OXIDATIVE REARRANGEMENTS OF 2′-HYDROXYCHALCONES WITH 1*H*-1-HYDROXY-5-METHYL-1,2,3-BENZIODOXATHIOLE 3,3-DIOXIDE

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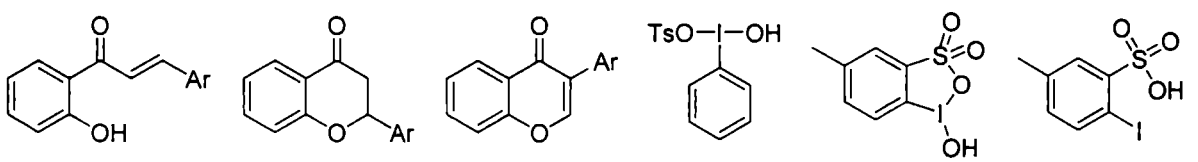
Abstract: 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI) has been found to effect the direct conversion of 2′-hydroxychalcones with various B-ring substituents to isoflavones in moderate to good yield (34-83%) in methanol under reflux. The reduced byproduct of HMBI is easily recovered by aqueous extraction and can be recycled and reused with high efficiency. Previous reports of conversions of this type required the use of toxic thallium(III) salts or initial protection of the 2′-hydroxyl group.

Application of the oxidative rearrangement of either 2′-hydroxychalcones **1** or flavanones **2** toward the preparation of isoflavones **3** has been well investigated.[1] In particular, considerable study of the thallium(III) induced oxidative rearrangement of **1** has been performed from both a synthetic[2] and mechanistic[3] viewpoint. Given the pharmacological application of **3**, preparations which use toxic thallium[4] salts are less than advantageous. Well known for their similar reaction modes to thallium(III) salts[5] hypervalent organoiodine reagents such as phenyliodine(III) bis(trifluoroacetate),[6] [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent, **4**),[6a,7] (diacetoxy)iodobenzene and its polymer-based analog[7] have also been employed for conversion of **2** to **3**. However, *direct* conversion of **1** to **3** using hypervalent iodine reagents has not been reported.



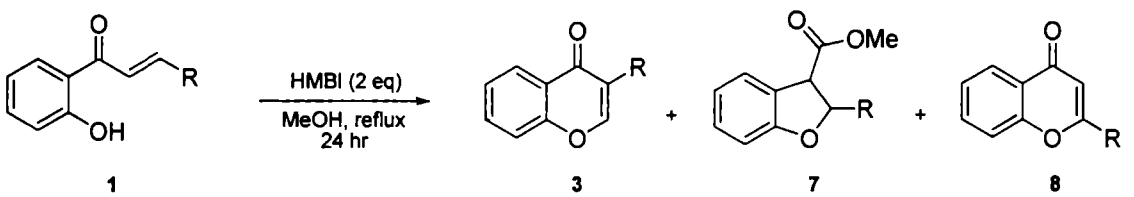
1 **2** **3** **4** **5** **6**

1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (**5**, HMBI) is structurally analogous to HTIB.[8] The reduced byproduct (**6**) is water soluble which allows recovery by simple liquid-liquid extraction, subsequent reoxidation and reuse. With our recent success in using HMBI for the oxidative rearrangement of arylalkanones to methyl 2-arylesters,[9] our attention turned to the possible preparation of **3** from **1**. Remarkably, Kawamura and coworkers observed that HTIB does not react with **1** unless the 2′-hydroxyl group was initially benzoyl protected.[7b,c] We reasoned that the reaction of **1** and HMBI merited study. Herein we wish to report the results of our investigation.

Results and Discussion

The preparation of substituted **1** was best effected using the method of Stoyanov et al.[10] This method is rapid and avoids co-formation of **2**.[11] In this initial survey, only B-ring substituted **1** were studied. In a typical reaction HMBI (2 eq.) was added to a stirred mixture of **1** in methanol and heated under reflux for a period of 24 hours

(Equation 1).[12] After aqueous work-up the crude products were separated and purified by preparative TLC using ethyl acetate/hexanes as eluant. In virtually all cases isoflavones were afforded as the major product. Methyl 2,3-dihydro-2-aryl-3-benzofurancarboxylates **7** and flavones **8** were also observed in low yield. All products were fully characterized by ^{1}H NMR, ^{13}C NMR, FT-IR and melting point and found to be in accord with literature values. The results are summarized in Table 1. Alternatively, **3** could be directly crystallized from the crude reaction mixture by trituration with methanol or ethanol, in slightly reduced yield. Only two substrates did not afford products comparative to the others. It is assumed that the strong electron withdrawing effect of the *p*-NO_2 group (Entry 9) reduces the overall electron density of the system as well as the migratory aptitude of the B-ring. In the case of Entry 12, oxidation of the furanyl moiety leading to an intractable mixture of products resulted.



1 3 7 8

Equation 1. Direct synthesis of isoflavones and minor products from 2'-hydroxychalcones using HMBI

Table 1. Products of the reaction of 2'-hydroxychalcones with HMBI (Equation 1)

		Yield,%[a]					Yield,%[a]		
Entry	1, R =	3	7	8	Entry	1, R =	3	7	8
1	phenyl	61	15	1[b]	8	3,4-(methylenedioxy)phenyl	72	5[b]	14
2	4-tolyl	64	15	11	9	4-nitrophenyl	--[c]	--	--
3	4-methoxyphenyl	83	2[b]	12	10	2-naphthyl	68	15	11
4	4-fluorophenyl	59	12	11	11	1-naphthyl	57	13	13
5	4-chlorophenyl	41	11	9	12	2-furanyl	--[c]	--	--
6	4-bromophenyl	47	13	11	13	2-thienyl	34	6[b]	0[b]
7	3,4-dimethoxyphenyl	61	4[b]	21					

[a] Isolated yields unless otherwise noted
[b] Yield determined by ^{1}H NMR using an internal standard in a separate experiment
[c] Intractable mixture of products

Several points of interest arose during this initial investigation. HMBI can induce the oxidative rearrangement of **1** to **3** without the need for initial protection or subsequent deprotection of the 2'-hydroxyl group as required for the reaction with HTIB.[7] Evidence has been presented by several investigators suggesting that substrates of this type coordinate strongly with the oxidant.[3a,13] It is speculated that the internal coordination of the *ortho*-sulfonyloxy group may inhibit full coordination of the iodine(III) moiety by **1** increasing reactivity.

The requirement for two equivalents of the reagent is unclear. During the initial survey, reaction mixtures were monitored by UV spectrometric analysis of a small an aliquot of the reaction mixture. It was determined that the reactions were sluggish and incomplete unless two equivalents of HMBI were used. The oxidant remaining after the reaction was less than one full equivalent as determined by iodometry. In control

studies, no degradation of the reagent was observed when heated in methanol for up to 48 hours nor when heated with isoflavone under similar conditions. In an effort to improve the yield of **3**, several protecting groups were applied to the 2′-hydroxyl group including tosyl, benzyl, and benzoyl. Under the reaction conditions, an intractable mixture of products resulted along with reduced recovery of protected or deprotected **1**.

Mechanisms for this transformation using thallium(III) salts have been proposed which suggest an intermediary 1,2-diaryl-3,3-dimethoxypropan-1-one,[3] which upon further reaction cyclizes to the isoflavone. It was observed during this study that reaction mixtures worked up prematurely contained substantial amounts of **2**. It is known that **1** can cyclize to **2** under acidic conditions.[14] To our knowledge, no example of the hypervalent iodine induced oxidative rearrangement of **1** with a free 2′-hydroxyl group is known, yet there are many examples of the oxidation or oxidative rearrangement of **2** under various conditions to give **3**,[15] **7**,[16] **8**[9,17] or mixtures of these compounds. In a control reaction 2′-hydroxychalcone and flavanone were treated under identical conditions with HMBI. Equivalent product distributions were observed within the crude products by ^{1}H NMR spectroscopy (as quantified using an internal standard). It is interesting to note that upon treatment with HTIB in methanol **2** produces **8** as the major product at r.t.[17c]

The advantages of using HMBI for this conversion include: reduced toxicity (compared to thallium salts), facile work up of the reaction mixtures and recovery of the reduced reagent. The recovered aqueous layers from the initial liquid-liquid extraction can be concentrated and the obtained crude **6** triturated with ether or hexanes to remove trace contaminants from the reaction mixture. Recovery of **6** is typically ~90%. A full discussion of the reoxidation efficiency and comparison to polymer based hypervalent iodine reagents has been reported previously.[9]

Conclusion

In conclusion, we have completed a preliminary investigation of the oxidative rearrangement of **1** to **3** using HMBI. This reagent is mild, easy to handle, and is readily recovered for reoxidation and reuse. Although no other oxidant of this type has been observed to effect the transformation of **1** with a non-protected 2′-hydroxyl group to **3**, evidence suggests the reaction may proceed through **2** formed under the reaction conditions.

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12. **General Procedure:** Crystalline HMBI (314 mg, 1.00 mmol) was added at once to a stirred mixture of **2** (0.50 mmol) in MeOH (7 mL), and heated under reflux for 24 hours. The resulting solution was allowed to cool to r.t. and concentrated to one half volume. H_2O (10 mL) was added and the mixture was then extracted with 90:10 ethyl acetate:hexanes (3 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated to an oil or oily solid. The crude material was separated by preparative TLC (1:3 ethyl acetate:hexanes) to afford three products identified as **3**, **7** and **8**. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), FT-IR and mp data was in accord with literature values.
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