2-aryl-substituted derivatives (flavones) are widely distributed in the plant kingdom. Some of these naturally occurring compounds and their synthetic analogues including thio derivatives (1-thiochromones and 1-thioflavones) have shown wide variety of significant biological activities (1,2) in humans, including anticancer (2a), antiviral (2c), anti-HIV (2d,e) and protein-tyrosine kinase inhibitory (2g,h) effects. Although numerous methods have been developed for their syntheses (3), there is a continuous effort to improve the procedures. Dimethyl sulfoxide (DMSO) containing catalytic amount of iodine has been reported as an efficient reagent for the synthesis of flavones from either 2'-hydroxychalcones or 2-aryl-2,3-dihydro-4*H*-1-benzopyran-4-ones (flavanones). (4) This methodology has also been applied successfully in the preparation of 2-styrylchromones. (4b,5) Related procedures using iodine/DMSO/sulfuric acid (6a) or sodium periodate/DMSO (6b) have also been published. On the other hand, only a limited set of substituents and substrates has been studied so far. Therefore, we decided to undertake some systematic studies to disclose scopes and limits of this methodology.

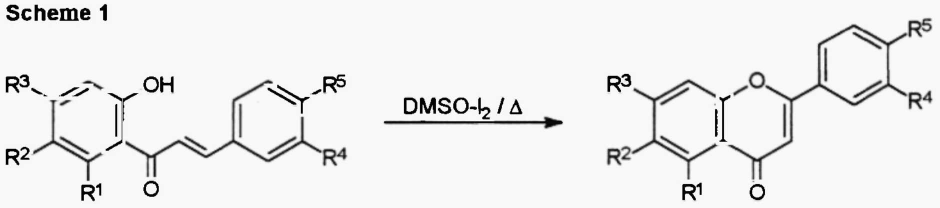
RESULTS AND DISCUSSION

Treatment of variously substituted 2'-hydroxychalcones **1** with catalytic amount of iodine in hot DMSO resulted in the corresponding flavones **2** in high yield (usually > 80%) (Scheme 1, Table 1).

[☆] Dedicated to Prof. Waldemar Adam on the occasion of his 60th birthday

Cyclodehydrogenation took place smoothly in the presence of both electron-withdrawing (Entries 3-6, 12-14) and electron-donating (Entries 7,15,16) substituents. Substituents sensitive to oxidation such as isopropyl (Entry 10) and formyl (Entries 2 and 12) tolerated well the conditions and no nuclear iodination or oxidation was observed even in the case of highly activated aromatic rings (Entries 15 and 16). Alkyl acetal protecting groups were completely cleaved (Entries 1,9,11) but aryl acetals remained intact (Entry 7) during the cyclodehydrogenation. In accordance with previous results (3c), benzyloxy group showed considerable stability in this reaction of short period of time (Entries 1 and 2). The observed clear differentiation between alkyl and aryl acetals, benzyloxy and alkoxy functionalities allows the easy and versatile synthesis of great variety of partially protected/alkoxylated naturally occurring hydroxyflavones.

Scheme 1



1 2

1,2	R^1	R^2	R^3	R^4	R^5
a	BnO	H	H	H	$CH(OEt)_2$
b	BnO	H	H	H	CHO
c	H	F	H	H	H
d	H	Cl	H	H	H
e	H	Cl	H	H	MeO
f	H	Br	H	H	
g	H	H	H	$-OCH_2O-$	
h	H	Me	Me	$-O(CH_2)_3O-$	
i	H	H	$MeOCH_2O$	$-O(CH_2)_3O-$	
j	H	H	HO	$-O(CH_2)_3O-$	
k	H	H	H	H	iPr
l	H	H	H	H	$CH(OEt)_2$
m	H	H	H	H	CHO
n	H	H	H	H	CN
o	H	H	H	H	F
p	H	H	H	H	OH
r	H	H	H	H	NMe_2

Table 1. Synthesis of Flavones 2, 3-Substituted Flavones 4, Chromones 7 and Thiochromones 9

Entry	Starting material	Product	Yield[a]
1	1a	2b	84
2	1b	2b	87
3	1c	2c	90
4	1d	2d	92
5	1e	2e	80
6	1f	2f	84
7	1g	2g	84
8	1h	2h	80
9	1i	2j	59
10	1k	2k	82
11	1l	2m	79
12	1m	2m	82
13	1n	2n	85
14	1o	2o	91
15	1p	2p	75
16	1r	2r	63
17	3a	4a	79
18	3b[b]	4b	18[c]
19	3c	4c	87
20	3d	slow decomposition	
21	5a	7a	31
22	5b	7b	44
23	6b	7b	70
24	6c	7c	48
25	6d	7d	66
26	5e	7e	30
27	5f	7f	68
28	5g	7g	36
29	8a	9a	47
30	8b	9b	77

[a] Refer to purified products [b] *cis/trans* (ca. 3:2) mixture [c] 11% of flavone was also isolated

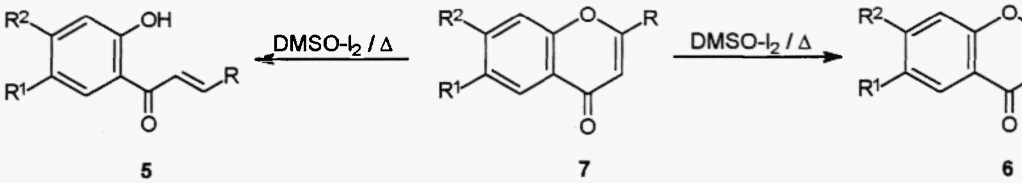
Treatment of 3-substituted flavanones **3a-c**, a family of compounds which has not been investigated previously, was found to afford the desired 3-substituted flavones **4a-c** (Scheme 2, Table 1). Low yield of **4b** may be rationalized in terms of the well-documented good leaving group ability of thiocyanato group. (7) The ammonium salt **3d** failed to yield any **4d**, only the slow decomposition of the starting material could be observed.

Scheme 2

3,4	X	R^1
a	Me	H
b	SCN	H
c	$NHCOCF_3$	Me
d	NHBn.HCl	H

As a further extension, the reaction of 1-(2-hydroxyphenyl)-2-propen-1-ones **5a,b**, 1-(2-hydroxy-4-methoxyphenyl)-2-buten-1-one (**5e**), 3-heteroaryl-1-(2-hydroxyphenyl)-2-propen-1-ones **5f,g** and 2,3-dihydro-4*H*-1-benzopyran-4-ones (chromanones) **6b-d** was also studied (Scheme 3, Table 1).

Scheme 3

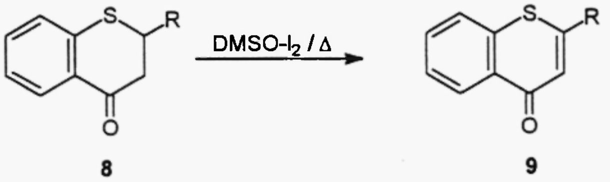


5,6,7	R	R^1	R^2
a	H	H	H
b	H	Cl	H
c	H	Me	H
d	H	MeO	H

5,6,7	R	R^1	R^2
e	Me	H	MeO
f	2-benzofuryl	H	H
g	1-methyl-2-pyrrolyl	H	H

Substrates listed above were found to give the appropriate chromones **7a-g** but the yields depended significantly on the structure of the starting material. Thus, yields for enones **5** with only hydrogen and alkyl group in their β position were lower (Entries 21,22,26) than those for chromanones **6** (Entries 23-25, also compare Entry 22 to Entry 23). Only cyclodehydrogenation but no functionalization of heteroaryl unit R was observed in the transformation of enones **5f,g**.

Scheme 4

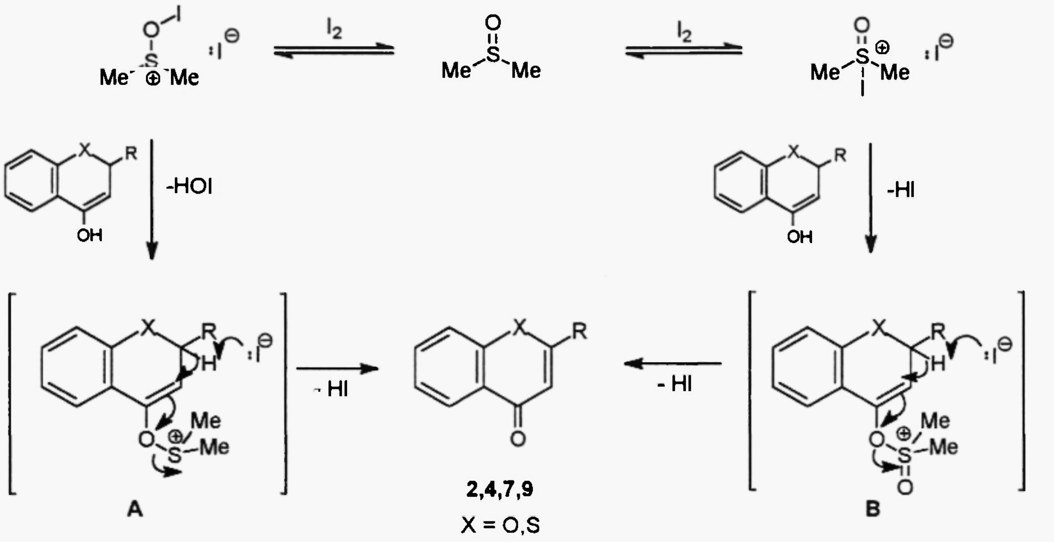


8,9	R
a	H
b	Ph

Upon treatment of 2,3-dihydro-4*H*-1-benzothiopyran-4-ones **8a,b** the desired thiochromones **9a,b** were obtained in moderate-to-good yield (Scheme 4, Table 1, Entries 29,30).

To explain our experimental findings, particularly the lack of any nuclear iodination of the activated aromatic rings, a mechanism closely related to Moffatt and Swern oxidations (8) could be postulated instead of the previous sequence (6a) with intermediacy of α-iodo ketones. In the case of 1-(2-hydroxyphenyl)-2,3-alkene-1-ones a ring closure to the corresponding chroman-4-ones takes place first. In the next step an iodide attack on allylic hydrogen of **A** or **B** intermediates formed from enolized benzoheterocyclanones and I_2/DMSO reagent (9) provides the cyclic enones **2,4,7,9** (Scheme 5).

Scheme 5



$HOI + HI \rightarrow H_2O + I_2$

$Me_2SO + 2\,HI \rightarrow H_2O + Me_2S + I_2$

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage apparatus and uncorrected. ^1H NMR (200 MHz) spectra were taken with a Bruker WP 200 SY instrument (internal standard TMS) in $CDCl_3$ solution unless otherwise stated. Elemental analysis were performed in-house on a Carlo Erba EA 1106 analyzer. Column chromatography was performed on Kieselgel 60 (0.063-0.2 mm) (Reanal). Thin-layer chromatography was performed on Kieselgel 60 F_{254} (Alurolle) (Merck) using toluene/EtOAc (4:1) and hexane/Me_2CO (2:1) mixtures as developing systems.

Synthesis of Substituted Chromones and Thiochromones. General Procedure: A solution of 5 mmole of enone **1,5** or benzocyclanone **3,6,8** and iodine (85 mg, 0.33 mmole) in abs. DMSO (10 mL) was slightly refluxed for 20-30 min (TLC monitoring). The mixture was poured in dil. Na_2SO_3 solution, the precipate was filtered off, washed with water. The crude product was purified by recrystallization from methanol, DMF-methanol, or hexane-ethyl acetate mixture or by column chromatography (eluent: toluene-ethyl acetate, 2:1-4:1, v/v). Physical and spectral characteristics of the products obtained are summarized in Table 2.

Table 2. Physical and Spectral Data of Flavones **2**, 3-Substituted Flavones **4**, Chromones **7** and Thiochromones **9**

Compd.	Mp [°C]	Lit. mp [°C]	^{1}H NMR δ [ppm], *J* [Hz]
2b	193-195	-	10.09 (s, 1H, CHO), 8.04 (AB q, 4H, 2’,3’,5’,6’-H), 7.63 (d, *J* = 8.6, 2H, 2”,6”-H), 7.55 (dd, *J* = 8.4, 8.3, 1H, 7-H), 7.27-7.43 (m, 3”,4”,5”-H), 7.15 (dd, *J* = 8.4, 0.6, 1H, 6-H), 6.88 (d, *J* = 8.3, 1H, 8-H), 6.81 (s, 1H, 3-H), 5.31 (s, 2H, CH_2)
2c	128-129	128-129 (8)	-
2d	183-185	182-183 (8)	-
2e	184-185	180-181 (8)	-
2f	194-195	189-190 (8)	-
2g	199-201	200-201 (9)	8.23 (dd, *J* = 7.9, 1.6, 1H, 5-H), 7.70 (ddd, 1H, 7-H), 7.37-7.57 (m, 4H, 6,8,2’,6’-H), 6.95 (d, *J* = 8.2, 1H, 5’-H), 6.72 (s, 1H, 3-H), 6.09 (s, 2H, OCH_2O)
2h	207-209	207-208 (10)	-
2j[b]	301-303	> 260 (11)	10.82 (s, 1H, 7-OH), 7.87 (d, *J* = 8.7, 1H, 5-H), 7.66 (m, 2H, 2’,6’-H), 7.11 (d, *J* = 9.0, 1H, 5’-H), 7.01 (d, *J* = 2.1, 1H, 8-H), 6.92 (dd, *J* = 8.7, 2.1, 1H, 6-H), 6.82 (s, 1H, 3-H), 4.24 (AB q, 4H, 3’,4’-$OCH_2CH_2CH_2O$), 2.17 (m, 2H, 3’,4’-$OCH_2CH_2CH_2O$)
2k	71-73	76.5-78 (12)	-
2m	162-164	-	10.12 (s, 1H, CHO), 8.25 (dd, *J* = 7.8, 1.7, 1H, 5-H), 8.12 (d, *J* = 8.6 Hz, 1H, 2’,6’-H), 8.05 (d, *J* = 8.6 Hz, 1H, 3’,5’-H), 7.75 (ddd, *J* = 8.2, 7.6, 1.7, 1H, 7-H), 7.61 (dd, *J* = 8.2, 1.1, 1H, 8-H), 7.46 (ddd, *J* = 7.8, 7.6, 1.1, 1H, 6-H), 6.92 (s, 1H, 3-H)
2n	217-219	220-221 (13)	-
2o	148-150	148-149 (14)	-
2p[b]	262-267	269 (15)	8.04 (dd, *J* = 8.1, 1.4, 1H, 5-H), 7.98 (d, *J* = 8.8 Hz, 2H, 2’,6’-H), 7.82 (m, 2H, 7,8-H), 7.49 (m, 1H, 6-H), 6.96 (d, *J* = 8.8 Hz, 2H, 3’,5’-H), 6.86 (s, 1H, 3-H)
2r	158-160	-	8.22 (dd, *J* = 8.0, 1.1, 1H, 5-H), 7.83 (d, *J* = 9.1, 2H, 2’,6’-H), 7.66 (ddd, 1H, 7-H), 7.53 (d, *J* = 8.4, 1H, 8-H), 7.39 (ddd, 1H, 6-H), 6.76 (d, *J* = 9.1, 2H, 3’,5’-H), 6.71 (s, 1H, 3-H), 3.07 (s, 6H, NMe_2)
4a	70-71	72-74 (16)	-
4b	154-155	150-152 (17)	-
4c	154-155	-	8.40 (br s, 1H, NH), 8.24 (dd, *J* = 7.9, 1.5, 1H, 5-H), 7.75 (ddd, 1H, 7-H), 7.67 (d, *J* = 8.2, 2H, 2’,6’-H), 7.42-7.58 (m, 2H, 6,8-H), 7.32 (d, *J* = 8.2, 2H, 3’,5’-H), 2.44 (s, 3H, Me)
7a	52-53	55-57, 58-60 (1c)	-
7b	135-137.5	140-142 (1c)	-
7c	86-88	88-89 (1c)	-
7d	81-82	97-98 (1c)	7.85 (d, *J* = 6.0, 1H, 2-H), 7.57 (d, *J* = 3.0, 1H, 5-H), 7.41 (d, *J* = 9.1, 1H, 8-H), 7.27 (dd, *J* = 9.1, 3.0, 1H, 7-H), 6.34 (d, *J* = 6.0, 1H, 3-H), 3.90 (s, 3H, 6-OMe)
7e	115-116	114-115 (1c)	-

Table 2. Physical and Spectral Data of Flavones **2**, 3-Substituted Flavones **4**, Chromones **7** and Thiochromones **9** (cont'n)

Compd.	Mp [°C]	Lit. mp [°C]	^{1}H NMR δ [ppm], *J* [Hz]
7f	134-135	-	8.23 (dd, *J* = 7.9, 1.6, 1H, 5-H), 7.32-7.76 (m, 8H, Ar-H), 6.96 (s, 1H, 3-H)
7g	121-123	-	8.33 (dd, *J* = 7.8, 1.5, 1H, 5-H), 7.67 (ddd, 1H, 7-H), 7.37-7.49 (m, 2H, 6,8-H), 6.87 (d, *J* = 3.3, 2H, 3',5'-H), 6.71 (s, 1H, 3-H), 6.25 (t, *J* = 3.3, 1H, 4'-H), 3.98 (s, 3H, 1'-Me)
9a	76-78	76-78 (18)	-
9b	121-124	125 (18)	-

[a] Satisfactory elemental analyses (C,H,N) were obtained for the new products

[b] ^{1}H NMR spectrum was recorded in DMSO-d_6

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REFERENCES

(1) For monographs and reviews see: (a) K. Böhm, *Die Flavonoide: Eine Übersicht über ihre Physiologie, Pharmakodynamik und therapeutische Verwendung*, Cantor, Aulendorf, 1967 - (b) N.S. Parmar and M.N. Ghosh, *Indian J. Pharmacol.* 12, 213 (1980) - (c) B. Havsteen, *Biochem. Pharmacol.* 32, 1141 (1983) - M. Gábor, *The Pharmacology of Benzopyran derivatives and related Compounds*, Akadémiai Kiadó, Budapest, 1988

(2) (a) M.C. Bibby, *Br. J. Cancer* 63, 3 (1991) - (b) D. Dauzonne and L. Martinez, *Tetrahedron Lett.* 36, 1845 (1995) - (c) N. De Meyer, A. Haemers, L. Mishra, H.-K. Pandey, L.A.C. Pieters, D.A Vanden Berghe and A.J. Vlietinck, *J. Med. Chem.* 34, 736 (1991) - (d) R.I. Brinkworth, M.J. Stoermer and D.P. Fairlie, *Bichem. Biophys. Res. Commun.* 188, 631 (1992) - (e) R. Tang, K Chen, M. Cosentino and K.-H. Lee, *Biomed. Chem. Lett.* 4, 455 (1994) - (f) M. Cushman, D. Nagarathnam, D.L. Burg and R.L. Geahlen, *J. Med. Chem.* 34, 798 (1991) - (g) M. Cushman, H. Zhu, R.L. Geahlen and A.J. Kraker, *J. Med. Chem.* 37, 3353 (1994)

(3) For details see: (a) T.A. Geissman (Ed.), *The Chemistry of Flavonoid Compounds*, Pergamon, Oxford, 1962 - (b) J.B. Harborne, T.J. Mabry and H. Mabry (Eds.), *The Flavonoids*, Chapman & Hall, London, 1975 - (c) G.P. Ellis (Ed.), *Chromenes, Chromanones and Chromones*, Wiley, New York, 1977 - (d) T. Patonay, D. Molnár and Z. Murányi, *Bull. Soc. Chim. Fr.* 132, 233 (1995)

(4) (a) A.G. Doshi, P.A. Soni and B.J. Ghiya, *Indian J. Chem.* 25B, 759 (1986) - (b) J.A.S. Cavaleiro, J. Elguero, M.L. Jimeno and A.M.S. Silva, *Chem. Lett.* 445 (1991)

(5) (a) J.K. Makrandi and Seema, *Indian J. Chem.* 30B, 788 (1991) - (b) W.A. Price, A.M.S. Silva and J.A.S. Cavaleiro, *Heterocycles* 36, 2601 (1993) - (c) A.M.S. Silva, D.C.G.A. Pinto and J.A.S. Cavaleiro, *Tetrahedron Lett.* 35, 5899 (1994) - (d) D.C.G.A. Pinto, A.M.S. Silva and J.A.S. Cavaleiro, *Tetrahedron Lett.* 35, 9459 (1994)

(6) (a) W. Fatma, J. Iqbal, H. Ismail, K. Ishratullah, W.A. Shaida and W. Rahman, *Chem. Ind. (London)* 315 (1979) - (b) N. Hans and S.K. Grover, *Synth. Commun.* 23, 1021 (1993)

(7) (a) T. Thorstenson and J. Songstad, *Acta Chem. Scand.* 32A, 133 (1978) - (b) K. Maartman-Moe, K. Sanderud and J. Songstad, *Acta Chem. Scand.* 36B, 211 (1982) - (c) S. Oae, N. Yamada, K. Fujimori and O. Kikuchi, *Bull. Chem. Soc. Jpn.* 56, 248 (1983)

(8) (a) T. Durst, in *Comprehensive Organic Chemistry, Vol. 3*, D.H.R. Barton and W.D. Ollis (Eds.), Pergamon, Oxford, 1979, 121 - (b) A.J. Mancuso and D. Swern, *Synthesis* 165 (1981)

(9) For the structure of DMSO-Hlg$_2$ (Hlg = Cl, Br, I) reagents see: (a) E.J. Corey and U. Kim, *Tetrahedron Lett.* 919 (1973) - (b) P.A. Zoretic, *J. Org. Chem.* 40, 1867 (1975) - (c) T.V. Lee, in *Comprehensive Organic Synthesis, Vol. 7*, B.M. Trost and I. Fleming, I. (Eds.), Pergamon, Oxford, 1991, 291 - (d) R.M. Munavu, *J. Org. Chem.* 45, 3341 (1980) - (e) M. Mikolajczyk and M. Luczak, *Synthesis* 114 (1975)

(10) C.T. Chang, F.C. Chen, T.S. Chen, K.K. Hsu, T. Ueng and M. Hung, *J. Chem. Soc.* 3414 (1961)

(11) K. Auwers and L. Anschütz, *Ber.* 54, 1543 (1921)

(12) G. Litkei, T. Patonay, R. Bognár, V.P. Khilya, A. Aitmambetov and F. Babichev, *Pharmazie* 39, 741 (1984)

(13) T. Patonay, G. Litkei, E. Peli, V.P. Khilya and A. Aitmambetov, *Pharmazie* 42, 662 (1987)

(14) T. Patonay, R. Bognár and G. Litkei, *Tetrahedron* 40, 2555 (1984)

(15) P. Da Re, A. Colleoni, L. Verlicchi, *Ann. Chim. (Rome)* 48, 762 (1958); *Chem. Abstr.* 53, 21924h (1959)

(16) F.C. Chen, T.S. Chen and T. Ueng, *J. Chinese Chem. Soc. (Taiwan)* 9, 308 (1962); *Chem. Abstr.* 60, 10639a (1964)

(17) S. Grossmann and. S. Kostanecki, *Ber.* 33, 2516 (1900)

(18) A.T.M. Dunne, J.E. Gowan, K. Keane, B.M. O'Kelly, D. O'Sullivan, M.M. Roche, P.M. Ryan and T.S. Wheeler, *J. Chem. Soc.* 1252 (1950)

(19) T. Patonay, G. Litkei and R. Bognár, *Tetrahedron* 40, 3425 (1984)

(20) F. Arndt, *Ber.* 58, 1612 (1925)

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