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FORMATIONS OF α -IODOENONES BY IODINE AND CATALYTIC AMOUNTS OF AMINES

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ABSTRACT: Iodine and catalytic amounts of amines in a variety of solvents react with cyclic and acyclic enones to afford the corresponding α -iodoenones.

In a recent investigation of the mode of action of pyridinium dichromate and iodine on secondary and tertiary alkynols, we noted that 2-cyclohexenone (1a) could be converted to 2-iodo-2-cyclohexenone (2a) by means of stoichiometric iodine and a catalytic amount of pyridine.¹ The combination of several cyclic and linear enones with iodine and excess quantities of pyridine had been reported earlier.² We wish now to present results of the catalytic effect of amines for the α -iodination of enones, a process of considerable synthetic interest for a broad range of compounds.^{3,4}



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The original report of the catalytic ratio for the iodination of 2-cyclohexenone was 0.6 (pyridine / 1a). Variations of this ratio are given in Table 1. A level of 0.2 is satisfactory for good catalysis. Control reactions without pyridine can give a range of products depending upon the solvent. In CCl₄ a conversion of 24% to five products was observed. In tetrahydrofuran only 6-iodo-2-cyclohexenone was noted in a yield of 28%. In methylene chloride the main non-catalytic product was the 6-iodo isomer (12%). This product occurred in cases where the catalytic levels were low as will be shown below.

The reaction times for these data have not been fully examined to date but optimum conditions can be found for much shorter times. For instance enone **1a** can lead to **2a** in 1h in 100% selectivity on a 94 % conversion in CH_2Cl_2 at an I_2 / **1a** ratio of 1.31 and a pyridine / **1a** ratio of 0.82. At 15 minutes the selectivity / conversion values were 100% and 88%, respectively.

| Mol (Pyridine / 1a) | Mol (12/1a) | Yield(%) 2a | |
|---------------------|-------------|-------------|--|
| 0.12 | 1,30 | 11 | |
| 0.25 | 1.26 | 48 | |
| 0.42 | 1.20 | 76 | |
| 0.53 | 1.21 | 81 | |
| 0.64 | 1.28 | 89 | |
| 0.79 | 1.20 | 92 | |

Table 1. Formation of 2-Iodo-2-cyclohexenone (2a) a

a) Conditions: 2- Cyclohexenone (1 -2 mmol), iodine and pyridine in 15 mL of CH_2Cl_2 stirred overnight at room temperature. Yields were determined by GC. All selectivities were >99% except the first entry wherein 1% of the 6-iodo isomer was detected.

Other solvents were examined as replacements for CH_2Cl_2 . At catalytic levels of 0.7 to 1 molar ratios of pyridine to iodine, conversions of 81 to 95% for 1a with greater than 98% selectivity to 2a were noted for acetonitrile, carbon tetrachloride, benzene and tetrahydrofuran (THF). In pentane the conversion of 1a was 90% but the selectivity to 2a was 52%. The other products were 6-iodo-2cyclohexenone (α '-iodination) in 41% selectivity and 2-iodophenol (aromatization) in 7% selectivity. These results are incorporated in Table 2. The seemingly high levels of catalysts should be tempered with the other function of the base to combine with all or part of the HI that is formed in the reaction.

| Solvent | Mol (Pyridine / 1a) | <u>Mol (1₂/1a)</u> | Yield(%) 2a |
|---------------------------------|---------------------|-------------------------------|-------------|
| CH ₂ Cl ₂ | 0.84 | 1.15 | 90 |
| CCl4 | 0.90 | 1.01 | 84 |
| CH ₃ CN | 0.77 | 1.00 | 81 |
| C6H6 | 0.77 | 1.02 | 90 |
| THF | 1.05 | 1.01 | 97 |
| C5H12 | 1.0 | 1.03 | 47 |

Table 2 Effect of Solvent on Iodination of 2-Cyclohexenone (1a)^a

a) Conditions: Enone 1a (1.3 - 1.37mmoles), pyridine and iodine in 15 mL of solvent at room temperature overnight. Yields determined by GC.

Several substituted 2-cyclohexenones were tested for reactivities. For 3methyl-2-cyclohexenone (1b) with stoichiometric iodine and catalytic pyridine (0.8 equivalent) in CCl₄ the selectivity of 2b was 100% on a 92% conversion of 2a. Without pyridine the only detected product (4%) was the 6-iodo isomer of 2b. In acetonitrile the selectivity of 2b was 99% on a conversion of 48% for 1b. The corresponding conversion / selectivity values for CH_2Cl_2 and tetrahydrofuran were 57 / 99 and 22 / 99, respectively.

Compound 1c, 4,4-dimethyl-2-cyclohexenone, in CCl₄ under the same conditions led to 2c in 80% selectivity on an 83% conversion. Unlike 1b and 2b, the oil 2c is a new compound and has the following analytical values: ¹H NMR (CDCl₃) δ 1.14 (s, 6H), 1.87 (t, 6.7 Hz, 2H), 2.61 (t. 6.7 Hz, 2H), 7.40 (s, 1H); ¹³C NMR (CDCl₃) δ 28.0, 33.9, 36.6, 38.6, 102.3, 168.4, 192,1; GC / MS *m*/z (rel int) 236 (100, M⁺), 208 (80); IR (neat) 1690, 1570, 1320, 1150, 800, 750 cm⁻¹; Anal CH. No reaction in CH₂Cl₂ or CCl₄ were observed for 3,5,5-trimethyl-2cyclohexenone (isophorone) (**3**) at room temperature but in refluxing CCl₄ overnight it was converted to an equimolar mixture of the 2-iodo and the 6-iodo isomers in 7% yield. These findings are consonant with the postulated mechanism (shown in the scheme) whereby the attack of the base at the 3-position of the enone would be subject to steric hindrance as in **1b**, **1c** and **3**. To circumvent this problem Sha and Huang used trimethylsilyl azide and iodine in a pyridinedichloromethane (1/1) solvent for such β -substituted cycloalkenones.⁵

The importance of accessibility is demonstrated by 2-cyclopentenone (4) which in tetrahydrofuran at room temperature with an iodine/ 4 ratio of 1.0 and a pyridine/ I_2 ratio of 0.54 is converted to 2-iodo-2-cyclopentenone (5) in 88% yield. In CH₂Cl₂ under similar conditions the yield was 96%.

Another possible pathway for the formation of the iodoenones would be an iodonium attack at the 2-position followed by proton elimination. Such a route has been noted for the iodine - ammonium hexanitratocerate (IV) (CAN) combination.⁶ This reagent can also iodinate aromatic rings.⁷ The yields of **2a** and **5** obtained by I_2 / CAN are lower than those reported here. Indeed another iodonium - producing system of iodine and Koser's reagent used for the iodination of polymethyl benzenes converted **1a** to **2a** in 47 % yield mixed with an equal amount of the 6-isomer of **2a**.⁸

A related approach to the halogenation-dehydrohalogenation for α -haloenones is the use of oxone (2 KHSO₅-KHSO₄-K₂SO₄) with chlorides or bromides followed by a tertiary amine.⁹ The combination of iodine and pyridine fails to generate an iodonium species since it does not iodinate mesitylene, an electron rich aromatic. Thus the proposal of Johnson, Uskokovic and colleagues that the reaction sequence is base addition - iodination - base elimination is appropriate.



Scheme 1. Mode of Amine Catalysis for Iodination of Enones

The mechanism is also reminiscent of the Baylis - Hilman reaction which often entails the use of 1,4-diazabicyclo[2.2.2]octane (Dabco) to catalyze the formation of α -(hydroxyalkyl)vinyl ketones from vinyl ketones and aldehydes.^{9,10} Its catalytic effect on the α -iodination of 2-cyclopentenone (4) is shown in Table 3. Also given therein are results with representative primary and secondary amines. Without amines less than one percent of **5** was formed.

Linear enones present a challenge with this procedure due to a lack of rigidity of the conjugated system. The simple enone, (E)-3-penten-2-one (6) did

| Amine | Mol (Amine / <u>4</u>) | $Mol(l_2/4)$ | Yield (%) of 5 |
|-------------|-------------------------|--------------|----------------|
| Dabco | 0.93 | 1.24 | 58 |
| piperidine | 0.63 | 1.23 | 81 |
| n-C4H9NH2 | 1.0 | 1.0 | 62 |
| a-methyl- | 1.0 | 1.0 | 74 |
| benzylamine | | | |

| Fable 3. Formatio | n of 2-Iodo | -2-cyclo | pentenone | (5) a |
|-------------------|-------------|----------|-----------|-------|
|-------------------|-------------|----------|-----------|-------|

a) Conditions: enone 5 (1.0-1.5 mmoles), amine and iodine in CH₂Cl₂ (15 mL) at room temperature overnight.

Yields calculated by GC.

| 1 able 4. Formation of $(2)^{-1}$ form-the energy $(3)^{-1}$ | | | |
|--|-----------------|-------------------------------|-------------|
| Mol (Pyridine / 8) | Mol $(I_2 / 8)$ | Solvent | Yield (%) 9 |
| 1.02 | 1.06 | CH ₃ CN | < 1 |
| 1.07 | 1.26 | CH ₃ CN | 62 |
| 0.68 | 1.01 | C ₆ H ₆ | 55 |
| 0.60 | 1.05 | CCl4 | 59 |

Table 4. Formation of (Z)-4-Iodo-4-hexen-3-one (9) a

a) Conditions: enone 8 (1.0-1.4 mmoles), iodine and pyridine in 15 mL of solvent, which was refluxed overnight except for the first entry. Yields were calculated by GC.

not respond to the condition suitable for 2-cyclohexenone. In refluxing CH₃CN overnight, however, the conversion to (Z)-3-iodo-3-penten-2-one (7) was 99% with an $I_2/6$ ratio of 1.23 and a pyridine / 6 ratio of 0.72. The isolated yield was 76%. A similar reaction after three hours afforded 7 in 77 % yield (GC). Values for the related (E)-4-hexen-3-one's (8) conversion to (Z)-4-iodo-4-hexen-3-one (9) were lower but significant for preparative purposes since the selectivities were 100%. Representative results are given in Table 4. Methyl vinyl ketone with equimolar amounts of iodine and pyridine in refluxing CCl₄ was converted fully to a mixture whose major component was 3-iodo-3-buten-2-one (66% selectivity).

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