# A Convenient Protocol for the α-Iodination of α,β-Unsaturated Carbonyl Compounds with $I_2$ in an Aqueous Medium

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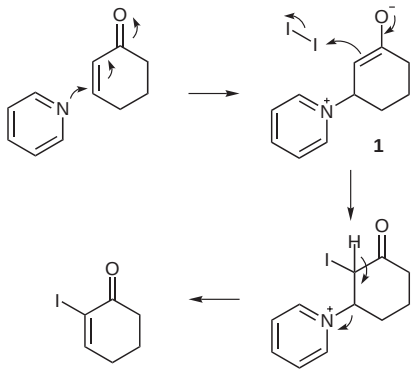
**Abstract:** A variety of cyclic and acyclic α,β-unsaturated carbonyl compounds undergo α-iodination exclusively, in high yields, with $I_2$ in aqueous THF catalyzed by DMAP and quinuclidine.

**Key words:** α,β-unsaturated carbonyl compounds, α-iodination, aqueous medium, regioselective

α-Iodinated, α,β-unsaturated carbonyl compounds are useful intermediates in organic synthesis, especially in transition metal-mediated reactions.[1] However, their preparation is somewhat limited. The α-iodination of α,β-unsaturated carbonyl compounds has previously been achieved with iodine-PDC[2] and iodine-bis(tetra-*n*-butylammonium) peroxydisulfate[3] systems. Indirectly, the Negishi group has iodinated α,β-unsaturated enones via α-silyl enones.[4] However, the most commonly employed approach, developed by the Johnson group, employs pyridine as a catalyst and co-solvent.[5] It is proposed that the reaction follows a Baylis–Hillman type pathway (Scheme 1).




**Scheme 1** Proposed Baylis–Hillman type pathway

Optimization by the McNelis group subsequently revealed that only sub-stoichiometric amounts of pyridine are required,[6] although in many cases long reaction times or high catalyst loading are necessary for high rates of conversion. It was also found that only cyclic α,β-unsaturated enones easily iodinate, while linear molecules require refluxing over extended periods of time for satisfactory conversion rates.

During our synthetic program, we required an expedient method for the synthesis of a range of α-iodo, α,β-unsaturated carbonyl compounds. We envisaged that, owing to its greater nucleophilicity, DMAP might be a superior catalyst to pyridine.[7] In addition, we speculated that an aqueous reaction medium would stabilize the zwitterionic intermediate **1**, both by solvation and through the Brønsted acid character of water, extending its lifetime and thus its reactivity towards electrophiles.

From our preliminary study with cyclohex-2-enone as the test substrate, we were pleased to find that both assertions were correct (Table 1). Employing 0.2 equiv of DMAP and excess iodine in organic solvents, little or no reaction was observed (entries 1 and 2). However, when a $H_2O$–THF (1:1) solvent system was used, a yield of 20% of **2a** was obtained (entry 3). With the addition of $K_2CO_3$ to remove the in situ generated HI, full conversion to **2a** was observed after two hours (entry 4). The reaction was completely regioselective and proceeded without the formation of any hydroiodination products. In contrast, after 5.5 hours under identical conditions with pyridine as the catalyst, only 33% conversion was observed (entry 5). With water as the solvent, the reaction appeared to be sluggish (entry 6), and the addition of a surfactant resulted in a messy reaction, giving rise to a mixture of products along with recovered starting material (entry 7). Without $K_2CO_3$ and employing a stoichiometric amount of DMAP, the reaction was also slow and had not gone to completion after 24 hours (entry 8). In the absence of DMAP (entry 9) no 'background' iodination was observed. Methanolic conditions failed to give clean conversion to the desired products and a 1:1 MeCN–$H_2O$ mixture was found to be a relatively efficient medium, but still inferior to a $H_2O$–THF mixture (entries 10 and 11, respectively). Although 1:1 $H_2O$–acetone and $H_2O$–*t*-BuOH mixtures (entries 12 and 13, respectively) were found to be as efficient as the $H_2O$–THF mixture with our test substrate, the conversion rates were generally inferior over a wider range of substrates.

The reactivity of several typical Baylis–Hillman catalysts was examined (Table 2).[8] None were found to be as efficient as DMAP, although the non-toxic nature of imidazole might make it the catalyst of choice in pharmaceutical applications (entry 1). Given the reactivity of imidazole, it was surprising that benzimidazole was unreactive (entry 2). Likewise, DABCO failed, as did triethylamine (entries 3 and 6, respectively). Surprisingly,

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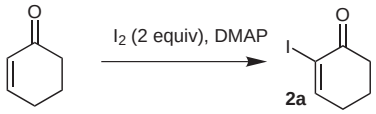
**Table 1** α-Iodination of Cyclohex-2-enone under Various Conditions

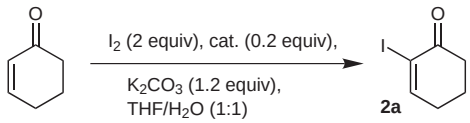



| Entry | DMAP (equiv) | Solvent | Base | Time (h) | Yield of **2a** (%) |
|---|---|---|---|---|---|
| 1 | 0.2 | $CH_2Cl_2$ | – | 20 | Trace |
| 2 | 0.2 | THF | – | 5 | 0 |
| 3 | 0.2 | $H_2O$–THF (1:1) | – | 20 | 20 |
| 4 | 0.2 | $H_2O$–THF (1:1) | $K_2CO_3$ | 2 | 99 |
| 5 | 0.2 (Pyridine) | $H_2O$–THF (1:1) | $K_2CO_3$ | 5.5 | 33 |
| 6 | 0.2 | $H_2O$ | $K_2CO_3$ | 2 | 20 |
| 7 | 0.2 | $H_2O$ (Triton-X) | $K_2CO_3$ | 5 | Mixture |
| 8 | 0.2 | $H_2O$–THF (1:1) | – | 24 | 86 |
| 9 | 0 | $H_2O$–THF (1:1) | $K_2CO_3$ | 2 | 0 |
| 10 | 0.2 | $H_2O$–MeOH (1:1) | $K_2CO_3$ | 2 | 57 |
| 11 | 0.2 | $H_2O$–MeCN (1:1) | $K_2CO_3$ | 2 | 86 |
| 12 | 0.2 | $H_2O$–$Me_2CO$ (1:1) | $K_2CO_3$ | 2 | 98 |
| 13 | 0.2 | $H_2O$–*t*-BuOH (1:1) | $K_2CO_3$ | 2 | 99 |

quinuclidine, *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine and DBU (entries 4, 7 and 8, respectively), reported to be very efficient catalysts for the Baylis–Hillman reaction,[9–11] were also ineffective. Although no clear trend emerged, it is likely that the catalyst suitability is governed by a combination of nucleophilicity verses steric hindrance, with DMAP having the most favorable combination of high nucleophilicity and low steric hindrance.

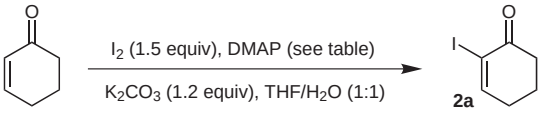
Optimization studies showed that reducing the amount of DMAP leads to a lower reaction rate (Table 3). In contrast, with a full equivalent of DMAP, iodination is complete in only 15 minutes (entry 1). However, useful conversions are still obtainable, even with very low catalyst loading (entries 5 and 6).

**Table 2** α-Iodination of Cyclohex-2-enone Using Commonly Employed Baylis–Hillman Catalysts




| Entry | Catalyst | Time (h) | Yield of **2a** (%) |
|---|---|---|---|
| 1 | Imidazole | 5.5 | 79 |
| 2 | Benzimidazole | 3 | Trace |
| 3 | DABCO | 3 | 0 |
| 4 | Quinuclidine | 5.5 | 36 |
| 5 | Piperidine | 5.5 | 70 |
| 6 | Triethylamine | 3 | 0 |
| 7 | TMPDA | 5.5 | 25 |
| 8 | DBU | 3 | 0 |

**Table 3** Effect of Catalyst Loading on α-Iodination of Cyclohex-2-enone




| Entry | DMAP (equiv) | Time (h) | Yield of **2a** (%) |
|---|---|---|---|
| 1 | 1 | 0.25 | 99 |
| 2 | 0.2 | 2 | 99 |
| 3 | 0.1 | 2 | 89 |
| 4 | 0.05 | 2 | 79 |
| 5 | 0.025 | 2 | 76 |
| 6 | 0.01 | 2 | 58 |

Additional equivalents of iodine do not accelerate the reaction, but if less than 1.5 equiv is employed the reaction fails to go to completion. This was also found to be true with the amount of $K_2CO_3$ where 1.2 equiv appeared optimum. Presumably, the equilibrium (Equation 1) caused by a slow reaction between iodine and water accounts for the need for an excess of these reagents.[12]

$$I_2 + H_2O \rightleftharpoons HOI + HI + K_2CO_3 \rightleftharpoons KOI + KI + CO_2 + H_2O$$

**Equation 1**

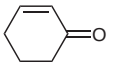
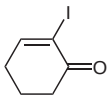
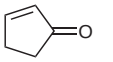
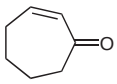
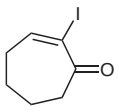
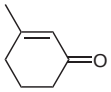
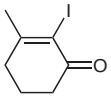
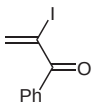
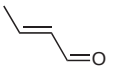
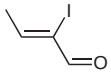
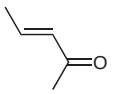
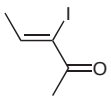
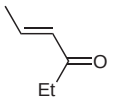
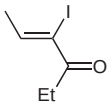
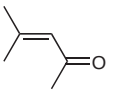
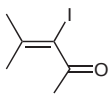
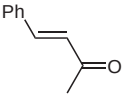
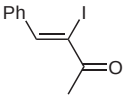
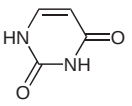
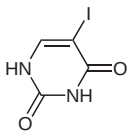
The scope of the method was investigated and the examples are illustrated in Table 4. Overall, a wide range of substrates was found to readily iodinate with no β-iodination or hydro-iodination products observed. As expected, relative reaction rates and overall yields were dependant on the ability of the substrate to act as a Michael acceptor.

Cyclic-enones unsubstituted at the β-position (entries 1 and 2) were rapidly converted to the iodide, although the iodination of cyclohepten-2-enone (entry 3) was sluggish and after 24 hours had undergone just 50% conversion. The presence of a β-substituent on a cyclic enone was found to be particularly deleterious to the reaction (entry 4). Linear enones (entries 5–11), which are generally poor substrates for iodination using available methods, were converted in high yields and in a relatively short period of time, with the exception of sterically hindered mesityl oxide (entry 10). Notably, no polymerization of the products was observed. For alkenes unsubstituted at the β-position (entries 5 and 6), quinuclidine was found to be a superior catalyst, owing to its greater nucleophilicity in the absence of steric inhibition. In addition to α,β-unsaturated aldehydes and ketones, uracil (entry 12), the C-5 substituted analogs of which are important intermediates for the synthesis of chemotherapeutic agents[13] and biological probes,[14] was found to quickly iodinate in nearly quantitative yield.

Unfortunately, more hindered systems gave less satisfactory results (entries 4, 10 and 11). Although increasing the amount of DMAP to 1 equiv had the effect of accelerating the reaction rate, overall yields were still low, and if left for long periods of time (>48 h) apparent in situ decomposition of the products was observed.

Our protocol was less efficient when extended to the iodination of α,β-unsaturated esters and nitriles (Table 5). When DMAP was employed as the catalyst, almost no iodination was observed even after extended periods of time, while quinuclidine was found to catalyze the iodination of methyl acrylate in a modest 45% yield (entry 1) and the more sterically hindered ethyl crotonate in a 25% yield (entry 2). The iodination of acrylonitrile gave only a trace amount of the desired product (entry 3). Unfortunately, further efforts at optimization such as longer reaction times, higher catalyst loading and performing the reactions in the dark, were not successful.

**Table 4** DMAP-Catalyzed α-Iodination of α,β-Unsaturated Carbonyl Compounds under Optimized Conditions[a]

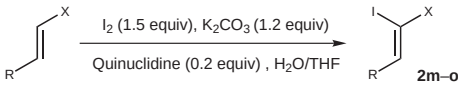
| Entry | Substrate | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | 2 | **2a**  | 99 |
| 2 |  | 1 | **2b**  | 99 |
| 3 |  | 24 | **2c**  | 50 |
| 4 |  | 48 | **2d**  | 16 |
| 5 |  | 6 | **2e**  | 68[b] |
| 6 |  | 2.5 | **2f**  | 92[b] |
| 7 |  | 2.5 | **2g**  | 99 |
| 8 |  | 4<br>20 | **2h**  | 75<br>85 |
| 9 |  | 4<br>20 | **2i**  | 70<br>90 |
| 10 |  | 45 | **2j**  | 27 |
| 11 |  | 44 | **2k**  | 32 |
| 12 |  | 5 | **2l**  | 97 |

[a] DMAP (0.2 equiv), $I_2$ (2 equiv), $K_2CO_3$ (1.2 equiv), $H_2O$–THF (1:1).
[b] 0.2 Equiv quinuclidine.

In conclusion, we have developed a method for the α-iodination of carbonyl compounds with iodine, employing mild aqueous conditions. The method appears to be of more general applicability than current literature procedures, except for highly sterically hindered substrates. In the absence of steric hindrance, substitution of DMAP for quinuclidine allows for the protocol to be extended to the

α-iodination of α,β-unsaturated esters, albeit in modest yields.

**Table 5** α-Iodination of α,β-Unsaturated Esters and Nitriles




| Entry | X | R | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | $CO_2Me$ | H | 24 | **2m** | 45 |
| 2 | $CO_2Et$ | Me | 24 | **2n** | 25 |
| 3 | CN | H | 24 | **2o** | Trace |

**Typical Procedure for α-Iodination Reaction**

To a stirred solution of cyclohex-2-enone (0.1 mL, 1.0 mmol) in 1:1 THF–$H_2O$ (5 mL) was added $K_2CO_3$ (166 mg, 1.2 mmol), $I_2$ (381 mg, 1.5 mmol) and DMAP (24 mg, 0.2 mmol) successively. Upon completion, the reaction mixture was diluted with EtOAc (10 mL) and washed with sat. $Na_2S_2O_3$ (20 mL) and 0.1 M HCl (20 mL) successively. The mixture was subsequently extracted with EtOAc[15] and dried over $MgSO_4$, before concentration and purification by flash column chromatography afforded 220 mg of the α-iodoenone **2a** (99% yield). All novel compounds were fully characterized;[16] all other compounds were identified from their $^1$H NMR spectra. Compounds **2a**, **2b**, **2k**: ref.[5]; compounds **2c**, **2i**: ref.[2]; compound **2d**: ref.[4]; compound **2e**: ref.[17]; compound **2g**: ref.[18]; compound **2h**: ref.[6]; compound **2l**: ref.[3]

## Acknowledgment

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(14) Goodwin, J. T.; Glick, G. D. *Tetrahedron Lett.* **1993**, *34*, 5549.
(15) Compound **2l** was extracted with acetonitrile.
(16) Selected data:
Compound **2f**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 2.1 Hz, 1 H, C*H*H=C), 6.86 (d, *J* = 2.1, 1 H, CH*H*=C), 7.46 (t, *J* = 6.8 Hz, 2 H, Ar), 7.59 (t, *J* = 7.5 Hz, 1 H, Ar), 7.81 (d, *J* = 7.2 Hz, 2 H, Ar). $^{13}$C NMR (75 MHz $CDCl_3$): δ = 107.9, 128.5 (2 C), 129.9 (2 C), 133.1, 133.8, 191.7.
Compound **2j**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3 H, C$H_3$), 2.04 (s, 3 H, C$H_3$), 2.50 (s, 3 H, C$H_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 22.1, 28.9, 30.9, 95.9, 145.7, 199.4.
Compound **2m**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OC$H_3$), 6.67 (s, 1 H, C*H*H=C), 7.55 (CH*H*=C). $^{13}$C NMR (75 MHz $CDCl_3$): δ = 53.7, 95.8, 139.9, 163.0.
Compound **2n**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_3$), 1.81 (d, *J* = 6.6 Hz, 3 H, $CH_3$CHC), 4.11 (q, *J* = 7.2 Hz, 2 H, $CH_2CH_3$), 7.15 (q, *J* = 6.6 Hz, 1 H, $CH_3CH$C). $^{13}$C NMR (75 MHz $CDCl_3$): δ = 14.2, 22.9, 62.5, 96.9, 148.3, 162.8.
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