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HYPERVALENT IODINE OXIDATION: SYNTHESIS OF 5-SUBSTITUTED-2(5H)-FURANONES USING IODOSOBENZENE

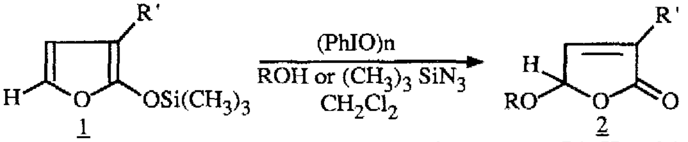
Robert M. Moriarty,* Radhe K. Vaid, Thomas E. Hopkins, Beena K. Vaid
Department of Chemistry, University of Illinois at Chicago, Chicago, IL 60607

Atilla Tuncay[1]
Department of Chemistry, Indiana University Northwest, Gary, IN 46408

Summary: Hypervalent iodine oxidation of 2-(trimethylsilyloxy)furan with iodosobenzene:boron trifluoride etherate in the presence of various nucleophiles yields 5-substituted-2(5*H*)-furanones.

5-Substituted-2(5*H*)-furanones are versatile intermediates for the synthesis of a number of important natural products and biologically active molecules.[2,3] Frequently, the presence of an unsaturated γ-lactone is found to impart antibiotic properties.[4,5] 5-Substituted-2(5*H*)-furanones have also been used as dienophiles in asymmetric Diels-Alder reactions.[6] The literature preparations of many useful 5-substituted-2(5*H*)-furanones are typically lengthy and do not always lend themselves to large scale reactions.[5]

Recently we reported the use of hypervalent iodine for the synthesis of α-functionalized ketones and β-diketones.[7,8] In continuation of our efforts, we became interested in the functionalization of 2(5*H*)-furanones at the γ-position starting with the precursor, 2-(trimethylsilyloxy)furan 1.[9] We now report the use of iodosobenzene for the preparation of 5-substituted-2(5*H*)-furanones as exemplified in Scheme 1.



2a, R=Ac	R'=H	2d, R=Et	R'=H
2b, R=Ms	R'=H	2e, RO=N_3	R'=H
2c, R=Ts	R'=H	2f, R=Ms	R'=CH_3

Scheme 1

Treatment of 2-(trimethylsilyloxy)furan (1) (0.010 mol) with a solution obtained by the addition of acetic acid (0.092 mol) or methanesulfonic acid (0.012 mol) or p-toluenesulfonic acid (0.012 mol) to a suspension of iodosobenzene (0.012 mol) in dichloromethane at room temperature, followed by boron trifluoride etherate (0.012 mol) afforded 5-acetoxy-, 5-mesyloxy- and 5-tosyloxy-2(5*H*)-furanones (2a,2b,2c) respectively.

In a typical experiment, methanesulfonic acid (1.15 g, 0.012 mol) was added to a suspension of iodosobenzene (2.64 g, 0.012 mol) in 30 mL of dichloromethane and the mixture was stirred at room temperature until a homogeneous solution was formed. 2-(Trimethylsilyloxy)furan (1) (1.56 g, 0.010 mol) was added followed by boron trifluoride etherate (1.69 g, 0.012 mol). The resulting solution was stirred for four hours and then treated with cold saturated sodium bicarbonate solution (100 ml). The methylene chloride layer was separated and the aqueous layer was extracted with additional methylene chloride (2x100 ml). The combined extracts were dried ($MgSO_4$) and concentrated to dryness in *vacuo* to yield crude 5-mesyloxy-2(5*H*)-furanone which upon purification by column chromatography yielded 1.19 g (67%) of 2b.

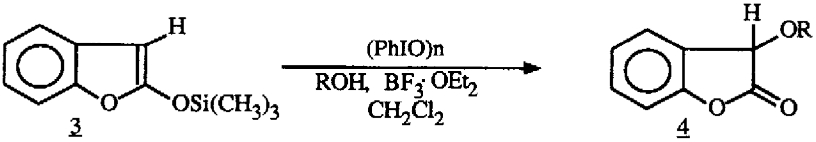
When 2-(trimethylsilyloxy)furan (1) is treated with iodosobenzene (0.012 mol):boron trifluoride etherate (0.012 mol) in ethanol at room temperature, 5-ethoxy-2(5*H*)-furanone (2d) is obtained.[10] Likewise, treatment of

2-(trimethylsilyloxy)furan (1) with a solution obtained by mixing iodosobenzene (0.012 mol) and azidotrimethylsilane (0.024 mol) in dichloromethane, followed by boron trifluoride etherate (0.012 mol) gave 5-azido-2(5*H*)-furanone (2f). A summary of the compounds produced by this method can be found in Table 1.

In all cases, the reaction was found to proceed regiospecifically, affording only 5-substituted-furanones (2) in good yield. Formation of 3-substituted-2(3*H*)-furanones was not observed by N.M.R examination of the crude product..

The products were not found to exhibit keto-enol tautomerism and exist exclusively in the keto form as shown by the lack of an O-H band in the infrared and the presence of a band at 1790-1805 cm^{-1} for γ-electron withdrawing substituted α,β-unsaturated-γ-lactone carbonyl.[11] Also, no deuterium exchange was observed upon treatment with D_2O, in the ^1H-NMR.

In order to support further structure 2, and the generality of the reaction, 3-acetoxy and 3-tosyloxy-2-coumaranone were prepared by treatment of 2-(trimethylsilyloxy)benzofuran (3) (0.010 mol) with a solution obtained by mixing iodosobenzene (0.012 mol) and acetic acid (0.024 mol) or p-toluenesulfonic acid (0.012 mol) in CH_2Cl_2 at room temperature, followed by boron trifluoride etherate (0.012 mol), respectively (Scheme 2).[12]



3

4

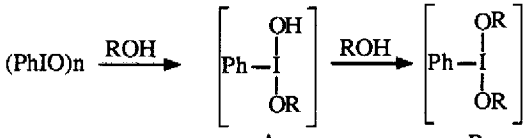
4a, $R=COCH_3$
4b, $R=SO_2C_6H_4CH_{3(p)}$

Scheme 2

The infrared spectrum of 4 showed carbonyl stretching at 1815-1821 cm^{-1}. The products 2(a-f), however, show absorption at shorter wavelength indicating the products are 5-substituted rather than 3-substituted.

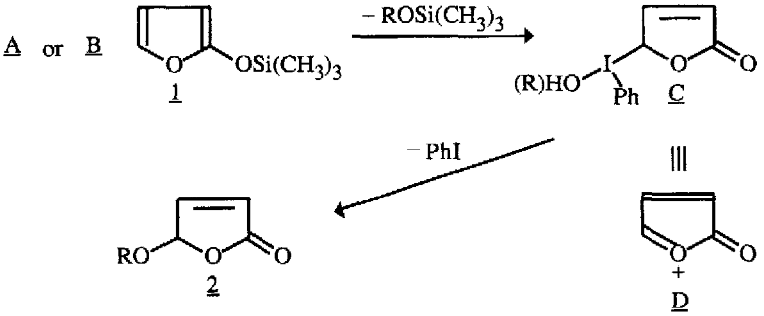
The formation of 5-acetoxy-, 5-ethoxy-, 5-azido-2(5*H*)-furanones (2a,d,e) may be explained by; (i) the addition of 2 equivalents of the nucleophile to iodosobenzene to generate the tricoordinate species B, (ii) the electrophilic addition of B at the γ-position of 2-(trimethylsilyloxy)furan (1) to generate C which can be thought of as being equivalent to the carbonium ion D, (iii) the attack by the appropriate nucleophile to yield the desired 5-substituted-2(5*H*)-furanones (2a,d-f) via reductive elimination of iodobenzene.

The formation of 5-mesyloxy, 5-tosyloxy-2(5*H*)-furanones (2b,c,f) may be explained by; (i) the addition of one equivalent of the nucleophile to iodosobenzene to generate [hydroxy(mesyloxy or tosyloxy)iodo]benzene (A), (ii) the electrophilic addition of A at γ-position of 2-(trimethylsilyloxy)furan (1) to generate C, which then undergoes attack by the nucleophile to generate product 2b or 2c via reductive elimination of iodobenzene. This sequence may be viewed as an umpolung of the anion formed by the cleavage of the enol silyl ether (Scheme 3).



A
R=Ms, Ts

B
R=Ac, Et,
$OR=N_3$



Scheme 3

Table 1

Product	Yield (%)[a] m.p. or b.p. (°C)/mm	IR (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ ppm (200 MHz)
2a	(72) oil[13,d]	1790 (C=O) 1760 (C=O)	2.1 (s,3H,(C=O)CH_3), 6.3(dd,1H,CH=CH), 7.0 (dd,1H,CH), 7.4 (dd,1H,CH=CH)
2b	(67)[b,c] 117-118°	1805 (C=O) 1184 (S=O)	3.3 (s,3H,OSO_2CH_3), 6.4 (dd,1H,CH=CH), 6.8 (dd,1H, CH), 7.5 (dd,1H,CH=CH)
2c	(66)[b,c] oil	1796 (C=O) 1181 (S=O)	2.5 (s,3H,CH_3), 6.5 (dd,1H,CH=CH), 7.0 (dd,1H,CH), 7.4-7.8 (m,3H,CH=CH and 2 aromatic), 8.1 (d,2H,aromatic)
2d	(55) oil[14,d]	1796 (C=O)	1.23 (t,2H,OCH_2CH_3), 3.8 (m,2H,OCH_2), 5.95 (dd, 1H), 6.2 (dd,1H), 7.3 (dd,1H)
2e	(51)[b,c] oil	2110 (N_3) 1795 (C=O)	6.1 (b,1H,CH), 6.35 (dd,1H,CH=CH), 7.4 (dd,1H,CH=CH)
2f	(74)[b] 66-68° [Lit.[5] m.p. 65-67°]	1790 (C=O) 1182 (S=O)	2.28 (s,3H,OSO_2CH_3), 7.02 (m,1H,CH=CCH_3) 6.68 (dd,1H, CH), 2.0 (m, 3H, CH=CCH_3)
6a	(65)[c] oil	1821 (C=O) 1753 (C=O)	2.1 (s,3H,$OCOCH_3$),6.0 (s,1H,CH), 7.0-7.4 (m,4H,aromatic)
6b	(62)[c] oil	1820 (C=O)	2.3 (s,3H,CH_3), 6.0 (s,1H,CH), 7.0-7.4 (m,6H,aromatic) 7.5-7.7 (d,2H,aromatic)

[a] Yields are based on pure products obtained by column chromatography on alumina using hexane-CH_2Cl_2 as eluents.

[b] These products are light sensitive and must be kept in the dark.

[c] Showed satisfactory analysis for carbon and hydrogen.

[d] The boiling points of these products were not determined in the cited literature. Their identities were confirmed by ^{1}H-NMR.

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10. Iodosobenzene (2.20 g, 0.01 mol) was added to 20 ml absolute ethanol. Then 2-(trimethylsilyloxy)furan (1) (1.569 g, 0.01 mol) was added to this slurry at 0°C followed by (1.41 g, 0.012 mol) of boron trifluoride etherate. The reaction mixture was stirred at room temperature overnight under nitrogen. The volume of the reaction mixture was reduced to one-third and the resulting solution was then treated with a saturated solution of NaHCO and the aqueous layer was extracted with dichloromethane. The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product which contained iodobenzene. Product was purified by column chromatography using hexane:CH_2Cl_2 as eluents (Table 1).

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