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Oxidative rearrangements of arylalkanones with 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide, a 'green' analog of Koser's reagent

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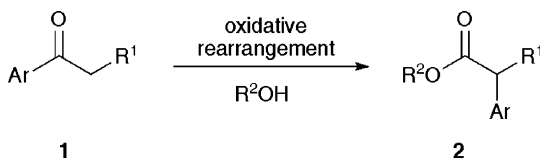
Abstract—Previous methods for the conversion of arylalkanones to alkyl 2-arylesters by oxidative rearrangement utilized reagents which either produced toxic metal salts or halogenated organics as by-products. In this report, 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI) is used to effect this useful transformation, where the reduced iodine reagent is water-soluble and readily recycled.

1. Introduction

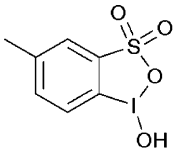
The conversion of arylalkanones **1** to alkyl 2-arylesters **2** by oxidative rearrangement (Scheme 1) and subsequent hydrolysis to the corresponding 2-arylacids is a facile and useful transformation. Many 2-arylacids are known for their anti-inflammatory, anti-pyretic, and analgesic properties and are the subject of continued interest.[1] Early methods used for this conversion utilized thallium(III),[2] silver (Woodward–Prevost conditions)[3] or lead salts.[4] Subsequently, due to the inherent toxicity[5] of these materials, alternative methods were developed which included the use of iodine, iodine monochloride, and iodine trichloride.[6]

Well known for their similar reaction modes to thallium(III) salts and Woodward–Prevost conditions,[7] hypervalent organoiodine reagents such as [hydroxy-(tosyloxy)iodo]benzene (HTIB, Koser's reagent),[8] (diacetoxy)iodobenzene[9] and its polymer-based analog[10] have also been employed for conversion of **1** to **2**. In the cases of HTIB and (diacetoxy)iodobenzene, the production of iodobenzene by reduction of the reagent complicates work-up, often necessitating removal by chromatographic techniques. While polymer based analogs of these reagents offer the facile removal of the reduced reagent and simplified work-up, they are difficult to prepare and fully characterize by methods other than iodometry and elemental analysis.

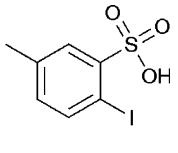


1 **2**

Scheme 1.



3, HMBI



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Concurrent with recent interest in *ortho*-substituted iodanes,[11] it was reasoned that the use of 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI, **3**), a cyclic analog of HTIB, would affect the conversion of arylalkanones to methyl 2-arylesters. The reduced 2-iodo-5-methylbenzenesulfonic acid (**4**) by-product could readily and quantitatively be removed from the reaction mixture by simple liquid–liquid extraction and could be reoxidized with high efficiency. We herein report the results of our investigation.

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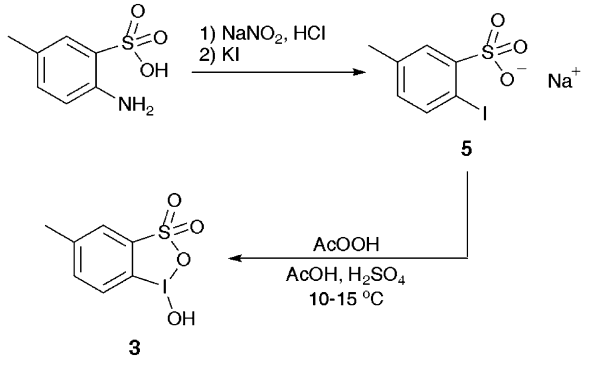
2. Results and discussion

HMBI was first prepared by Koser and co-workers for the preparation of alkynyliodonium salts.[12] Diazotization and iodination of commercial 2-amino-5-methylbenzene-sulfonic acid, followed by protonation of sodium 2-iodo-5-methylbenzenesulfonate **5** and oxidation with peracetic acid afforded HMBI in an overall synthetic yield of 46%. The limitation of this preparation is protonation of the sodium salt, which occurred in only moderate yield (62%). In the current work it was determined that the sodium salt could be directly oxidized through in situ protonation of **5** during the oxidation step with the addition of a small amount of concentrated sulfuric acid to afford HMBI (Scheme 2). An optimized preparation of the reagent is provided here.[13]

Although many reagents have been applied in the conversion of **1** to **2**, similar reaction conditions were employed.[2–4,8–10] It was found that only a slight modification gave the optimum conditions for the conversion of **1** to **2** with HMBI. In a typical experiment HMBI was added to a stirred solution of **1** in methanol, trimethylorthoformate (TMOF) and sulfuric acid and either stirred at room temperature or heated under reflux. In many cases the product esters were directly isolated by liquid–liquid extraction. In instances where multiple products were produced, the crude products were separated and purified by preparative TLC using ethyl acetate/hexanes as eluant. All products were fully characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR and found to be in accord with literature values. Starting ketones were either commercially available or prepared by Friedel–Crafts acetylation.



Scheme 2.

Oxidative rearrangement of acetophenones (Scheme 3) bearing electron donating groups proceeded smoothly to afford methyl phenylacetates in high yield at room temperature (Table 1, entries 1–6). The conversion of acetophenone to methyl phenylacetate with HMBI is given as a representative procedure.[14] However, when acetophenones bearing electron withdrawing groups were subjected to the same reaction conditions, small amounts of α-methoxyacetophenones were isolated in addition to the major product. The amount of this by-product appears to be in line with the increasing positive value of sigma constants for the electron withdrawing substituent.[15] In addition, 2-acetylfuran, 2-acetylthiophene and 2-acetylnaphthalene also underwent the conversion to the corresponding esters in moderate to high yield (54%, 78%, and 92%, respectively).

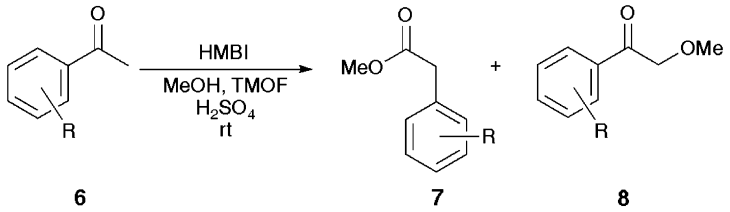
Propiophenones (Table 2, entries 1–8) were readily converted to the corresponding methyl 2-arylpropionates rapidly if heated under reflux (Scheme 4). Of particular interest is the preparation of methyl 2-(4-isobutylphenyl)propionate, which upon basic hydrolysis and acidification affords ibuprofen (entry 3).

Higher homologs of alkanophenones were also studied to determine the effect of extension and branching of the alkyl chain of **9** on the reaction outcome (Table 2, entries 10–13). Attempts to convert isobutyrophenone to the corresponding ester with HMBI resulted in an

Table 1. Products[a] of the reaction of acetophenones with HMBI via Scheme 3

Entry	**6**, R=	Time, min	Yield[b] %, **7**	Yield %, **8**
1	4-H	20	85	
2	2-CH_3	20	91	
3	4-CH_3	20	97	
4	4-Ph	20	86	
5	4-CH_3O	20	99	
6	3,4-OCH_2O–	20	77	
7	4-F	20	74	
8	2-Cl	60	86	
9	3-Cl	60	41	11[b]
10	4-Cl	60	92	3[c]
11	4-Br	20	80	7[b]
12	4-COOH	180	71	3[c,d]
13	4-NO_2	180	31	64[b]

[a] All products were fully characterized by ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and FT-IR.
[b] Isolated yield.
[c] Yield determined by integration of crude ^{1}H NMR spectrum.
[d] Product isolated as the dimethyl diester.

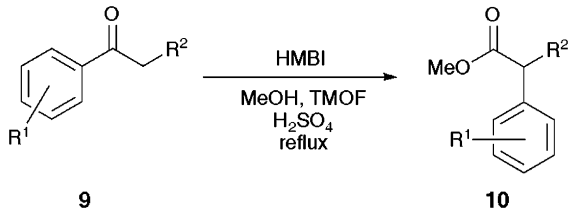


Scheme 3.

Table 2. Products[a] of the reaction of propiophenones with HMBI via Scheme 4

Entry	9		Time	Yield[b] %, **10**
	R^1=	R^2=		
1	4-H	CH_3	20	72
2	4-CH_3	CH_3	20	88
3	4-Isobutyl	CH_3	20	94
4	4-CH_3O	CH_3	20	98
5	4-F	CH_3	20	81
6	3-Cl	CH_3	20	81
7	4-Cl	CH_3	20	85
8	4-Br	CH_3	60	88
9	3-NO_2	CH_3	120	64
10	H	CH_2CH_3	20	92
11	H	$(CH_2)_3CH_3$	20	92
12	H	$(CH_2)_5CH_3$	20	94
13	H	$CH(CH_3)_2$	20	86
14	H	CH_2COOH	20	78[c]
15	H	$(CH_2)_2COOH$	20	84[c]

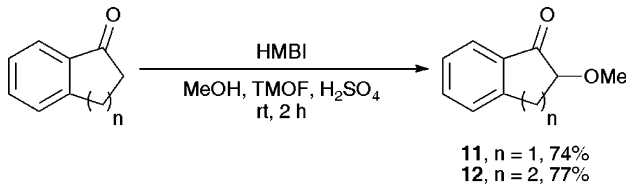
[a] All products were fully characterized by ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), and FT-IR.
[b] Isolated yield.
[c] Products isolated as dimethyl diesters.



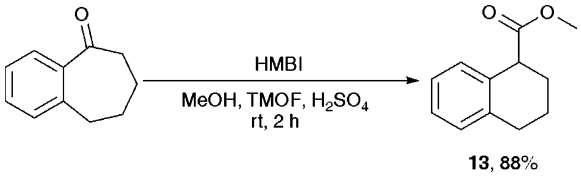
Scheme 4.

intractable mixture. However, branching of the 3-position (entry 13) or lengthening of the alkyl chain did not preclude the formation of esters in high yield (entries 10–12). The scope of substrates that undergo the conversion was further expanded with the observation that 3-benzoylpropionic acid and 4-benzoylbutanoic acid were converted to dimethyl 2-phenylsuccinate and to dimethyl 2-phenylglutarate, respectively, with HMBI under the reaction conditions (entries 14 and 15).

1-Benzocycloalkenones displayed differing reaction modes dependent upon ring size. Treatment of 1-indanone or 1-tetralone with HMBI under the reaction conditions afforded α-methoxyketones **11** and **12** in 74 and 77% yield, respectively, (Scheme 5). However, when 1-benzosuberone was reacted with HMBI under the same conditions, only the product of ring contraction **13** was isolated (Scheme 6).



Scheme 5.

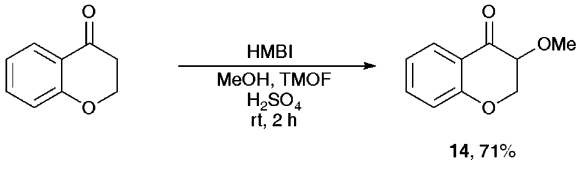


Scheme 6.

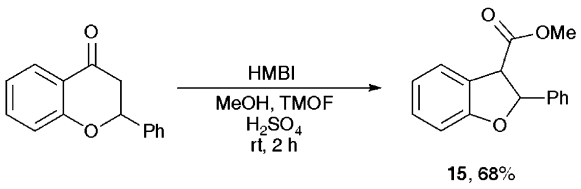
When chromanone is treated with HMBI under the reaction conditions, the principle product is 2,3-dihydro-3-methoxy-4*H*-1-benzopyran-4-one (**14**) isolated in 71% yield (Scheme 7). In contrast flavanone affords methyl 2,3-dihydro-2-phenyl-3-benzofurancarboxylate (**15**) under identical treatment (Scheme 8). While these reaction modes are divergent for two similar substrates, they are in accord with previous investigations of the oxidation of chromanones with thallium(III) nitrate[16] and the oxidative rearrangement of flavanones with (diacetoxy)iodobenzene-H_2SO_4 or HTIB.[17]

A plausible mechanism for the production of 2-arylesters from arylalkanones with HMBI, similar to that proposed by Higgins and Thomas for the same conversion using thallium(III) nitrate,[3] is presented in Scheme 9. It would be logical to assume that the stability of iodonium intermediate **16** and the rate of ketal **17** formation dictate the course of reaction for a particular substrate. Competitive methanolysis of **16** or **17** would account for the formation of α-methoxyketones as products. Depending on the substrate, it is reasonable that this competition becomes important due to either slow formation of **17** or diminished migratory aptitude of the aryl moiety.

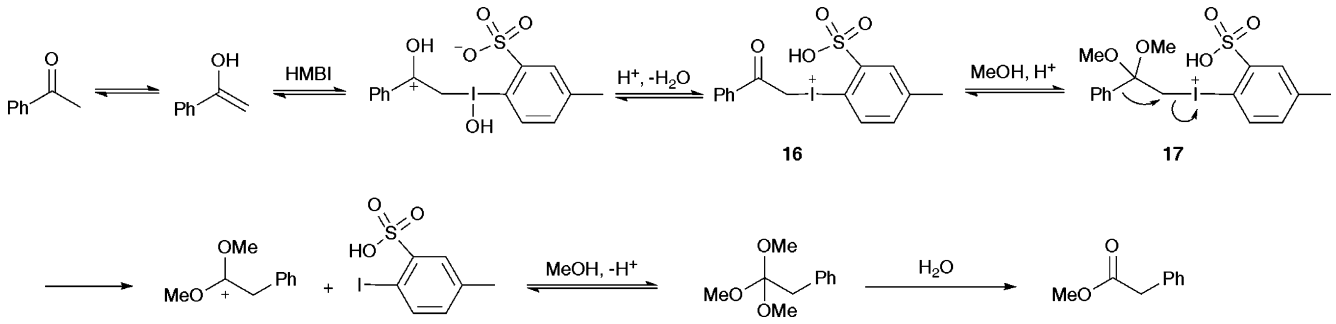
The prime advantage of HMBI for this conversion is the facile workup of the reaction mixtures and recovery of the reduced reagent. Following the initial liquid–liquid extraction, concentration of the organic layers led directly to methyl 2-arylesters of reasonable purity in cases where only one product was observed. The recovered aqueous layers can be concentrated and the obtained crude **4** triturated with ether or hexanes to remove trace



Scheme 7.



Scheme 8.



Scheme 9.

contaminants from the reaction mixture. Recovery of **4** is typically ~90%. Coupled with the yield of reoxidation (93%) the recycling rate of this material compares favorably with that observed for poly[4-(diacetoxyiodo)styrene].[10a] Recovery of the reduced poly(4-iodostyrene) was 80% and a diminishment of the amount of iodinated sites that could be reoxidised (64 vs 74%) was reported.

3. Conclusion

In conclusion, we wish to report the conversion of arylalkanones to 2-arylesters with HMBI, a cyclic analog of HTIB, by oxidative rearrangement. The use of toxic metal salts or reagents whose reduced by-products interfere with facile purification of the product are avoided. Once more, the reagent is easily recovered from the reaction mixture, and reoxidized for reuse at high efficiency.

Acknowledgments

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13. 1*H*-1-Hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (**3**, HMBI) from **4**; procedure adapted from Ref. 12; Peroxyacetic acid (35%, 58 mL) was added dropwise to a stirred mixture of sodium 2-iodo-5-methylbenzenesulfonate (25.40 g, 75.0 mmol) in AcOH (60 mL) and conc. H_2SO_4 (10 mL) maintained at 10–15 °C. The mixture was stirred at this temperature for 1 hour and overnight at rt. The solid component was isolated by vacuum filtration and washed with $Et_2O{\cdot}H_2O$ was added to a mixture of this material in boiling MeCN (300 mL) until the solid had mostly dissolved. The mixture was filtered hot and allowed to cool to room temperature. HMBI separated as a colorless crystalline solid and was isolated by filtration. The filtrate was concentrated to one third its volume and a second crop of crystals was obtained. Combined yield of HMBI: 22.03 g (94%); mp and ^1H NMR spectrum identical with material prepared by Ref. 12.
14. Methyl phenylacetate: Acetophenone (117 μL, 1.00 mmol) was added to a stirred solution of MeOH (4.0 mL), TMOF (250 μL) and H_2SO_4 (213 μL). Crystalline HMBI (346 mg, 1.10 mmol) was added at once and the resulting

mixture stirred for 20 minutes to afford a light yellow solution. The solution was concentrated to one half volume and H_2O (15 mL) added. The mixture was then extracted with Et_2O (2×10 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated to a colorless oil identified as the title compound (127 mg, 85%): ^1H NMR, ^{13}CNMR, and IR spectral data in accord with accepted values.

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