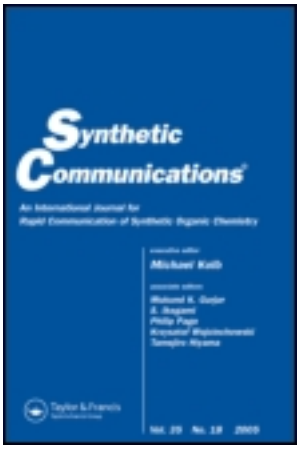

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Sodium Perborate Tetrahydrate-Mediated Transformations of 2′-Hydroxychalcones to Flavanones, Flavones, and 3′, 5′-Diiodoflavone Under Mild, Environmentally Friendly Conditions

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SODIUM PERBORATE TETRAHYDRATE–MEDIATED TRANSFORMATIONS OF 2′-HYDROXYCHALCONES TO FLAVANONES, FLAVONES, AND 3′, 5′-DIIODOFLAVONE UNDER MILD, ENVIRONMENTALLY FRIENDLY CONDITIONS

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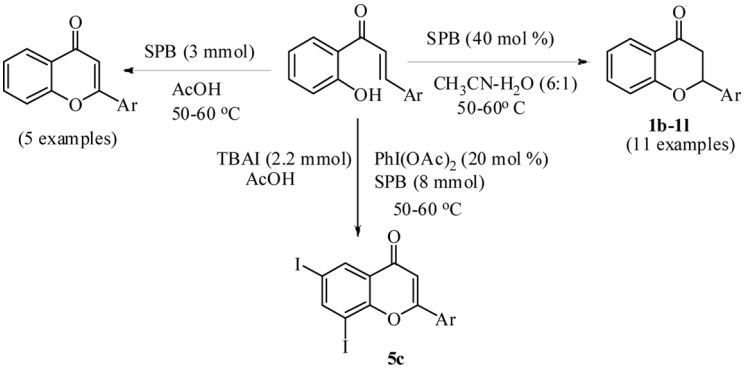
GRAPHICAL ABSTRACT



Abstract *Sodium perborate tetrahydrate has been utilized as a nucleophilic catalyst for facile conversion of 2′-hydroxychalcones to flavanones in warm aqueous acetonitrile, and then these chalcones, upon oxidative cyclization in warm acetic acid with an excess of the same reagent, afforded flavones in acceptable yields. One-pot synthesis of 3′,5′-diiodoflavone has been accomplished by diacetoxyiodobenzene-catalyzed iodination of 2′-hydroxychalcone with tetra-n-butylammonium iodide in acetic acid in the presence of sodium perborate as a terminal oxidant.*

Keywords 3′,5′-Diiodoflavone; flavanone; flavone; 2′-hydroxychalcone; sodium perborate tetrahydrate

INTRODUCTION

Flavonoids (C6–C3–C6 compounds of natural origin) are a versatile class of secondary plant metabolites that are widely distributed in vascular plants and endowed with a broad range of bioactivities including antitumor,[1] antimetastatis,[2]

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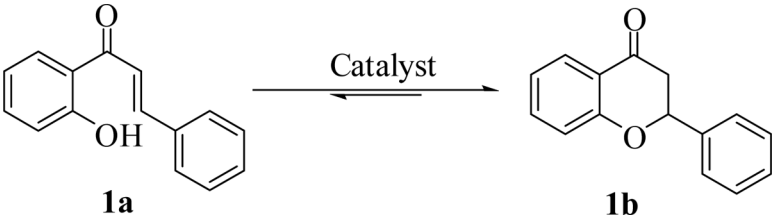


Scheme 1. Biosynthesis of flavonoids catalyzed by chalcone isomerase enzme.

antioxidant,[3] antimicrobial,[4] antiviral,[5] and neuron protection[6] properties. Flavanones are characterized by a 2-arylchroman-4-one core and constitute an important subclass of flavonoids. Because of their antitumor and anti-inflammatory properties, flavanones have currently attracted interest as promising selective estrogen receptor modulators[7] and tumor necrosis factor (TNF)-α inhibitors.[8] They occupy a crucial position in the biosynthetic route of flavonoids connecting 2′-hydroxychalcones as precursors to other substructures of this group, such as flavones, isoflavones, cyanidins, and dihydroflavonols. The oxa-Michael type cyclization of 2′-hydroxychalcones that generates the chroman core of flavanones is a fundamental step in the biosynthesis of flavonoids (Scheme 1) and is catalyzed by the chalcone isomerase enzyme in plant, fungi, and bacteria with astonishing high levels of enantioselectivity. However, the isomerization is typically sluggish, particularly for nonsubstituted 2′-hydroxychalcones under ambient and neutral conditions.

An unabated search for efficient and selective procedures to realize the transformation has continued over the years, leading to the development of a host of protocols employing various reagents and conditions ranging from aqueous buffers at variable pH values,[9] mineral acids,[10] acidic ion-exchange resin,[11] NaOH with and without phase-transfer catalysts,[12] CH_3CO_2Na,[13] KF,[14] amino acids,[12] Co^{III}-salen complex catalyst,[15] and Lewis acids[16] to photoirradiation,[17] thermal reaction in the solid state,[18] and electrochemical reactions.[19] However, a good number of reported methods employ either stoichiometric or excess of reagents and some of them have serious environmental constraints such as solvent-intensive separation of products from unreacted starting materials and by-products. In continuation of our interest in developing environmentally friendly synthetic protocols,[20] we felt the need to develop an efficient protocol for cyclization under environmentally compatible conditions. To this end, we identified sodium perborate tetrahydrate ($NaBO_3$, $4H_2O$; SPB) as a nucleophilic oxidant in view of its ability to deliver perhydroxyl anion through the associated species $[B(OH)_3OOH]^-$ at a lower pH than is available from H_2O_2 in aqueous organic solvents.[21a] It is an inexpensive, nontoxic, and shock-insensitive reagent with good storage stability and has been widely used in the detergent industry as a safe bleaching and antiseptic agent on large scale without any waste disposal problem. Despite versatile applications as a nucleophilic oxidizing agent in functional group oxidations,[21a–d] the catalytic role of SPB is rarely exploited.[21e] This prompted us to assess the hitherto unexplored efficacy of SPB for the transformation of 2′-hydroxychalcones to flavanones, particularly under catalytic or substoichiometric conditions.

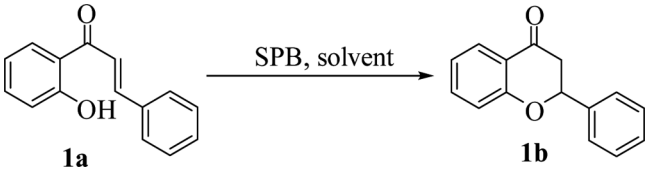
RESULTS AND DISCUSSION

For initial optimization experiments, 2′-hydroxychalcone (**1a**) was allowed to undergo SPB-mediated cyclization to flavanone (**1b**) under various conditions (Table 1).

The reaction did not proceed to completion with a suspension of SPB (40 mol%) in dry acetonitrile at 50–60 °C, providing an unsatisfactory yield (52%) of **1b**. Gratifyingly, aqueous acetonitrile proved to be the medium of choice, with the yield of **1b** showing modest dependence on the composition of the solvent. The most rewarding result was obtained in CH_3CN-H_2O (6:1) with an exclusive yield of **1b** (86%) in a clean reaction within 1 h (entry 4). Optimization of catalyst loading revealed that use of neither lower nor stoichiometric amounts of SPB delivered better result (entries 5 and 6). Protic solvents such as aqueous ethanol, methanol, and acetic acid were also screened, but with poor results. The optimized reaction conditions [40 mol% SPB, CH_3CN-H_2O (6:1), 50–60°C] were successfully extended to a good number of 2′-hydroxychalcones to demonstrate generality and compatibility with a number of common functional and protecting groups (Cl, OH, OMe, allyloxy, propargyloxy, methylenedioxy). 2′-Hydroxychalcone analogs derived from heterocyclic aldehydes such as furfural and thiophene-2-aldehyde were also accommodated in the protocol, albeit the yields of the corresponding flavanone analogs were on the lower side (entries 9 and 10, Table 2). The results of these experiments are summarized in Table 2.

The stereoelectronic requirement for the 6-*endo-trig* mode of ring closure is the decisive factor in the cyclization process. Earlier model studies of 2′-hydroxychalcone system revealed that the optimum Bürgi–Dunitz trajectory[23a] for this mode of six-membered ring closure was not attainable as the hydroxy group is well offline for a 109° approach of its lone pairs with respect to the plane of the

Table 1. Optinization experiments on SPB-mediated concersion of 2′-hydroxychalcone **1** to flavanone **1a**

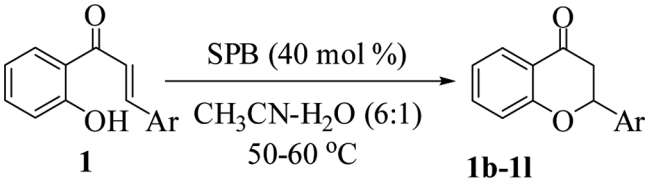


1a **1b**

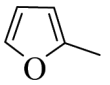
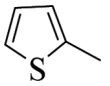
Entry	Amount of SPB (mol%)	Solvent (4 mL)	Reaction time[a] (h)	Yield of **1b**[b]
1	40	dry CH_3CN	3	52
2	40	CH_3CN-H_2O (4:1)	3	64
3	40	CH_3CN-H_2O (6:1)	3	85
4	40	CH_3CN-H_2O (6:1)	1	86
5	30	CH_3CN-H_2O (6:1)	1	68
6	100	CH_3CN-H_2O (6:1)	1	75
7	40	EtOH-H_2O (6:1)	1	70
8	40	MeOH-H_2O	1	78
9	40	CH_3CO_2H-H_2O	1	10

[a]The reactions were carried out on a 1-mmol scale of **1a** at 50–60 °C using 4 mL of solvent each case.
[b]Isolated yield after chromatographic separation.

Table 2. SPB-catalyzed conversion of 2′-hydroxy chalcone to flavanone in aqueous acetonitrile



1 **1b-1l**

Entry	Ar	Product[a]	Time (h)	Yield[b] (%)	Mp (°C) (lit. mp)
1	C_6H_5	**1b**	1	86	74–76 (75–76)[12]
2	3-Cl C_6H_4	**1c**	2.5	74	98–100 (98–99)[22a]
3	4-Cl C_6H_4	**1d**	1	80	82–84 (84–85)[22b]
4	4-OH C_6H_4	**1e**	4	54	192–194 (190–192)[22c]
5	4-OMe C_6H_4	**1f**	2	68	96–98 (96–97)[22b]
6	4-*O*-ally C_6H_4	**1g**	2	76	70–72
7	3,4-(-OCH_2O-)C_6H_3	**1h**	3	64	118–120
8		**1i**	2.5	50	72–74 (74–75)[22d]
9		**1j**	1.5	54	86–88
10	3-OMe, 4-*O*-propargyl C_6H_3	**1k**	4	72	80–82
11	4-MeC_6H_4	**1l**	1.5	76	82–84 (82–83)[22a]

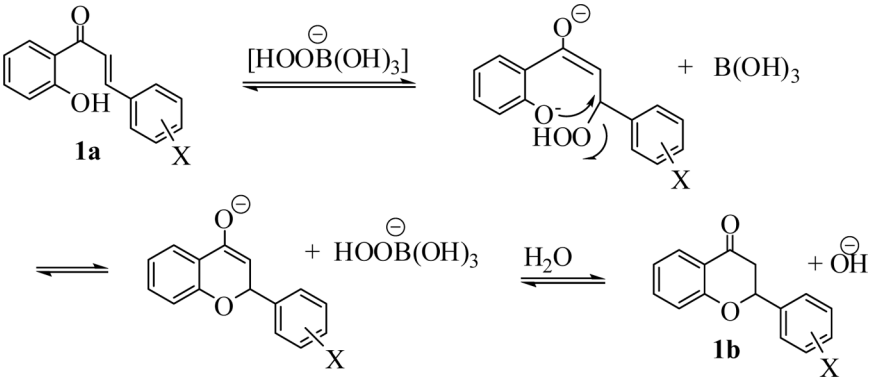
[a]The known compounds exhibit spectral data (FT-IR, ^{1}H CNMR, ^{13}CNMR, MS) and melting points in agreement with those reported in the literature.

[b]Isolated yield after column chromatographic separation.

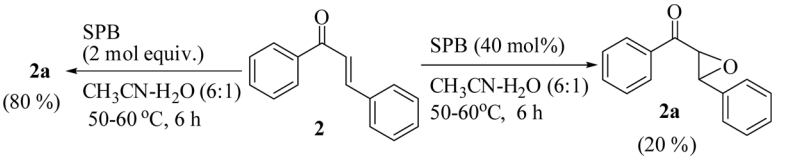
double bond, due to the unfavorable nature of the connecting chain comprising sp^2-hybridized carbons with larger bond angle of 120° coupled with the rigidity of the conjugated system to remain in plane.[23b] Consequently upon the stereoelectronic restriction imposed upon the 2′-hydroxy group as a intramolecular Michael donor, perhydroxyl anion from SPB initiates external nucleophilic attack on the enone moiety. This softens the rigidity of the connecting chain, making the β-carbon end sp^3-hybridized and paving the way for subsequent oxyanion-mediated Michael ring closure to **1b** by 6-*exo-tet* mode (Scheme 2). Thus SPB essentially functions as a nucleophilic catalyst rather than an oxidant in this reaction.

Complete nonformation of epoxychalcones was somewhat surprising in view of the reported epoxidation of α, β-unsaturated ketones with SPB (2 mol equiv.) in the presence of phase-transfer catalyst under aqueous conditions.[24a] Presumably, this is due to the presence of 2′-OH, which plays a key facilitatory role to bias the reaction toward cyclization by fast evicting the perhydroxyl anion. To test this hypothesis, the chalcone **2**, which lacks the 2′-OH group, was treated under the optimized conditions to afford the corresponding epoxide[24b] **2a** in 20% yield, which vastly improved to 80% with an excess of the reagent (Scheme 3).

The success of SPB-induced flavanone cyclization motivated us to evaluate its oxidizing potential for entry into other subclasses of flavonoids of greater oxidation



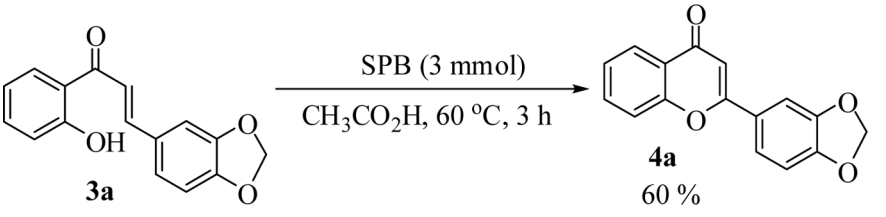
Scheme 2. Oxyanion-mediated Michael ring closure by 6-exo-tet mode.



Scheme 3. Epoxidation fo unsubtituted chaclone **2** with SPB.

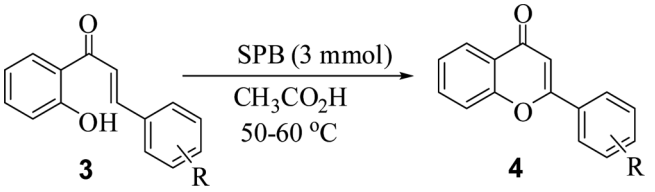
level. To realize this, SPB in warm acetic acid, which generates powerful peracetoxyboron anion species,[21a] was envisaged to be a suitable oxidant for electron-deficient chalcones. Exposure of the chalcone **3a** to an excess of SPB in warm acetic acid for 3 h afforded the flavone **4a** in 60% yield (Scheme 4). The results of some similar conversions are shown in Table 3

Despite varied biological activities of iodinated heteroaromatic compounds,[26] only sporadic attempts toward synthesis of iodoflavones by way of oxidative condensation of iodinated flavones is documented in literature.[27] There is no literature precedence, to the best our knowledge, of one-pot conversion of 2′-hydroxychalcone to iodoflavones. Encouraged by the report of iodolactonization[28] catalyzed by diacetoxyiodobenzene in the presence of tetra-*n*-butylammonium iodide (TBAI) and sodium perborate in acetic acid, we reasoned that the reagent combination might accomplish iodination of activated phenolic ring of 2′-hydroxychalcone with



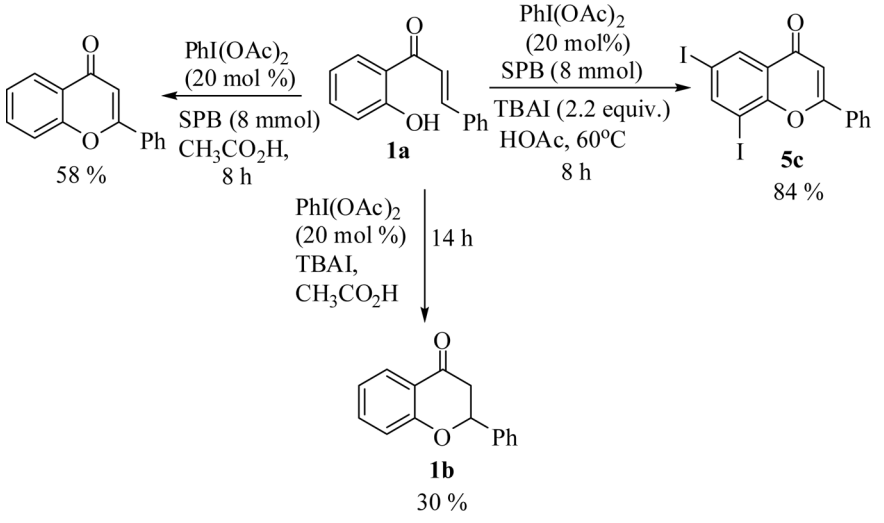
Scheme 4. Oxidative cycllization of 2′-hydroxychalcone to flavones with SPB.

Table 3. SPB-mediated synthesis of flavones



Entry	R	Product	Time (h)	Yield of flavones (%)	Mp (°C) (lit. mp)
1	H	**4b**	3	65	98–99 (97–99) [25a,b]
2	4-HCl	**4c**	3	58	186–188 (185–187)[25c]
3	4-CH_3	**4d**	3.5	55	106–107 (108–109)[25d]
4	4-OMe	**4e**	4	55	156–158 (157–158)[25d]

concomitant cyclization and oxidation to iodoflavone. Treatment of 2′-hydroxychalcone (**1a**) with TBAI (2.2 mol equiv.) in the presence of 20 mol% of diacetoxyiodobenzene, $PhI(OAc)_2$, and an excess of SPB in warm acetic acid resulted in a one-pot formation of 3′,5′-diiodoflavone (**5c)** in 84% yield. Attempted controlled monoiodination using 1 mol equiv. of TBAI while maintaining other conditions indentical was unsuccessful, giving **5c** only in poor yield. In the absence of TBAI, no iodoflavone was formed, but the flavone was isolated in 58% yield. On the other hand, exclusion of SPB from the reagent combination resulted in a sluggish, unclean conversion of **1a** to the corresponding flavanone **1b** in a disappointingly poor yield of 30% along with unconverted starting material. This observation attests to the key role of SPB as terminal oxidant in the hypervalent iodine–catalyzed oxidation of TBAI to iodonium ion equivalent for iodination of **1a** (Scheme 5).



Scheme 5. One-pot synthesis of 3',5′-diiodoflavone from 2′-hydroxychalcone.

In conclusion, the biogenetically relevant transformation of 2′-hydroxychalcones to flavanones has been accomplished using sodium perborate as a nucleophilic catalyst in warm aqueous acetonitrile. Utilization of an excess of the reagent in warm acetic acid provided access to flavones from the same precursor. One-pot synthesis of 3′,5′-diiodoflavone in excellent yield (by employing a catalytic amount of diacetoxyiodobenzene in the presence of TBAI as iodide source and SPB as a terminal oxidant) adds to synthetic utility of the protocol.

EXPERIMENTAL

Typical Procedure for the Conversion of 2′-Hydroxychalcone 1a into Flavanone 1b

2′-Hydroxychalcone **1a** (1.1 mmol, 246 mg) was added slowly to a stirred suspension of sodium perborate tetrahydrate (40 mol%, 61 mg) in CH_3CN-H_2O (6:1, 4 mL) maintained at 50–60 °C. The reaction mixture was thoroughly stirred for 1 h [thin-layerchramatography (TLC)monitoring]. The residue remaining after removal of organic solvent was extracted with ethyl acetate (3×5 mL) and the combined extract was washed with water (2×3 mL), dried (Na_2SO_4), and concentrated. It was subjected to column chromatography over silica gel (60–120 mesh) using light petrol–ethyl acetate (50:1) as eluent to afford **1b** (211 mg, 86%), as white solid, mp 74–76 °C, (lit.[12] 75–76 °C); IR (KBr): 3039, 2896, 1689, 1605, 1462, 1322, 1303, 1227, 1114, 1067, 907, 7066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (dd, $J = 1.5$, 8.1 Hz, 1H), 7.54–7.39 (m, 6H), 7.09–7.04 (m, 2H), 5.49 (dd, $J = 2.7$, 13.2 Hz, 1H), 3.00 (dd, $J = 13.5$, 16.8 Hz, 1H), 2.90 (dd, $J = 3$, 16.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.9, 161.5, 138.7, 1360.1, 128.8, 128.7, 127.0, 126.1, 121.6, 120.9, 118.1, 79.5, 44.6. Anal. calcd. for $C_{18}H_{16}O_3$: C, 80.03; H, 5.39. Found: C, 80.12; H, 5.46.

General Procedure for the Synthesis of Flavones from 2′-Hydroxychalcones

Sodium perborate tetrahydrate (3 mmol) was added to a stirred solution of 2′-hydroxychalcone (1 mmol) in acetic acid (4 mL), and the mixture was stirred at 50–60 °C for an appropriate time (TLC monitoring; Table 3). The reaction was quenched by pouring in ice-cold water and then neutralized by $NaHCO_3$. It was extracted with ethyl acetate (3×6 mL); the combined extract was washed with water, dried (Na_2SO_4), and concentrated. Column chromatographic purification over silica gel (60–120 mesh) using light petrol–ethyl acetate as eluent afforded the corresponding flavone.

Representative Procedure for the Conversion of 2′-Hydroxychalcone 1a into 3′,5′-Diiodoflavone 5c

2′-Hydroxychalcone **1a** (1 mmol, 224 mg) was added to a stirred suspension of sodium perborate tetrahydrate (8 mmol, 1.232 g) in glacial acetic acid (3 mL) followed by TBAI (2.2 molar equiv., 812 mg) and diacetoxyiodobenzene (20 mol%,

33 mg). The mixture was vigorously stirred at 50–60 °C for 8 h (TLC monitoring). The reaction was quenched by pouring the mixture in ice-cold water (15 mL) and then neutralized with solid $NaHCO_3$. It was extracted by ethyl acetate (3×6 mL) and the combined extract was washed with water (2×3 mL), dried over anhydrous Na_2SO_4, and concentrated. Column chromatography of the concentrated extract over silica gel (60–120 mesh) using light petrol–ethyl acetate (50:1) as eluent afforded **5c** (398 mg, 84%) as white solid; mp 188–190 °C; IR (KBr): 2922, 1653, 1439, 1346, 1249, 1097, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (d, $J = 2.0$ Hz, 1H), 8.41 (d, $J = 2.0$ Hz, 1H), 8.05–8.03 (m, 2H), 7.57 (d, $J = 6.8$ Hz, 3H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 163.9, 154.7, 150.5, 135.0, 132.2, 130.8, 129.2, 126.7, 125.8, 107.1, 89.7, 86.6; ESI-MS: $m/z = 475$ $[M + 1]^+$. Anal. calcd. for $C_{18}H_{16}O_3$: C, 38.01; H, 1.70. Found: C, 38.10; H, 1.76.

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