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Concerning the Formations of α-Iodoenones

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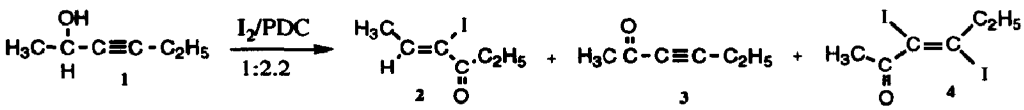
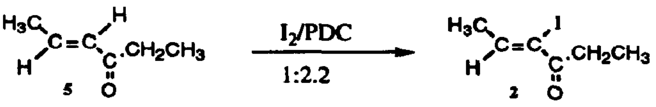
Abstract:. The formations of α-iodoenones from secondary alkynols with NIS/HTIB (cat.), tertiary alkynols with I_2/PDC and enones with I_2/pyridine have been compared. In the latter two reactions the PDC and the pyridine have been found to be catalytic.

We wish to present unifying views and supporting data on the formations of α-iodoenones. In 1991 we reported a reaction whereby secondary α-alkynols such as 3-hexyn-2-ol (**1**) were converted to α-iodoenones by iodonium-producing reagents such as N-iodosuccinimide (NIS) and catalytic amounts of [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent).[1] This reaction was extended to phenylethynylcyclopentanols.[2] These reactions had affinity to the conversions of tertiary ethynyl alcohols to α-iodoenals by means of iodine and pyridinium dichromate (PDC) (1:2) reported by Piancatelli and colleagues in 1981.[3] The pyridine component of PDC in turn drew into our sphere of interest the recent report of Johnson and Uskokovic on the α-iodination of cyclic enones with iodine and pyridine.[4]

In order to establish any common factors of the NIS/HTIB (cat.) and the I_2/PDC systems, **1** was treated with I_2/PDC. None of the starting material was recovered. The selectivity to the product of the NIS/HTIB (cat.) reaction, (Z)-4-iodo-4-hexen-3-one (**2**) was 27%. In addition, two products of PDC oxidation of secondary alcohols, 3-hexyn-2-one (**3**) and 3,4-diiodo-3-hexen-2-one (**4**), were formed in selectivities of 15% and 37%, respectively. The latter compound is not formed by the iodination of the former as shown by a negative iodination reaction. The source of the diiodoketone was the corresponding starting alkynol which under the reaction procedure stood with iodine for thirty minutes prior to the addition of PDC. When authentic diiodohexenol was treated with PDC, the principal products were the two ketones indicative of deiodination as well as oxidation. Their yields were 37% for **3** and 17% for **4**. A trace amount of **2** was detected.



The differences between the NIS/HTIB (cat.) and the I_2/PDC systems were further accentuated by the fact that I_2/PDC was unable to iodinate the aromatic ring of mesitylene. Such aromatic iodinations are readily carried out by the NIS/HTIB (cat.) system. Indeed the aromatic iodinations have been used as a firing range to test the effectiveness of iodonium-producing reagents such as NIS/HTIB (cat.) and I_2/HTIB.[5,6]



The mode of reaction of the I_2/PDC reagent was tested further by a reaction whereby 4-hexen-3-one (**5**) was converted to (**2**), the product of the NIS/HTIB (cat.) reaction with 3-hexyn-2-ol. It would seem that the PDC/I_2 was capable of iodinating enones. To extend this observation to tertiary alkynols, 2,4-diphenyl-3-butyn-2-ol (**6**) was treated with 88% formic acid to obtain (E/Z)-1,3-diphenyl-2-buten-1-one (**7**). The product of a Meyer-Schuster reaction was then reacted with I_2/PDC to form (E/Z)-1,3-diphenyl-2-iodo-2-buten-1-one (**8**). Thus the steps in the PDC/I_2 reaction with tertiary alkynols would be a Meyer-Schuster rearrangement to an enone followed by its iodination. The ability of PDC to behave as an acid catalyst was demonstrated by Corey's use of the Dauben transposition of tertiary alkenols with Cr(VI) to secondary alkenols, which are then oxidized to enones.[7,8]

Parallel attempts to convert ketones **5** and **7** to α-iodoenones **2** and **8** by means of NIS/HTIB (cat.) failed. The only products were minor amounts of the α' iodoenones. This does not rule out the possibility that iodonium-producing reagents will not form α-iodoenones directly from enones. The iodonium-producing system cerium ammonium nitrate/I_2 has been used recently to give α-iodoenones in flavone systems.[9] The pathway of NIS/HTIB (cat.) may involve iodonium attack on the alkyne portion of the alkynol parallel to the proton function in the mechanism of the Meyer-Schuster reaction.[10] The resulting β-hydroxy ketone could then be dehydrated to the enone.

Since the I_2/PDC reagent functions to iodinate Meyer-Schuster enones, it should have value as an iodination agent with a variety of enones. Some interesting results for the iodination of 2-cyclohexen-1-one are shown in Table 1.

Table 1 Formation of 2-Iodocyclohex-2-en-1-one [a]

PDC/I_2 molar ratio	Conversions of 2-cyclohexenone	Selectivity to 2-iodocyclohex-2-en-1-one
2.2 [b]	82	100
1.5	100	95
1.0	100	94
0.5	90	94
0.3	100	95
0.1	84	93
0.05	65	89

a) Conditions: 2-Cyclohexenone (2 mmol), iodine (2 mmol) in 15 mL of CH_2Cl_2. PDC added and mixture stirred at room temperature overnight. b) Conditions of ref. 3: 2-cyclohexenone (1 mmol), iodine (1 mmol), PDC (2.2 mmol) in CH_2Cl_2 with 4 A mole sieves under nitrogen.

These data demonstrate that the PDC is catalytic. This catalytic arrangement was then extended to other enones with mixed results as shown in Table 2. The less effective reaction with 3-methyl-2-cylohexenone is another indication that no iodonium ion is involved, since such a structure would have been favored by its ability to stabilize a positive charge at C-3 if an iodonium ion had attacked C-2. It speaks for an attack at the β-carbon of an enone which would be sensitive to these steric factors.

The 2-cycloheptenone conversion was increased to 53% and the selectivity to 87% when the reaction medium was refluxing acetonitrile overnight. These same conditions could also be extended to the iodination step of the I$_2$/PDC reaction wherein (E)-3-penten-2-one with I$_2$(1)/PDC(0.3) afforded an 86% yield of (Z)-3-iodo-3-penten-2-one. Data that support this assignment are as follows: ^{1}H-NMR (200MHz, CDCl$_3$) δ 2.09 (d, 3H, 6.6Hz), 2.51 (s, 3H), 7.13 (q, 1H, 6.6Hz); ^{13}C-NMR (50MHz, CDCl$_3$) δ 192.53 (C-2), 148.54 (C-4), 114.48 (C-3), 25.86 (C-1), 25.50 (C-5); GC/MS *m/z* (rel. int.) 210 (100, M$^+$), 195 (40), 167 (20), 43 (80); IR (film) 1675, 1610, 1230, 850 cm^{-1}.

The importance of heat on the reaction of acyclic enones with catalytic PDC is demonstrated in Table 3 for the iodination of **5**. Higher conversions, however, led to the introduction of α' iodination. The 2-iodo-4-hexen-3-one (**9**) was identified by GC/MS wherein its cracking pattern *m/z* (rel. int.) 224 (5, M$^+$), 97 (20, (M-I)$^+$), 69 (100) contrasted with that of its 4-iodo isomer (**2**): 224 (60, M$^+$), 195 (100, (M-Et)$^+$), 167 (40, (M-Et-CO)$^+$). The differences in the stability of the vinyl iodine atom versus the α-ketonic atom are apparent. An α' iodo isomer (13% selectivity) was also observed for the cycloheptenone case but not for the cyclohexenone cases.

Table 2. I$_2$/PDC (catalytic) and Enones

	α-Iodoenones		
Enones	Conversions (%)	Selectivity (%)	m/z (rel. int.) of α-iodoenones
3-Methyl-2-cyclohexenone	49	95 (5% m-cresol)	236 (100, M$^+$), 208 (80, (M-20)$^+$), 81 (15, (M-I-CO)$^+$), 53 (50)
3-t-Butyl-2-cyclohexenone	< 1	100	278 (30, M$^+$), 151 (15, (M-I)$^+$), 109 (60), 28 (100)
4,4-Dimethyl-2-cyclohexenone	10	100	250 (40, M$^+$), 123 (100, (M-I)$^+$), 95 (20), 67 (40)
2-Cyclopentenone	100	99 (1% 5-iodo)	208 (100, M$^+$), 180 (10), 81 (10, (M-I)$^+$) 53 (70)
(E)-4-Hexen-3-one	<5	100	224 (65, M$^+$), 195 (100, (M-Et)$^+$), 167 (50, (M-Et-CO)$^+$)
2-Cycloheptenone	1	100	236 (100, M$^+$), 207 (20), 81 (50)

Conditions: 1 mmol enone, 1 mmol I$_2$, 0.3 mmol PDC 10 mL CH$_2$Cl$_2$, room temperature, overnight.

Table 3. Iodination of 4-Hexen-3-one with I$_2$/PDC (catalytic) ^{a}

		Product selectivities	
Solvent	Conversion	(Z)-4-iodo-4-hexen-3-one	(E)-2-iodo-4-hexen-3-one
CCl$_4$	49	87	13
CH$_3$CN	64	83	17
CH$_2$Cl$_2$	24	92	8
Benzene	30	79	21

a) Conditions: 4-hexen-3-one (2 mmol), iodine (2 mmol), PDC (0.3 equiv), 15 mL solvent, reflux overnight.

If the PDC is catalytic, could it be replaced by pyridine and another acid? To this end pyridine (0.6 equiv) was added to a CH_2Cl_2 solution of 2-cyclohexenone (1 equiv), iodine (1 equiv) and p-toluenesulfonic acid (TsOH) (0.6 equiv). After a room temperature stirring overnight 2-iodo-2-cyclohexenone was formed as the only product on a 63% conversion. Furthermore, in one critically additional control without TsOH, the conversion was 88% with a 98% selectivity to the α-iodoenone. In a final control TsOH without pyridine gave no conversion of starting material.

This finding of iodination of enones with catalytic amounts of pyridine impinges on the Johnson-Uskokovic reaction wherein pyridine is 50% of the reaction medium (the other half being CCl_4) but is consistent with their postulated mechanism of nucleophilic addition of pyridine at the 3-position to form an α-carbanion which can attacked by iodine and elimination of the 2-H atom and the pyridine adduct.[4] Such a proposal had been foreshadowed by Jirkovsky's report of the mild iodination of enamine-like 3-benzylamino-5,5-dimethyl-2-cyclohexenone.[11] The sensitivity of the steric enviroment around C-3 as shown by the entries in Table 2 is also consistent with this postulate.

The differences between the acyclic and cyclic enones rest with the latter's abilities to maintain conjugation. The exocyclic enals of the Pianciatelli work could do likewise. The acyclic enones as well as cycloheptenone can twist out of conjugation and allow enolization to the α' position. The mixtures of Table 3 do not mean these processes have little synthetic potential. The direction of iodination may be controlled. For example, the enone **5** can be converted to **2** in an 83% selectivity on a 64% conversion by the use of I_2/PDC (cat.) in refluxing acetonitrile but **5** affords the 2-iodo-4-hexen-3-one in 90% selectivity on a 40% conversion in the same medium with I_2/pyridine (cat.)/TsOH (cat.)

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