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An iodine-promoted Meyer–Schuster rearrangement for the synthesis of α-iodo unsaturated ketones†

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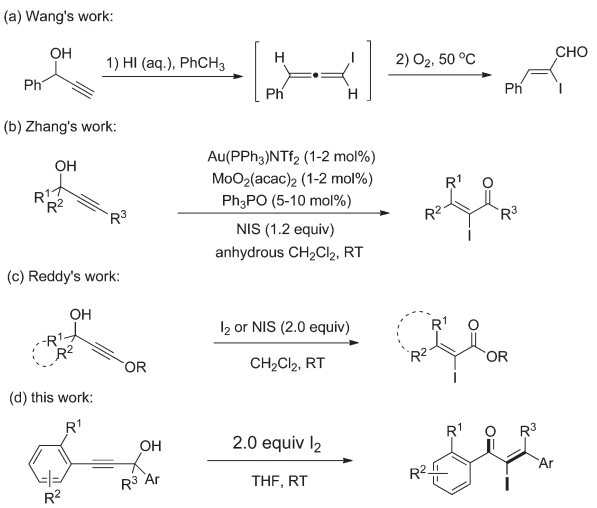
A facile and efficient iodine-promoted Meyer–Schuster rearrangement of propargyl alcohols for the synthesis of α-iodo-α,β-unsaturated ketones is presented. The reaction is concisely conducted at ambient temperature and shows good functional group tolerance.

α-Iodo unsaturated ketones are versatile intermediates which have been used for the synthesis of biologically active heterocyclic compounds[1] and palladium-catalyzed cross coupling.[2] Typically, the direct iodination of unsaturated enones was achieved by 1,4-conjugate addition of a nucleophile to enones sequentially with electrophilic iodination and elimination.[3] Lots of α-iodo enones, such as α-iodo cycloalkenones,[4,1b,d] α-iodo enaminones[5] and α-iodo chalcones,[6] were synthesized by using the protocol. However, the synthesis of acyclic β-mono/disubstituted α-iodo enones is still a challenging task. Therefore, the development of facile and efficient methods toward these valuable compounds is of great significance.

Recently, Lewis acid[7] or Brønsted acid[8,9] catalyzed Meyer–Schuster rearrangements of propargyl alcohols have been developed for the synthesis of useful compounds, such as heterocycles, carbocycles, enones and esters. In 2007, an aqueous HI-promoted Meyer–Schuster rearrangement for the synthesis of α-iodo-α,β-unsaturated aldehydes was developed by Wang and coworker (Scheme 1a).[9] The reaction was achieved through a stepwise mechanism that included the formation of iodoallene intermediates and their oxygen-mediated oxidation. After that, an Au and Mo co-catalyzed Meyer–Schuster rearrangement for the synthesis of α-iodo-α,β-unsaturated ketones was developed by Zhang and coworker where an iodonium ion was needed for the Au–I exchange (Scheme 1b).[10] Recently, Reddy *et al.* reported an iodine-induced Meyer–Schuster rearrangement of 3-alkoxy propargyl alcohols for the synthesis of α-iodo-α,β-unsaturated esters (Scheme 1c).[11] Despite these advances, versatile and efficient methods for the synthesis of α-iodo unsaturated ketones that are easily accessible and the use of readily accessible starting materials remains highly desirable. As a part of our ongoing research on the transformations of propargylic alcohols,[12] we herein report a facile iodine-promoted Meyer–Schuster rearrangement of propargylic alcohols for the synthesis of α-iodo unsaturated ketones.



Scheme 1 Synthesis of α-iodo unsaturated ketenes.

Initially, the methyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl) benzoate **1a** was selected as the substrate to study the Meyer–Schuster rearrangement in the presence of I_2 (1.2 equiv.). To our delight, the desired product methyl-2-(2-iodo-3,3-diphenylacryloyl) benzoate **2a** was isolated in 73% yield in THF at room temperature (Table 1, entry 1). The structure of the representative product **2a** was determined by X-ray crystallographic analysis (Fig. 1).[13] By increasing the loading of I_2 to 1.5 equivalents,

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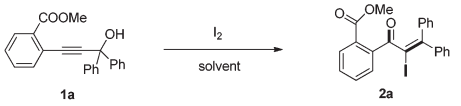
Table 1 Optimization of the iodine-promoted Meyer–Schuster rearrangement of methyl-2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl) benzoate (**1a**)[a]



Entry	Solvent	I_2 (equiv.)	Temperature (°C)	Yield[b] (%)
1	THF	1.2	RT	73
2	THF	1.5	RT	76
3	THF	2.0	RT	80
4	THF	3.0	RT	68
5	CH_3CN	1.5	RT	68
6	CH_3OH	1.5	RT	74
7	THF	2.0	80	75

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1a** with I_2 in 4 mL of solvent at room temperature. [b] Isolated yield.

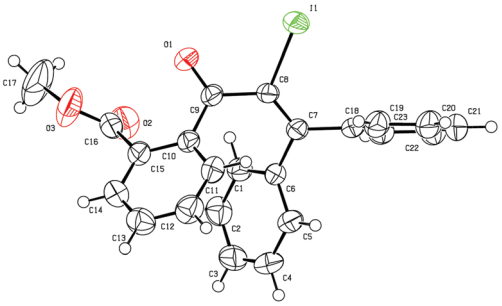
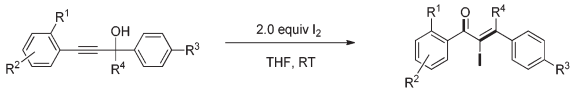
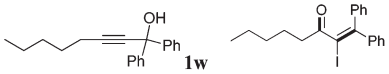


Fig. 1 Structure of **2a**.

Table 2 Synthesis of α-iodo-α,β-unsaturated ketones **2**[a]



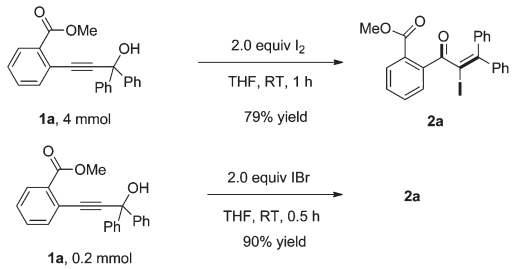
Entry	Substrate (R^1, R^2, R^3, R^4)	Product	Yield[b] (%)
1	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = Ph **1a**	**2a**	80
2	R^1 = COOEt, R^2 = H, R^3 = H, R^4 = Ph **1b**	**2b**	85
3	R^1 = COOBn, R^2 = H, R^3 = H, R^4 = Ph **1c**	**2c**	81
4	R^1 = CHO, R^2 = H, R^3 = H, R^4 = Ph **1d**	**2d**	73
5	R^1 = OMe, R^2 = H, R^3 = H, R^4 = Ph **1e**	**2e**	82
6	R^1 = CH_2COOMe, R^2 = H, R^3 = H, R^4 = Ph **1f**	**2f**	93
7	R^1 = H, R^2 = 4-Et, R^3 = H, R^4 = Ph **1g**	**2g**	86
8	R^1 = H, R^2 = 4-OMe, R^3 = H, R^4 = Ph **1h**	**2h**	76
9	R^1 = H, R^2 = H, R^3 = H, R^4 = Ph **1i**	**2i**	84[c]
10	R^1 = H, R^2 = 3-COOMe, R^3 = H, R^4 = Ph **1j**	**2j**	74[c]
11	R^1 = H, R^2 = 4-COOMe, R^3 = H, R^4 = Ph **1k**	**2k**	56[c]
12	R^1 = COOMe, R^2 = 4-NO_2, R^3 = H, R^4 = Ph **1l**	**2l**	86
13	R^1 = COOMe, R^2 = 4-Cl, R^3 = H, R^4 = Ph **1m**	**2m**	92
14	R^1 = COOMe, R^2 = 4-F, R^3 = H, R^4 = Ph **1n**	**2n**	91
15	R^1 = COOMe, R^2 = 3-Cl, R^3 = H, R^4 = Ph **1o**	**2o**	86
16	R^1 = COOMe, R^2 = 5-Cl, R^3 = H, R^4 = Ph **1p**	**2p**	88
17	R^1 = COOMe, R^2 = 5-F, R^3 = H, R^4 = Ph **1q**	**2q**	92
18	R^1 = COOMe, R^2 = 4-Me, R^3 = H, R^4 = Ph **1r**	**2r**	75
19	R^1 = COOMe, R^2 = H, R^3 = Me, R^4 = 4-MeC_6H_4 **1s**	**2s**	88
20	R^1 = COOMe, R^2 = H, R^3 = Cl, R^4 = 4-ClC_6H_4 **1t**	**2t**	85
21	R^1 = COOMe, R^2 = H, R^3 = F, R^4 = 4-FC_6H_4 **1u**	**2u**	81
22	R^1 = COOMe, R^2 = H, R^3 = OMe, R^4 = 4-$OMeC_6H_4$ **1v**	**2v**	76
23	 **1w**	**2w**	62
24	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = H **1x**	**2x**	73 (>19 : 1)[d]
25	R^1 = COOEt, R^2 = H, R^3 = H, R^4 = H **1y**	**2y**	60 (17 : 1)[d]
26	R^1 = COOMe, R^2 = H, R^3 = H, R^4 = Me **1z**	**2z**	46 (15 : 1)[d]

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with I_2 in 4 mL of THF at room temperature. [b] Isolated yield. [c] The solvent was CH_3CN. [d] The ratio was determined by ^1H NMR.

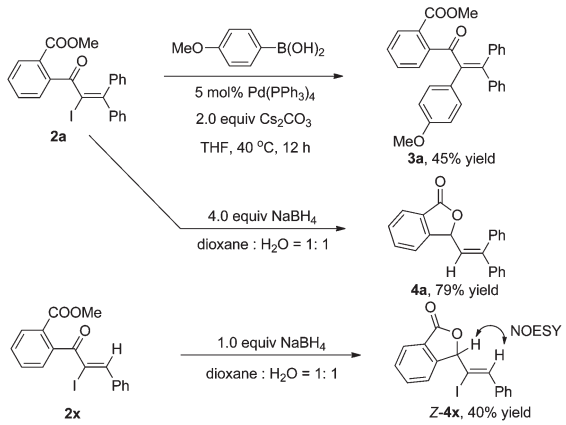
76% yield of **2a** was obtained (entry 2), and 80% yield of **2a** was achieved in the presence of 2.0 equivalents of I_2 (entry 3). However, the yield decreased when 3.0 equivalents of I_2 were used (entry 4). The screening of different solvents showed that CH_3CN and CH_3OH were less effective than THF (entries 5 and 6). Furthermore, no better results were obtained when the reaction temperature was varied (entry 7).

With the optimized reaction conditions established, the scope of the reaction was investigated (Table 2). This iodine-promoted Meyer–Schuster rearrangement of propargylic alcohols[14] showed high functional group tolerance and proved to be a concise methodology for the synthesis of α-iodo enones. A variety of substituents, such as carboalkoxyl, formyl, alkyl, alkoxyl, nitro and halo substituents, tolerated the reaction conditions and the corresponding substrates gave α-iodo enones **2a–z** in moderate to good yields. The *o*-carboethoxyl and *o*-methoxyl phenyl-substituted **2b** and **2e**, were smoothly obtained in 85% and 82% yields, respectively. These results suggested that the rearrangement was insensitive to the electronic effect of the *ortho*-substituent on aryl rings (entries 2 and 5). However, substrate **1i** with no substituent on the phenyl ring, gave the corresponding product **2i** in low yield under the optimized conditions. We also found that *m*- and *p*-carbomethoxyl phenyl-substituents α-iodo enones **2j** and **2k** were not achieved in THF. Fortunately, on changing the solvent from THF to CH_3CN, we got better results (entries 9–11). Remarkably, products **2m–q**, having *m*- or *p*-halo (Cl, F) substituents on a methyl benzoate ring were afforded in excellent yields (entries 13–17). Substrate **1l** with an electron-withdrawing nitro group showed a slightly better result than **1r** with an electron-rich methyl group (entries 12 and 18). Moreover, we examined the electronic effects of the substituents on R^4 and R^3 of the aromatic ring. It was found that electron-withdrawing or electron-donating substituents did not affect this transformation (entries 19–22). Interestingly, aliphatic substituted α-iodo enone **2w** was also obtained in 62% yield (entry 23).

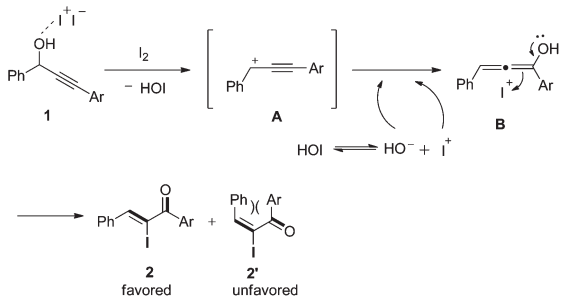
Secondary propargyl alcohols (R^4 = H) did not affect this transition. The methyl 2-(3-hydroxy-3-phenylprop-1-yn-1-yl)-



Scheme 2 Scale-up of the iodo Meyer–Schuster rearrangement and application of other electrophiles.



Scheme 3 Utilizations of functional groups of α-iodo conjugated enones **2a** and **2x**.



Scheme 4 Proposed mechanism for the formation of α-iodo unsaturated ketones.

benzoate **1x** stereo-selectively produced the rearrangement product **2x** in good yield (entry 24). However, substrate **1y**, bearing an ethoxycarbonyl on R^1, formed the inseparable mixture (*Z* and *E*) in a 17 : 1 ratio (entry 25). Compound **1z**, bearing a methyl on R^4, gave a similar result (entry 26).

Noteworthily, we also investigated the scale-up of this reaction. The 4 mmol of **1a**, upon exposure to I_2 in THF, afforded the desired product **2a** in 79% yield in 1 h. Furthermore, when using IBr as the electrophilic reagent, the desired adduct **2a** was also obtained in 90% yield (Scheme 2). The result indicated that the Meyer–Schuster rearrangement is probably induced by the iodonium ion.

As shown in Scheme 3, the α-iodo unsaturated ketone **2a** produced by the iodo Meyer–Schuster rearrangement can be further transferred in palladium-catalyzed cross-couplings or reductions. For example, the Suzuki coupling of **2a** with *p*-methoxyl phenyl boronic acid afforded the corresponding product **3a** in 45% yield.[15] Reductive lactonization and deiodination of **2a** and **2x** in the presence of $NaBH_4$ produced cyclic compounds **4a** and **4x** in 79% and 40% yields, respectively.[16] The structure of **4** was determined by the 1D NMR, 2D NMR and NOESY spectra (see the ESI†).

On the basis of the results obtained above, a tentative mechanism was proposed in Scheme 4. Presumably, in the presence of Lewis acidic iodine, the propargyl hydroxyl group of substrate **1** is activated to afford the intermediate propargyl cation **A** and hypoiodous acid (HOI).[17] Then, **A** reacts with a hydroxyl anion derived from hypoiodous acid ionization to give allenol intermediate **B**. Finally, **B** is induced by an iodide cation to isomerize and produce the major α-iodo unsaturated ketone **2**. The *E* isomer **2′** is unfavorable due to steric hindrance between the two aryl groups.

Conclusions

In conclusion, we have developed a concise and efficient approach to synthesize highly substituted α-iodo-α,β-unsaturated ketones from readily accessible propargylic alcohols under mild reaction conditions. The reaction shows high *Z*-stereoselectivity and the resulting α-iodo enones can be further exploited by cross-couplings and reductions. The application of α-iodo-α,β-unsaturated ketones for the synthesis of useful polycyclic compounds is in progress.

Experimental section

General procedure for synthesis of α-iodo unsaturated ketones

To a solution of propargyl alcohol derivatives **1** (0.20 mmol) in THF (4.0 mL) was added I_2 (2.0 equiv., 0.4 mmol) at room temperature. When the reaction was complete, the reaction mixture was quenched by the addition of saturated aqueous sodium thiosulfate, extracted with ethyl acetate (3 × 15 mL), washed with water and saturated brine, dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford the corresponding α-iodo unsaturated ketenes **2**.

Methyl-2-(2-iodo-3,3-diphenylacryloyl)benzoate 2a

^{1}H NMR (400M Hz, $CDCl_3$) δ ppm 7.33 (d, J = 7.6 Hz, 2H), 7.32–7.26 (m, 3H), 7.19–7.12 (m, 4H), 6.95–6.91 (m, 5H), 3.90 (s, 3H). ^{13}C NMR (100M Hz,$CDCl_3$) δ ppm 193.3, 168.5, 158.6, 144.8, 139.7, 136.7, 132.1, 131.0, 130.4, 130.1, 129.7, 128.8, 128.7, 128.6, 128.2, 127.9, 101.3, 53.0. IR (neat, cm^{-1}): 2921,

1734, 1654, 1234, 1097, 763. HRMS (ESI) Calcd for $C_{23}H_{17}INaO_3$: M + Na = 491.0115. Found: 491.0121.

Acknowledgements

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13 CCDC 1044075 (**2a**) contains the supplementary crystallographic data for this paper.

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