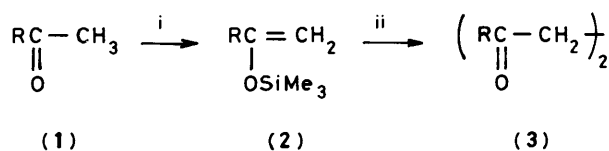# Carbon–Carbon Bond Formation Using Hypervalent Iodine Under Lewis Acid Conditions: Scope of the Method for the Synthesis of Butane-1,4-diones

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Hypervalent iodine oxidation of the silyl enol ethers of various acetophenones (**2a—g**), 2-acetyl-thiophenes (**2i—k**), 2-acetylfuran (**2l**) and 2-acetylbenzofuran (**2m**) with iodosobenzene–boron trifluoride–diethyl ether results in carbon–carbon coupling to yield the corresponding 1,4-disubstituted butane-1,4-dione (**3a—m**). Cross coupling (dissimilar coupling) between 4-methoxyacetophenone silyl enol ether (**2c**) and 4-nitroacetophenone silyl enol ether (**2e**) affords 1-(4-methoxyphenyl)-4-(4-nitrophenyl)butane-1,4-dione (27%); the other minor products (**3c**) (18%) and (**3e**) (15%) resulting from similar coupling in this reaction. The sterically hindered aliphatic silyl enol ether (**2h**) obtained from pinacolone also undergoes smooth coupling whereas other aliphatic ketones do not. This method is likewise unsuccessful in case of nitrogen-containing heterocycles, *viz.* 2-, 3-, 4-acetylpyridine silyl enol ethers and tropinone silyl enol ether.

Since 1,4-diketones are versatile intermediates for the synthesis of natural products and related compounds,[1,2] many methods have been devised for their preparation.[3] In a preliminary communication we reported that oxidation of the silyl enol ethers (**2**) of aryl methyl ketones (**1**) with iodosobenzene and boron trifluoride–diethyl ether resulted in carbon–carbon bond formation[4] (Scheme 1). Here we describe the scope of this hypervalent oxidation.

RC—CH₃ $\xrightarrow{i}$ RC=CH₂ $\xrightarrow{ii}$ $\left(\text{RC—CH}_2\right)_2$

(with structures: RC(=O)CH₃ (**1**); RC(OSiMe₃)=CH₂ (**2**); (RC(=O)CH₂)₂ (**3**))

a; Ph
b; *p*-HOC₆H₄
c; *p*-MeOC₆H₄
d; *p*-ClC₆H₄
e; *p*-FC₆H₄
f; *p*-O₂NC₆H₄
g; *p*-MeC₆H₄

h; Buᵗ
i; 2-Thienyl
j; 4-Methyl-2-thienyl
k; 5-Chloro-2-thienyl
l; Furan-2-yl
m; Benzofuran-2-yl

Scheme 1. *Reagents:* i, ClSiMe₃–Et₃N; ii, (PhIO)ₙ–BF₃·Et₂O

Treatment of the silyl enol ethers of acetophenones (**2**) (2.2 equiv.), readily available from the respective ketones (**1**; R = Ar),[5] with iodosobenzene (1.0 equiv.) in dichloromethane or ether at −40 °C and then room temperature gave the 1,4-diketone (**3**), the iodosobenzene to iodobenzene being concurrently reduced. In studying the scope of the reaction we have used the ketones (**1a—m**) and found that the silyl enol ether of each undergoes smooth coupling with no change in the product yield on variation of the aryl ring substituent (Table 1). In all cases variable amounts of acetophenones were also recovered, (unchanged silyl enol ether being hydrolysed in the work up). Since the amount of iodosobenzene used is limited by its solubility in dichloromethane or ether, optimum conditions for the reaction are 1.1 equiv. of iodosobenzene, 2 equiv. of silyl enol ether, and *ca.* 3 equivalent of boron trifluoride–diethyl ether (under these conditions most of the iodosobenzene dissolves). Among the heterocyclic ketones we studied, the silyl enol ethers (**2i—m**) underwent carbon–carbon coupling reaction without difficulty giving the crystalline 1,4- diketones (**3i—m**)

Table 1. Butane-1,4-diones (known) prepared by the hypervalent iodine oxidation of silyl enol ethers

Compd.	Yield (%)[a]	M.p. (°C)	Lit m.p. (or b.p.) (°C)
(**3a**)	48	143—144	144[b]
(**3b**)	43	184—185	186[c]
(**3c**)	58	150—151	151[d]
(**3d**)	62	150—151	150[e]
(**3g**)	57	159—160	158—60[f]
(**3h**)	55	57—59/0.5 mmHg	57—58/0.5 mm[g]
(**3i**)	56	131—132	130—131[h]
(**3l**)	50	130—131	132[i]

[a] Based on pure recrystallized/distilled product with respect to the silyl enol ether. [b] P. S. Bailey and R. E. Lutz, *J. Am. Chem. Soc.*, 1948, **70**, 2412. [c] F. Eiden and L. Prielipp, *Arch. Pharm. (Weinheim, Ger.)*, 1977, **310**, 109. [d] E. E. Compaigne and W. O. Faye, *J. Org. Chem.*, 1952, **17**, 1405. [e] E. Lutz, *J. Am. Chem. Soc.*, 1923, **13**, 1306. [f] See ref. 3c. [g] P. W. Ford, *Aust. J. Chem.*, 1974, **27**, 2525. [h] H. J. Kooremen and J. Wynberg, *Recl. Trav. Chim. Pays-Bas.*, 1967, **86**, 37. [i] E. Niwa and M. Miyake, *Chem. Ber.*, 1969, **102**, 1443.

in fairly good yields; these products are of interest in the synthesis of biologically active compounds (*e.g.* cyclization of 1,4-di-2-thienylbutane-1,4-dione (**3i**)[6,7] affords α-terthiophene which possesses strong nematicidal[8] and photosensitising properties[9]).

The silyl enol ethers of 2-acetyl-, 3-acetyl-, and 4-acetyl-pyridine and tropinone failed to react both under the standard reaction conditions and with an excess of BF₃·Et₂O, starting material being recovered.

Although the oxidative coupling procedure was unsuccessful with the silyl enol ethers of cyclopentanone and cyclohexanone, the reaction works well for a sterically hindered molecule such as the silyl enol ether of t-butyl methyl ketone to give 2,2,7,7-tetramethyloctane-3,6-dione (**3h**) (55%).

This reaction may also be used to cross couple two dissimilar molecules yielding three possible 1,4-diketones. Thus (**2c**) and (**2f**) gave as the major product 1-(4-methoxyphenyl)-4-(4-nitrophenyl)butane-1,4-dione (27%), together with (**3c**) and (**3f**) in 18 and 15% yields respectively.

The pathway which we favour for the reaction involves formation of the intermediate (**5**) which gives rise to the carbonium ion (**6**). Reaction of the latter (**7**) leads to coupling.

This sequence may be viewed as producing an umpolung of the carbanion equivalent (7). The validity of this proposition was tested by addition of water, methanol and ethanol to yield respectively the α-substituted products (8), (9), and (10) in high yield (Scheme 2). In a further study of the scope of the α-substituted reaction, α-hydroxylation [10] and α-methoxylation [11] of ketones has been accomplished in good yields.
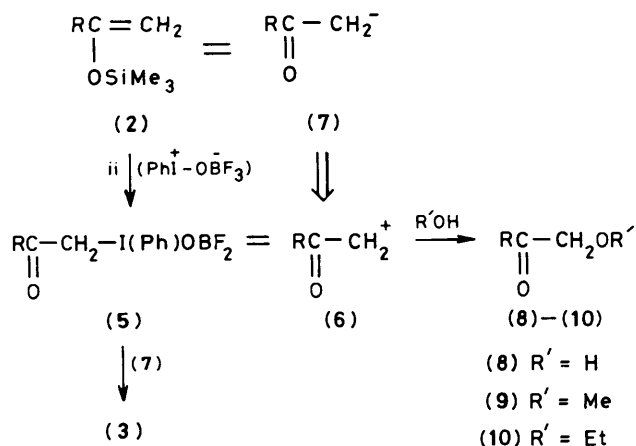
Scheme 2.

Experimental

M.p.s were determined using a Thomas capillary melting point apparatus and are uncorrected. The i.r. spectra were obtained using a Unicam SP1000 spectrophotometer and peak positions are expressed in cm^{-1}. ^{1}H N.m.r. spectra were recorded at 60 MHz with a Varian A60 or EM-360 spectrometer using SiMe$_4$ as an internal standard. Mass spectra were scanned with Hewlett Packard GC/MS 5985 apparatus at 70 eV.

Starting Materials.—Ketones (1a—m), iodobenzene, chloro-trimethylsilane, and triethylamine were obtained from Aldrich and Co. Fresh boron trifluoride–diethyl ether (Aldrich) was used. All the solvents were dried and distilled before use. Iodosobenzene was prepared by oxidation of iodobenzene with 35% peracetic acid (Spectrum Chemical Mfg. Corp.) followed by hydrolysis with aqueous sodium hydroxide.[12]

Silyl Enol Ethers.—The silyl enol ethers (2a—m) prepared from the ketones (1a—m) according to the General Method A

of House *et al.*[5] were purified by distillation before use although, dilute hydrochloric acid was not used in the work-up to avoid acid hydrolysis of the products. A typical preparation of the silyl enol ether (2j) is described.

Silyl Enol Ether of 4-*Methyl*-2-*thienyl Methyl Ketone* (2j).—To a solution of chlorotrimethylsilane (16.30 g, 0.15 mol) and triethylamine (30.30 g, 0.30 mol) in dimethylformamide (125 ml) was added 4-methyl-2-thienyl methyl ketone (1j) (17.5 g, 0.125 mol). The resulting mixture was refluxed and stirred overnight and then cooled, diluted with pentane (400 ml), and washed with ice cold aqueous sodium hydrogen carbonate (10%, 3 × 200 ml). The aqueous layer was extracted with pentane (2 × 100 ml) and the combined organic extracts were washed with cold brine (200 ml). The resulting pentane solution was dried (MgSO$_4$) and concentrated under reduced pressure to yield crude silyl enol ether (90% from ^{1}H n.m.r.). Distillation gave the pure product (2j) (19.9 g, 75%), b.p. 60—61 °C/5 mmHg, δ(CDCl$_3$) 0.21 [9 H, br s Si(CH$_3$)$_3$], 2.21 (3 H, s, CH$_3$), 4.25 (1 H, d), 4.75 (1 H, d, C=CH$_2$), 6.75—6.95 (2 H, thienyl H): (2i), b.p. 45—47 °C/4 mmHg; (2k), b.p. 52—53 °C/5 mmHg; (2m) 67—69 °C/5 mmHg.

General Procedure for the Preparation of Butane-1,4-*Diones* (3a—m).—To a suspension of iodosobenzene (11 mmol) in dry dichloromethane (100 ml) under nitrogen was added boron trifluoride (0.03 mol) with stirring. The mixture was cooled to −40 °C and then to the resulting stirred and cold mixture was added silyl enol ether (20 mmol). The reaction mixture was stirred for 1 h at −40 °C and then for an additional 1 h at room temperature. During this period the light yellow reaction mixture changed to a dark brown (or light green) solution. This solution was basified with a saturated aqueous solution of sodium hydrogen carbonate and the aqueous layer was extracted with dichloromethane (3 × 25 ml). The organic extracts were combined, dried (MgSO$_4$), and concentrated under reduced pressure to yield the crude product which contained iodobenzene and small amount of recovered ketone (1) as impurities. Addition of ethanol (5—10 ml) separated the crystalline product. Analytical samples were prepared by recrystallization from a suitable solvent. The results of this reaction on known compounds are summarized in Table 1 and the data on new 1,4-diketones are included in Table 2.

Cross-Coupling between the Silyl Enol Ether of p-*Methoxy-acetophenone* (2c) *and the Silyl Enol Ether of* p-*Nitroaceto-phenone* (2f).—To a stirred mixture of iodosobenzene (1.10 g, 5 mmol) and boron trifluoride–diethyl ether (2.12 g, 15 mmol) in

Table 2. New butane-1,4-diones prepared by the hypervalent iodine oxidation of silyl enol ethers

Compd.[a]	M.p. (°C)	Yield (%)[d]	ν$_{max}$(Nujol)/ cm^{-1} C=O	[^{1}H N.m.r. δ(CDCl$_3$)]		m/z (70 eV)		
				(CH$_2$CO)$_2$	ArH	M^+	Base peak[f]	Other important peaks[g]
(3e)	135.5—136	60[b]	1 670	s 3.38	m 7.00—8.25	274	123	151
(3f)	195—197	50[c]	1 695	s 3.40	m 7.81—8.33	328	150	178
(3j)	187—188	59[b]	1 655	s 3.34[e]	m 7.30—7.65	278	125	153
(3k)	138—139	54[b]	1 650	s 3.22	m 6.91—5.71	318	145	173
(3m)	172—173	63[c]	1 685	s 3.46	m 7.18—7.95	318	145	173

[a] (3e) Found: C, 69.67; H, 4.41; F, 13.73. C$_{16}$H$_{12}$F$_2$O$_2$ requires C, 70.07; H, 4.38; F, 13.87%. (3f) Found: C, 58.17; H, 3.63; N, 8.49. C$_{16}$H$_{12}$N$_2$O$_6$ requires C, 58.54; H, 3.66; N, 8.54%. (3j) Found: C, 60.35; H, 5.11; S, 23.34. C$_{14}$H$_{14}$O$_2$S$_2$ requires C, 60.40; H, 5.07; S, 23.03%. (3k) Found: C, 45.20; H, 2.46; S, 20.28. C$_{12}$H$_8$Cl$_2$O$_2$S$_2$ requires C, 45.15; H, 2.53; S, 20.09%. (3m) Found: C, 74.30; H, 4.32. C$_{20}$H$_{14}$O$_4$ requires C, 75.46; H, 4.43%. [b] Recrystallized from ethanol. [c] Recrystallized from chloroform. [d] Isolated yields of pure products with respect to the silyl enol ether. [e] Methyl protons (at 4 position of thiophene) appear at δ 2.31 as a singlet (s). [f] Corresponds to R–C̅O. [g] Corresponds to RCOCH$_2$–CH$_2$.

dry dichloromethane at −70 °C under nitrogen was added (2c) (1.11 g, 5 mmol) and then (2f) (1.19 g, 5 mmol). The reaction was stirred for 1 h at −70 °C and then slowly warmed up to room temperature (1.5 h). The reaction was worked up as described above the three products (3f), (5), and (3c) were isolated by column chromatography (Silica Gel G) using dichloromethane as eluant: (3f) (0.25 g, 15%), m.p. 195—197 °C (CHCl₃); (5) (27%), m.p. 146—147 °C (Found: C, 64.95; H, 4.72; N, 4.51. $C_{17}H_{15}NO_5$ requires C, 65.14; H, 4.79; N, 4.47%), m/z 313 (M^+), 150, 135 (100%); (3c) (0.27 g 18%), m.p. 150—151 °C (EtOH).

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