Syntheses of α-Iodocarbonyl Compounds Using Bis(*sym*-collidine)Iodine(I) Tetrafluoroborate/Dimethyl Sulfoxide

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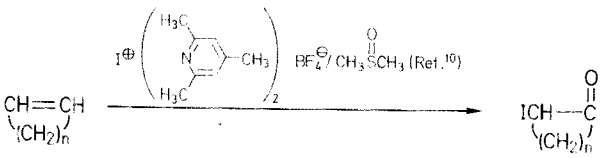
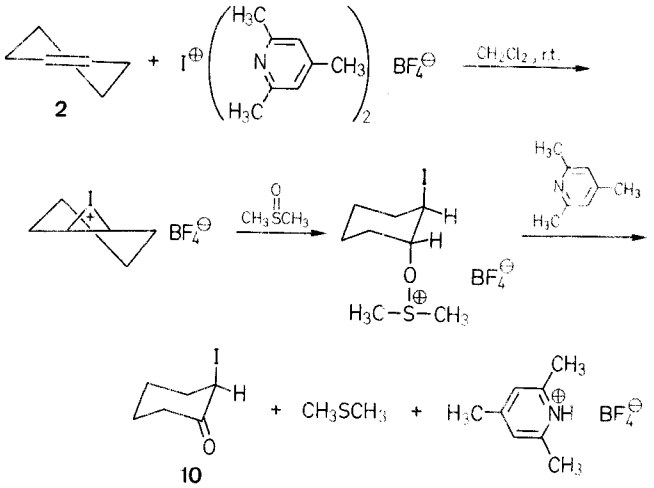
$I^+(Collidine)_2BF_4^-$/DMSO has been found to be a convenient reagent for the direct conversion of alkenes to α-iodocarbonyl compounds. Using conformationally biased alkenes, the reactions proceed stereospecifically giving axial iodoketones. Application of the reagent in reactions with unsaturated carbohydrates provides a unique method for the conversion of certain glycals to their corresponding α-iodo-α,β-unsaturated lactones.

In contrast to their chloro and bromo analogs, α-iodo carbonyl compounds have been studied infrequently. This is due primarily to the relative instability of such compounds and also to the fact that methods available for their synthesis are limited. α-Iodoketones have previously been prepared by halogen interchange of bromo compounds with sodium iodide[1], and by the reaction of N-iodosuccinimide or iodine (I) chloride with the enol acetates of ketones[2]. More recently it has been reported that the reaction of enol acetates and enol silyl ethers with various metal acetates and iodine result in the formation of α-iodoketones[3–6]. Two methods are known for the direct conversion of alkenes to the corresponding α-iodocarbonyl compounds. One such method utilizes silver chromate and iodine[7], while a more recent method involves the use of pyridinium dichromate and iodine[8].

In continuation of our investigations on the use of bis(*sym*-collidine)iodine (I) tetrafluoroborate – $I^+(collidine)_2\ BF_4^-$ – as an iodonium ion transfer reagent[9], we have found this compound in combination with dimethyl sulfoxide (DMSO) to be effective for the facile oxidation of alkenes to the corresponding α-iodocarbonyl compounds[10].

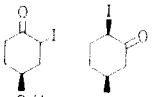
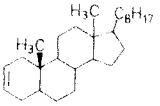
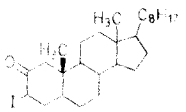
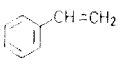
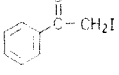
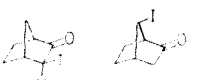


The ability of bis(*sym*-collidine)iodine (I) reagents to transfer iodine (I) cation to the carbon-carbon double bond of alkenes is well documented[11–13]. It is believed that the $I^+(collidine)_2BF_4^-$/DMSO oxidation reaction discussed herein involves initial I^+ transfer to the carbon-carbon double bond forming a three membered iodonium ring intermediate (Scheme **A**). Subsequent nucleophilic addition of dimethyl sulfoxide forming the dimethyloxysulfonium salt, followed by proton abstraction by collidine gives the α-iodocarbonyl compound, along with dimethyl sulfide and collidinium tetrafluoroborate.

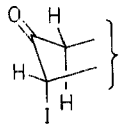


Scheme A

Table 1.

Alkene	Product (yield)	Alkene	Product (yield)
 1	 9 (62 %)	 5	 14 (78 %)
 2	 10 (61 %)	 6	 15 (69 %)
 3	 11 (30 %) 12 (30 %)	 7	 16 (69 %)
 4	 13 (80 %)	 8	 17 (40 %) 18 (40 %)

Some of the α-iodocarbonyl compounds prepared are shown in Table 1. As can be seen, the method is applicable to a wide range of alkenes and proceeds with a high degree of regio- and stereoselectivity to give relatively good yields of products. The ^{1}H-NMR spectra of compounds **11**, **12**, and **16** showed multiplets at 4.64–4.75 ppm for the iodomethine (CH—I) protons which are characteristic in peak width at half-height, and chemical shift for the α-equatorial protons in these types of compounds. The axial disposition of iodine in these compounds was further confirmed by the presence of long range planar W-type coupling between the two equatorial α-protons:

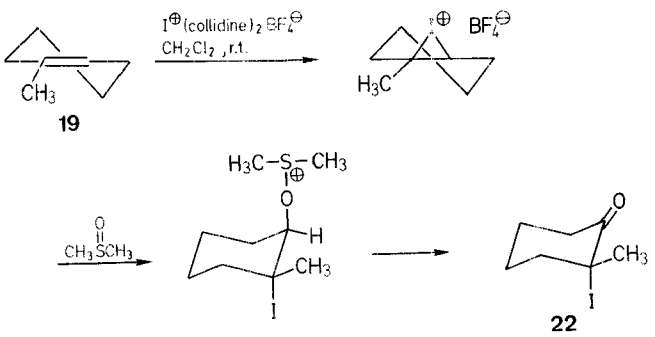


The existence of this type of long range coupling through an sp^2 hybridized carbon atom has been previously documented[14], and in the present work was observed using proton decoupling as well as 2D, J-correlated NMR experiments.

The $I^+(collidine)_2BF_4^-$/DMSO reaction was also found to be useful for the conversion of enol ethers to the corresponding α-iodolactones. This is demonstrated by preparation of α-iodo-δ-valerolactone **(14)** and α-iodo-γ-butyrolactone **(15)** from dihydropyran **(5)** and dihydrofuran **(6)**, respectively. It should be noted that previously reported attempts to prepare α-iodolactones from enol ethers have either been unsuccessful or gave low yields.

With certain *gem*-disubstituted and trisubstituted alkenes, e.g. **19–21** the $I^+(collidine)_2BF_4^-$/DMSO oxidation proceeded giving products arising *via* anti-Markownikov addition (I^+ becoming attached to the carbon with *less* hydrogens). An example is seen in the formation of 2-iodo-2-methylcyclohexanone **(22)** from the 1-methylcyclohexene **(19)**, (Scheme **B**).

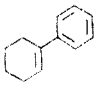
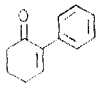
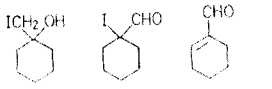
The alternate oxysulfonium intermediates arising *via* Markownikov addition would, of course, be unable to undergo elimination to α-iodoketones, but would be expected to hydrolyze to the corresponding iodohydrins upon aqueous workup[15].



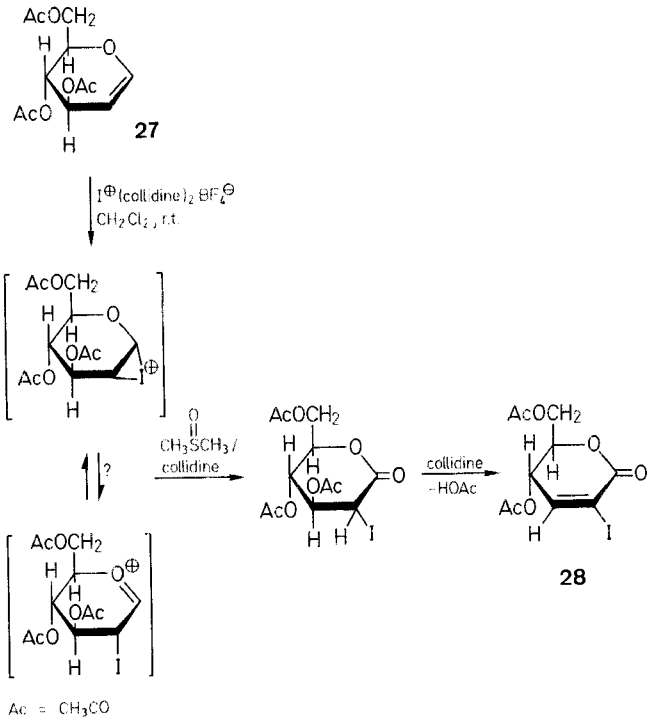
Scheme **B**

Reaction of methylenecyclohexane **(21)** with $I^+(collidine)_2BF_4^-$/DMSO does, in fact, yield such an iodohydrin **(24)** as the major product, in addition to 1-iodo-1-cyclohexanecarbaldehyde **(25)** and a minor amount of 1-cyclohexenecarbaldehyde **(26)** (Table 2). The latter is presumably formed *via* elimination of HI from the iodoketone **(25)**. 1-Phenylcyclohexene **(20)** reacts to afford the enone **(23)**, apparently *via* elimination of HI from 2-iodo-2-phenylcyclohexanone.

Table 2.

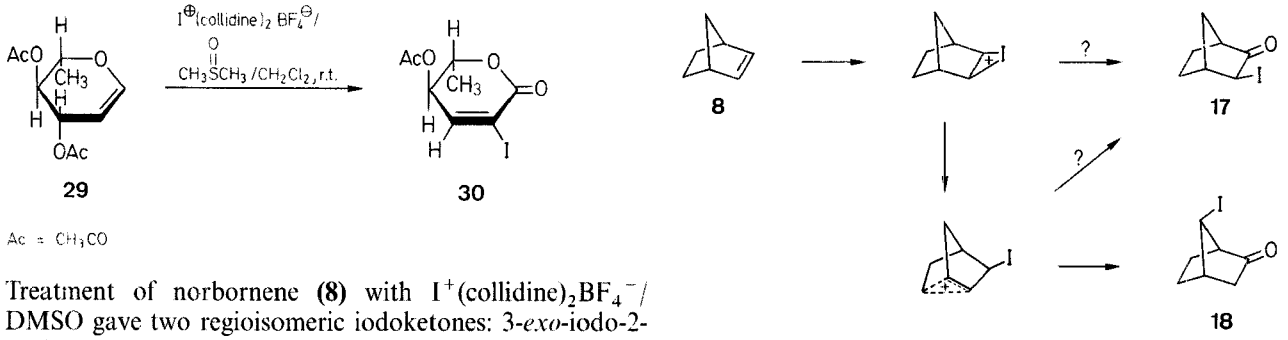
Alkene	Product (yield)
 **19**	 **22** (55%)
 **20**	 **23** (58%)
 **21**	 **24** (55%) **25** (25%) **26** (5%)

The I^+-DMSO reaction was extended to the oxidation of unsaturated carbohydrates. Upon treatment of tri-O-acetyl-D-glucal **(27)** with $I^+(collidine)_2BF_4^-$/DMSO, the expected α-iodolactone was not isolated, but apparently underwent further elimination to give a high yield of the α-iodo-α,β-unsaturated lactone, (5*R*,6*R*)-5-acetoxy-6-acetoxymethyl-3-iodo-5,6-dihydro-2-pyrone **(28)** (Scheme **C**).



Scheme **C**

Analogous results were obtained upon reaction of 3,4-di-O-acetyl-6-deoxy-L-glucal **(29)**, which gave relatively high yields of (5*S*,6*S*)-5-acetoxy-3-iodo-6-methyl-5,6-dihydro-2-pyrone **(30)**. Thus, it appears that $I^+(collidine)_2BF_4^-$ will prove useful for converting certain glycals to the corresponding α-iodo-α,β-unsaturated lactones in one step.



Ac = CH_3CO

Treatment of norbornene **(8)** with $I^+(collidine)_2BF_4^-$/ DMSO gave two regioisomeric iodoketones: 3-*exo*-iodo-2-norbornanone **(17)**, and 7-*syn*-iodo-2-norbornanone **(18)**. Scheme **D**

Table 3. Analytical and Spectral Data for α-Iodoketones, Lactones, and Related Products

Product	b.p. [°C]/torr[a] or m.p. [°C]	Molecular Formula[b] or Lit. Data	IR $\nu_{C=O}$ [cm^{-1}]	^{1}H-NMR ($CDCl_3$/TMS) δ[ppm]
9	51/1	C_5H_7IO	1730	2.24 (m, 6H); 4.60 (m, 1H, CHI)
10	55/1	C_6H_9IO	1708	1.56–2.36 (m, 7H); 3.28 (m, 1H, H-6_{ax}); 4.73 (m, 1H, CHI, $\omega_{\frac{1}{2}}^{1}$ = 8.8 Hz[c])
11, 12[d]		$C_{10}H_{14}IO$		**(6):** 3.37 (ddd, 1H, J = 6.1, 14.6, 14.6 Hz, H-6_{ax}); 4.75 (m, 1H, XHI, $\omega_{\frac{1}{2}}^{1}$ = 8.4 Hz[c]) **(7):** 3.17 (t, 1H, H-6_{ax}); 4.67 (m, 1H, CHI)
13	34.5 (hexanes)	m.p. 34–34.5[7] m.p. 35.5–36[5]	1675	4.40 (s, 2H, $-CH_2I$); 7.60 (m, 3H, $H_{m,p}$); 8.05 (m, 2H, H_o)
14	78/1	$C_5H_7IO_2$	1730	1.60–1.80 and 2.20–2.25 (2m, 4H, $-CH_2CH_2-$); 4.23 (m, 2H, $-OCH_2-$); 4.41 (m, 1H, CHI)
15		$C_4H_5IO_2$	1770	2.23 (m, 1H); 2.73 (m, 1H); 4.46 (m, 2H, $-CH_2O-$); 4.57 (dd, 1H, J = 2.2, 7.2 Hz, CH_2I)
16	120.2		1700	2.31 (dd, 1H, J = 1.8, 14.9 Hz, H-1_{eq}); 3.07 (dd, 1H, J = 14.9, 0.9 Hz, H-1_{ax}); 4.64 (m, 1H, CHI, $\omega_{\frac{1}{2}}^{1}$ = 6.0 Hz[e])
17		C_7H_9IO	1750	2.75 (m, 1H, H-4); 2.87 (m, 1H, H-1); 4.20 (d, 1H, J = 3.5 Hz[f], CHI)
18		C_7H_9IO	1750	2.81 (m, 1H, H-3_{endo}); 2.84 (m, 1H, H-1); 4.07 (q, 1H, CHI[g])
22		[h]	1700	1.20–1.80 (m, 4H); 1.80–2.10 (m, 1H); 2.10 (s, 3H, $-CH_3$); 2.26–2.56 (m, 2H); 3.54 (ddd, 1H, J = 6.3, 13.8, 15.5 Hz, H-6_{ax})
23	94.4[i] (hexanes)	m.p. 94–94.5[16]	1660	2.15 (m, 2H); 2.60 (m, 4H); 7.09 (m, 1H, H-3); 7.36 (m, 5H, H_{arom})
24	70.4 (hexanes)	$C_7H_{13}IO$	[j]	1.21–1.90 (m, 10H); 1.64 (s, 1H, —OH)
25			1710	1.40–1.80 (m, 6H); 1.80–2.20 (m, 4H); 9.26 (s, 1H, —CHO)
28		$C_{10}H_{11}IO_6$	1740	2.14 and 2.20 (2s, 2 × 3H, 2 × $COCH_3$); 4.27 (dd, 1H, ^3J = 12.5 Hz, ^4J = 3.7 Hz, CH_aOAc); 4.36 (dd, 1H, ^4J = 4.2 Hz, CH_bOAc); 4.79 (m, 1H, H-6); 5.46 (dd, 1H, $J_{5,6}$ = 7.2 Hz, $J_{4,5}$ = 3.5 Hz, H-5); 7.53 (d, 1H, H-4)
30			1740	1.50 (d, 3H, $-CH_3$); 2.19 (s, 3H, $COCH_3$); 4.74 (m, 1H, H-6); 5.26 (dd, 1H, $J_{5,6}$ = 6.8 Hz, $J_{4,5}$ = 3.7 Hz, H-5); 7.56 (d, 1H, H-4)

[a] The α-iodoketones and lactones were obtained as labile liquids, except **16** (white crystals).

[b] Satisfactory microanalyses were obtained: C ±0.30 except **11, 12** (−0.49), **18** (+0.40) and **24** (±0.37); H ±0.20 except **11, 12** (+0.41); I ±0.34 (for **9, 10, 15, 24**); and O ±0.17 (for **10, 11** and **12, 15, 17**).

[c] δ and $\omega_{\frac{1}{2}}^{1}$ values were consistent for α-equatorial H; thus, −I is axial.

[d] **11, 12** were inseparable by TLC, on silica gel. Microanalytical and NMR data were obtained on the mixture.

[e] Upon decoupling H-1_{eq} the CHI signal collapsed (dd). The remaining splitting results from *vic* coupling to the two anisochronous H's at C-4.

[f] The proton at C-3 was revealed to be *endo* due to absence of coupling between H-3 and H-4, and the presence of long range (*anti*) coupling between H-3 and H-7.

[g] The *syn* orientation of −I is supported by the presence of long range coupling between H-7 and H-3_{endo}.

[h] Unsatisfactory microanalysis due to lability.

[i] Yellow needles; 2,4-DNP: m.p. 163.5; lit[17] m.p. 163–165.

[j] ν_{OH} = 3280 cm^{-1}.

The 3-*exo* isomer **(17)** is apparently formed by initial *exo* addition of I^+ reagent to the alkene, followed by *endo* attack of DMSO either on the three membered ring iodonium intermediate or on the non-classical carbocation. 7-*syn*-Iodo-2-norbornanone is apparently formed *via* the same carbocation, with subsequent addition of DMSO to the original bridgehead carbon (Scheme **D**).

IR spectra were obtained with a Perkin-Elmer Model 680 Grating Infrared Spectrometer. NMR spectra were recorded on a Varian Associates XL-200 instrument, using $CDCl_3$ or CD_2Cl_2 solutions and TMS as the internal standard. Melting points were determined on a Mettler FPI instrument. All reactions were conducted under nitrogen using anhydrous reagents and solvents. Liquid alkenes were purified by passage through a neutral alumina column, followed by distillation just prior to use.

Bis(*sym*-collidine)iodine(I) Tetrafluoroborate:

A procedure paralleling that reported by Lemieux and Morgan and modified by Magee for preparation of the corresponding perchlorate salt was used[9-11]. *sym*-collidine (2,4,6-trimethylpyridine) (45 g, 370.8 mmol) is added to an aqueous solution (150 ml) of silver nitrate (13.5 g, 79.5 mmol) and sodium tetrafluoroborate (14.82 g, 147 mmol). *Bis(sym-collidine)silver(I) tetrafluoroborate* precipitates immediately as a white solid, is isolated by vacuum filtration, and washed successively with distilled water (100 ml), ethanol (150 ml), and ethyl ether (2 × 100 ml). The compound is dried for 24 h over phosphorus pentoxide at 30 torr. The yield is quantitative.

$C_{16}H_{22}AgBF_4N_2$	calc.	C 44.00	H 5.04	F 17.40	N 6.41
(437.2)	found	43.93	5.21	17.45	6.61

IR (KBr) ν = 1005–1160 (strong, BF_4^-), 1615, 840 cm^{-1}.

^1H-NMR (CD_2Cl_2): δ = 7.18 (2 H, H_{arom}); 2.76 (s, 6 H, CH_3's at C-2 and C-6); 2.40 ppm (s, 3 H, CH_3 at C-4).

Bis(*sym*-collidine)silver(I) tetrafluoroborate (12.67 g, 29 mmol) is dissolved in dry methylene chloride (110 g). Iodine (3.68 g, 29 mmol) is added in one portion and the mixture is agitated for 30 min or until all of the iodine has reacted. Silver iodide is removed by vacuum filtration leaving a clear, amber, methylene chloride solution of bis(*sym*-collidine)iodine(I) tetrafluoroborate. Analytical samples are obtained by evaporation of the methylene chloride, followed by recrystallization of the crude product from hexane.

$C_{16}H_{22}BF_4IN_2$	calc.	C 42.15	H 4.83	B 2.37	I 27.84	N 6.14
(456.2)	found	42.24	4.85	2.46	27.64	6.30

Preparation of α-Iodocarbonyl Compounds; General Procedure:

To a solution of bis(*sym*-collidine)iodine(I) tetrafluoroborate (13.2 g, 29 mmol) in methylene chloride (60 ml), is added, under nitrogen at room temperature, a solution of the alkene (28 mmol), and dry dimethyl sulfoxide (21.9 g, 0.28 mol) in methylene chloride (10 ml). The mixture is agitated for 2 h, filtered, and washed successively with distilled water (75 ml), 10% sodium thiosulfate (75 ml), cold 10% hydrochloric acid (75 ml), and then dried over anhydrous magnesium sulfate. After filtering the magnesium sulfate, the solvent is removed under reduced pressure. The crude reaction products are purified by flash chromatography (Kieselgel 60, methylene chloride). The chromatographed products were homogeneous on TLC (silica gel, methylene chloride). Yields of isolated products are reported in Tables 1 and 2. The relative yields of **11** to **12** and of **24** to **25** to **26** were determined from the NMR spectra of the product mixtures. Analytical and spectral data for all α-iodocarbonyl and related compounds are given in Table 3.

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