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Hypervalent Iodine Oxidation: α-Functionalization of β-Dicarbonyl Compounds Using Iodosobenzene

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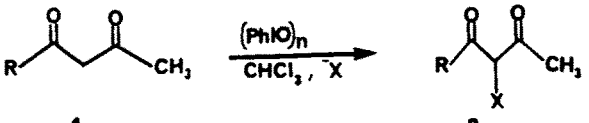
Summary: Hypervalent iodine oxidation of β-diketones and β-ketoesters with iodosobenzene-boron trifluoride etherate in chloroform using appropriate nucleophiles results in α-functionalization. Benzoylacetone on reaction with iodosobenzene or iodosobenzene boron trifluoride-etherate in methanol yields α-methoxyacetophenone (9) and methyl phenylacetate (10). The possible mechanisms for these reactions are discussed.

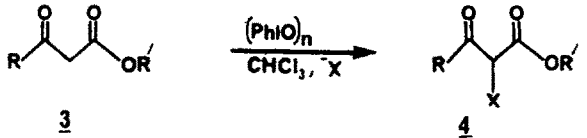
α-Functionalized β-dicarbonyl compounds are versatile intermediates for the synthesis of a variety of heterocyclic compounds of medicinal interest,[1,2] as well as natural products and related compounds.[3,4] α-Acetoxylation and α-tosyloxylation of β-dicarbonyl compounds have been reported using iodobenzene diacetate[5] and hydroxy(tosyloxy)iodobenzene,[6] respectively. Recently, we reported the use of hypervalent iodine oxidation for the synthesis of α-hydroxyketones from ketones under basic conditions.[7] Under neutral and Lewis acid conditions, the oxidation of enol silyl ethers of ketones using iodosobenzene in water/methanol results in α-hydroxy/α-methoxy ketones, respectively.[8] Encouraged by these results, we turned to the functionalization of β-dicarbonyl compounds at the α-position using hypervalent iodine. We now describe a one-pot synthesis of α-substituted 2,4-pentanedione (2a-d), α-substituted benzoylacetone (2e-g), α-substituted methylacetoacetate (4a-d) and α-substituted ethyl benzoylacetate (4e-h) using iodosobenzene and various nucleophiles. (Scheme I and II).



1 2

2. a, R = CH_3, X = N_3
b, R = CH_3, X = OSO_2CH_3
c, R = CH_3, X = OCH_3
d, R = CH_3, X = $CH(COCH_3)_2$
e, R = C_6H_5, X = N_3
f, R = C_6H_5, X = OSO_2CH_3
g, R = C_6H_5, X = $CH(COC_6H_5)COCH_3$

Scheme I



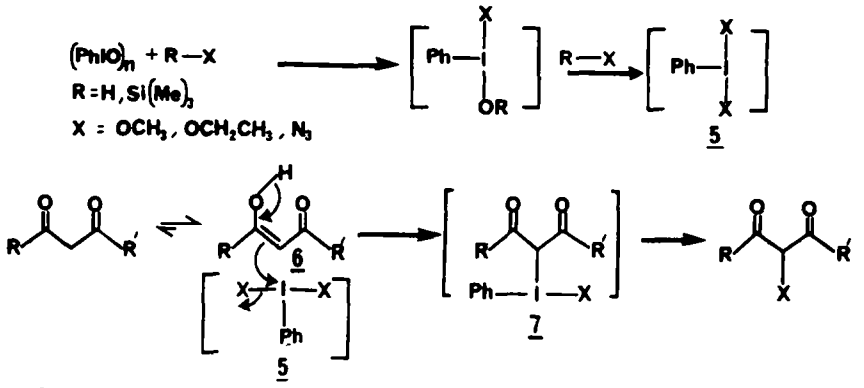
3 4

4. a R = R' = CH_3, X = N_3
b, R = R' = CH_3, X = OSO_2CH_3
c, R = R' = CH_3, X = OCH_3
d, R = R' = CH_3, X = $CH(COCH_3)CO_2CH_3$
e, R = C_6H_5, R' = C_2H_5, X = N_3
f, R = C_6H_5, R' = C_2H_5, X = OSO_2CH_3
g, R = C_6H_5, R' = C_2H_5, X = OC_2H_5
h, R = C_6H_5, R' = C_2H_5, X = $CH(COC_6H_5)CO_2C_2H_5$

Scheme II

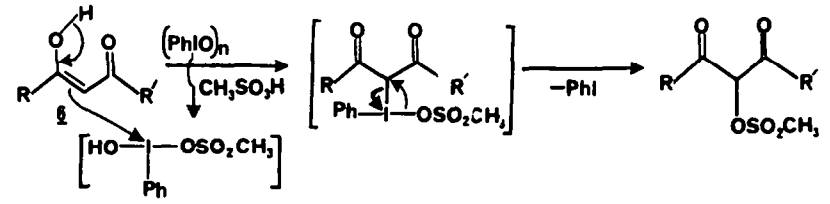
Treatment of the β-dicarbonyl compounds (1.0 equiv) with iodosobenzene (1.0 equiv) and azidotrimethylsilane (2.0 equiv) in chloroform under refluxing conditions gave α-azido β-dicarbonyl compounds (2a, 2e, 4a, 4e). Similarly, α-mesyloxy β-dicarbonyl compounds (2b, 2f, 4b, 4f) were obtained when 1.0 equivalent of β-dicarbonyl compounds with 1.0 equiv of iodosobenzene and 1.2 equivalent of methanesulfonic acid in chloroform under refluxing conditions. When one equivalent of iodosobenzene dissolved in alcohol is added to a β-dicarbonyl compound (1.0 equiv) at room temperature, α-alkoxy β-dicarbonyl compounds (2c, 4c, 4g) are obtained. The possible steps involved in the synthesis of α-azido and α-alkoxy β-dicarbonyl compounds are i) addition of the nucleophile to iodosobenzene to generate the tricoordinate iodine species (5) ii) reaction of the

enol form of β-dicarbonyl compound (6) with 5 to give the intermediate 7. The reaction is completed by 1,2 shift of the group X in 7 from iodine to carbon to yield the α-substituted product (Scheme III). (This sequence may be viewed as an umpolung of the enolate anion.)



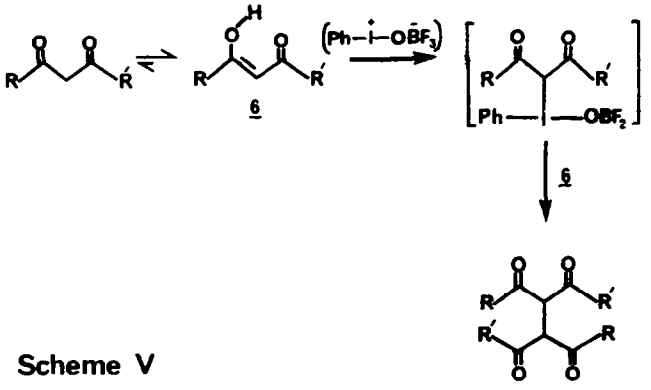
Scheme III

Formation of α-mesyloxy β-dicarbonyl compounds may be explained by the electrophilic addition of [hydroxy(mesyloxy)iodo]benzene formed in situ (by the reaction of $(C_6H_5IO)_n$ and CH_3SO_3H) to 6 to yield intermediate analogous to 7 which undergoes 1,2 shift of the $-OSO_2CH_3$ group (Scheme IV).



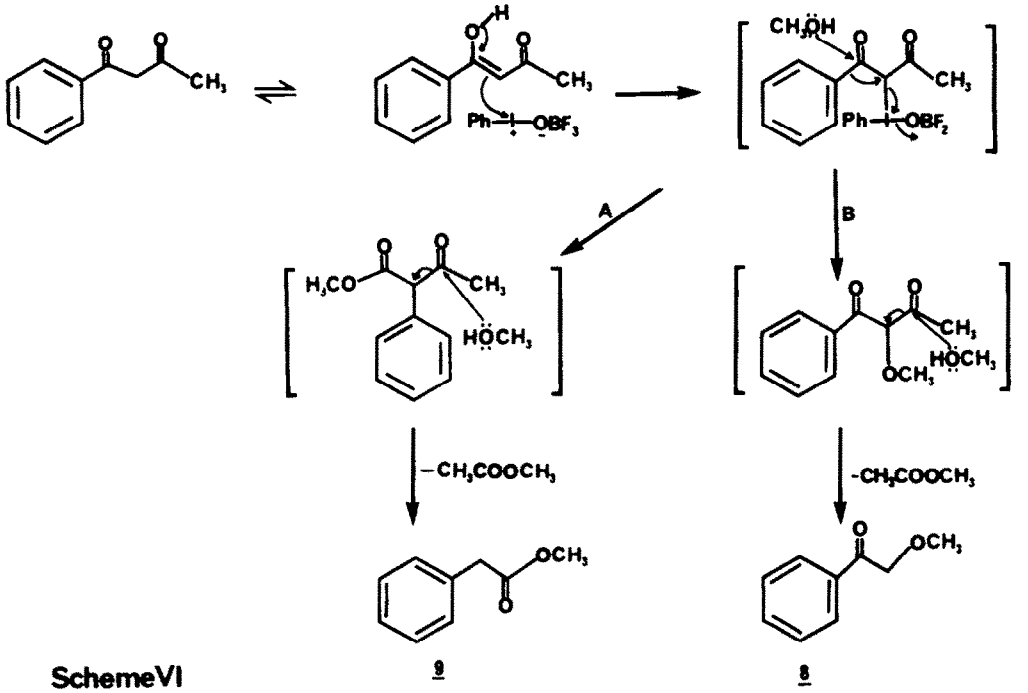
Scheme IV

When 2 equivalents of the β-dicarbonyl compounds are treated with 1.2 equivalents of iodosobenzene-boron trifluoride etherate (1.3 equiv) in chloroform under refluxing conditions self-coupling at the α-position occurs. The mechanism of self-coupling is explained in a manner analogous to the synthesis of 1,4-diketones obtained by reaction of enol silyl ether of ketones with iodosobenzene in dichloromethane[9], i.e. electrophilic addition of iodosobenzene to enol form of β-dicarbonyl compounds (6) followed by nucleophilic attack of second molecule of β-dicarbonyl compound (6) possibly by initial coordination at iodine (Scheme V).



Scheme V

In the case of α-methoxylation of benzoylacetone using iodosobenzene in methanol with or without boron trifluoride etherate either at room temperature or under reflux conditions, rather than the expected product α-methoxybenzoylacetone, the NMR of the crude product showed signals for α-methoxy acetophenone and methyl phenylacetate. On purification of the crude product on a silica gel column using hexane: ether as eluent, α-methoxyacetophenone (8) and methyl phenylacetate (9) were obtained. The formation of 9 may be visualised as phenyl migration to the α-position (in analogy to rearrangement of acetophenone to methyl phenylacetate[10]), followed by cleavage of acetyl group. A possible pathway for this transformation is shown in Scheme VI. Oxidation of β-dicarbonyl compounds using benzylalcohol (instead of methanol or ethanol) under the standard conditions did not afford the corresponding α-benzyloxy β-dicarbonyl compounds; benzyl alcohol itself is oxidized to benzaldehyde. Similarly, we were unsuccessful in the synthesis of α-amino β-dicarbonyl compounds by treating iodosobenzene in amines with β-dicarbonyl compounds. Under the reaction conditions amines undergo oxidations in a reaction which will be discussed in detail in a future publication.



SchemeVI

9 8

Experimental

Melting points were determined using a Thomas capillary melting point apparatus and are uncorrected. I.R. spectra were obtained using an IBM system 9000 IR/32 spectrophotometer and peak positions are expressed in cm^{-1}. ^1H NMR spectra were recorded at 60 MHz with a Varian 360-L spectrometer using Me_4Si as an internal standard. Mass spectra were scanned with Hewlett Packard GC/MS 5985 apparatus at 70 eV.

Starting Materials: 2,4-Pentanedione, 1-benzoylacetone, methyl acetoacetate, ethyl benzoylacetate, azidotrimethylsilane and methanesulfonic acid were obtained from Aldrich Chemical Co. Inc,. Fresh boron trifluoride-diethyl ether (Aldrich) was used. All solvents were dried and distilled before use. Iodosobenzene was prepared by the oxidation of iodobenzene using 35% peracetic acid (Spectrum Chemical Manufacturing Corp.) followed by hydrolysis with aqueous sodium hydroxide[11].

General procedure for the preparation of α-azido β-dicarbonyl compounds (2a, 2e, 4a, 4e): To a cooled suspension of iodosobenzene (0.01 mole) in dry chloroform (50 ml) under nitrogen was added azidotrimethylsilane (0.02 mole). The mixture was stirred for 20 minutes and then the β-dicarbonyl compound (0.01 mole) was added. Stirring was continued at room temperature for 2 hr and then at reflux for 3 hr. The reaction mixture was washed with water (4 x 50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product which was purified over silica gel using hexane: ether (9:1) as eluents. Compounds thus obtained are listed in Table 1.

General procedure for the preparation of α-mesyloxy β-dicarbonyl compounds (2b, 2f, 4b, 4f): To a suspension of iodosobenzene (0.01 mole) in dry chloroform was added methanesulfonic acid (0.01

Table 1. Products Obtained in Hypervalent Iodine Oxidation of β-Dicarbonyl Compounds.

Compound	(Yield %)[a] m.p. or b.p.(°C)/mm [Lit b.p.]	MS m/e (rel. int %)	IR (neat)	^{1}H NMR ($CDCl_3$) δ ppm
2a	(76)[b]	141(4), 113(8) 99(7), 43(100)	2108 (sharp, N_3), 1709 (sharp, C=O), 1616 (sharp, C=C)	2.1 (s, 6H, 2xCH_3), 5.5 (s, 1H, CH)
2b	(83)[f]	194(4), 115(26) 87(48), 43(100)	1740 (broad, C=O), 1620 (broad, C=C) 1270, 1180 (broad S=O)	2.25 (s, 6H, 2xCH_3), CH_3),3.1 (s, 3H, OSO_2CH_3), 5.6 (s, 1H, CH)
2c	(67) 57-58°/15 [57/58°/15][c]	130(6), 99(8) 87(12), 43(100)	3450 (br, O-H), 1716 (sharp, C=O) 1601 (br, C=C)	2.25 (s, 6H, 2xCH_3); 3.45 (s, 3H, OCH_3), 14.8 (b, 1H, OH)
2d	(74)[f]	198(7), 99(6) 43(100)	3240 (br, O-H), 1726 (sharp, C=O), 1582 (br, C=C)	2.3 (s, 12H, 4xCH_3), 6.1 (s, 2H, 2xCH)
2e	(70)[f]	203(3), 175(7) 161(10), 105(100)	2108 (sharp, N_3), 1700 (sharp, C=O), 1616 (br, C=C)	2.3 (s, 3H, $COCH_3$), 6.3 (s, 1H, CH), 7.3-7.8 (m, 5H, aromatic)
2f	(73)[f]	256(5), 167(9) 134(10), 105(100)	1734 (sharp, C=O), 1693 (sharp, C=O), 1280 1170 (sharp, S=O)	2.1 (s, 3H, CH_3), 3.1 (s, 3H, OSO_2CH_3), 6.1 (s, 1H, CH), 7.3-8.2 (m, 5H, aromatic)
2g	(76)[f] 155°	322(4), 236(6) 161(6), 105(100)	1715 (sharp, C=O), 1780 (sharp, C=O)	2.5 (s, 6H, 2xCH_3), 6.7 (s, 2H, 2xCH), 7.5-8.3 (m, 10H, aromatic)
4a	(52)[f]	157(3), 129(12) 85(15), 43(100)	3381 (br, O-H), 2135 (sharp, N_3), 1716 (br, C=O), 1651 (sharp, C=C)	2.2 (s, 3H, CH_3), 3.9 (s, 3H, $COOCH_3$), 4.8 (s, 1H, CH)
4b	(76)[f]	220(4), 179(26) 89(48), 43(100)	3380 (br, O-H), 1730 (br, C=O), 1280 1176 (br, SO_2)	2.1 (s, 3H, $COCH_3$), 3.1 (s, 3H, OSO_2CH_3), 3.8 (s, 3H, $COOCH_3$), 5.4 (s, 1H, CH)
4c	(63) 44-46°/1 [44-48°/1][d]	146(12), 116(7), 103(7), 89(12) 43(100)	3441 (br, O-H), 1730 (br, C=O) 1635 (sharp, C=C)	2.1 (s, 3H, CH_3), 3.4 (s, 3H, OCH_3), 3.9 (s, 3H, $COOCH_3$), 4.4 (s, 1H, CH)
4d	(46) 136-138°C [138-140°C][e]	290(6), 115(8), 43(100)	(KBr)1730 (sharp, C=O), 1680 (C=O)	2.2 (s, 6H, 2xCH_3), 3.9 (s, 6H, 2x$COOCH_3$), 5.8 (s, 2H, 2xCH)
4e	(48)[f]	233(6), 191(6), 105(100), 77(9)	2108 (sharp, N_3) 1720 (sharp, C=O) 1680 (sharp, C=O)	1.2 (t, 3H, CH_2CH_3), 4.1 (q, 2H, $COOCH_2CH_3$), 5.8 (s, 1H, CH), 7.3-7.8 (m, 5H, aromatic)
4f	(76)[f]	286(3), 105(100)	3480 (br, O-H), 1750(C=O), 1700(C=O) 1260 1160 (br, SO_2)	1.2 (t, 3H, CH_3), 3.2 (s, 3H, OSO_2CH_3), 4.2 (q, 2H, $COOCH_2CH_3$), 6.3 (s, 1H, CH), 7.3-8.3 (m, 5H, aromatic)
4g	(59)[f]	236(2), 163(4), 105(100)	3480 (br, O-H), 1750 (sharp, C=O) 1700 (sharp, C=O)	1.2 (t, 6H, 2xCH_3), 3.5 (q,2H, OCH_2CH_3), 4.2 (q, 2H, $COOCH_2CH_3$), 5.2 (s, 1H, CH), 7.3-7.7 & 7.8-8.3 (m, 5H, aromatic)
4h	(68) 178-79°C (178-79°C)[g]	382(8), 191(12), 105(100), 77(8)	1740 (C=O), 1700 (C=O)	1.3 (two t, 6H, 2x$COOCH_2CH_3$), 3.6-4.2 (two q, 4H, 2xCH_2CH_3), 6.2 (s, 2H, 2xCH_3), 7.6-8.4 (m, 10H, aromatic)

[a]Yields are based on pure products obtained either by column chromatography or reduced pressure distillation.

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[f]Purified by column chromatography using hexane: ether as eluents. 2b, Found %S=16.23 $C_6H_{10}SO_5$ requires %S=16.49; 2d Found %C=59.60, H=6.91 $C_{10}H_{14}O_4$ requires %C=60.6, H=7.07; 2e, Found %C=58.89, H=4.13, N=20.3 $C_{10}H_9N_3O_2$ requires %C=59.1, H=4.43, N=20.68; 2f Found %C=51.30, H=4.35, S=11.96, $C_{11}H_{12}SO_5$ requires %C=51.56, H=4.68, S=12.5; 2g Found %C=74.31, H=5.98 $C_{20}H_{18}O_4$ requires %C=74.53, H=5.59; 4a Found %N=26.31, $C_5H_7N_3O_3$ requires %N=26.75; 4b Found %C=34.12, H=4.43, S=4.43, S=15.1, $C_6H_{10}SO_6$ requires %C=34.28, H=4.76, S=15.23; 4e Found %C=561, H=436, N=17.8, $C_{11}H_{11}N_3O_3$ requires %C=56.65, H=4.72, N=18.02; 4f Found %C=50.21, H=4.63, S=11.1 $C_{12}H_{14}SO_6$ requires %C=50.34, H=4.89, S=11.18; 4g Found %C=66.01, H=5.61, $C_{13}H_{16}O_4$ requires %C=66.10, H=6.77.

[g]T. Suchiro, Nippon Kagaku Zasshi, 79, 457 (1958).

mole). The contents were stirred for 10 minutes at room temperature followed by the addition of the β-dicarbonyl compound. The mixture is refluxed for 2 hr and then treated with aqueous sodium hydrogen carbonate. The organic layer is dried over $MgSO_4$ and concentration of the organic layer afforded crude product which was purified by column chromatography using hexane: ether as eluents. The compounds so obtained are listed in Table-1.

General procedure for the preparation of α-methoxy or α-ethoxy β-dicarbonyl compounds (2c, 4c, 4g): To a suspension of iodosobenzene (0.01 mole) in methanol (40 ml) was added boron trifluoride etherate (0.01 mole) with stirring. To the resulting mixture was added the β-dicarbonyl compound (0.01 mole). The contents were allowed to stir at room temperature for 5 hr. The volume of the reaction mixture was reduced under reduced pressure to one-third and the resulting solution treated with a saturated solution of sodium hydrogen carbonate and aqueous layer was extracted with dichloromethane (3 x 40 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product which contained iodobenzene and a small amount of recovered β-dicarbonyl compound. The pure product was separated by column chromatography using hexane: ether (9:1) as eluents. Compounds thus obtained are listed in Table-1.

General procedure for the preparation of 2d, 2g, 4d, 4h: To a suspension of iodosobenzene (0.0065 mole) in 50 ml of dry chloroform under nitrogen was added boron trifluoride etherate (0.0065 mole). The mixture is stirred at room temperature for 10 minutes and then the β-dicarbonyl compound was added. The reaction mixture was refluxed for 3 hr. This solution was basified with a saturated solution of sodium hydrogen carbonate and the aqueous layer extracted with chloroform (3 x 50 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. Pure products were obtained either by column chromatography or by crystallization from a suitable solvent. The results of this reaction are summarized in Table-1.

Reaction of benzoylacetone with iodosobenzene: To a stirred suspension of iodosobenzene (0.01 mole) in methanol was added boron trifluoride etherate (0.01 mole). To the resulting mixture was added benzoylacetone (0.01 mole). The contents were allowed to stir at room temperature for 8 hr. The volume of the reaction mixture was reduced to one-third and the resulting solution treated with a saturated solution of sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product. On purification of the crude product on a silica gel column using hexane: ether as eluents, α-methoxyacetophenone IR (Neat) cm^{-1}: 1710 (sharp C=O stretching), ^1H NMR ($CDCl_3$) δ: 3.85 (s, 2H, CH_2), 3.9 (s, 3H, OCH_3), 7.3-7.6 (m, 5H, aromatic protons), Yield = 0.94 g (63%), b.p. 119-121/15 mm, Lit[8] b.p. 118-120/15 mm and methyl phenylacetate IR (Neat) cm^{-1}: 1710 (sharp C=O stretching), ^1H NMR ($CDCl_3$) δ: 3.3 (s, 3H, OCH_3), 4.65 (s, 2H, CH_2), 7.2-8.0 (m, 5H, aromatic protons), Yield = 0.36 g (24%), b.p. 218°C, Lit[12] b.p. 218°C were obtained.

The reaction was repeated in the absence of boron trifluoride etherate and also under refluxing conditions. In all these cases α-methoxy acetophenone and methyl phenyl acetate were obtained.

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