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One-Pot Synthesis of α-Iodo-Substituted α,β-Unsaturated Aldehydes from Propargylic Alcohols

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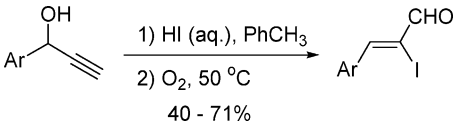

An efficient one-pot method for the preparation of α-iodo-substituted α,β-unsaturated aldehydes (α-iodoenals) from propargylic alcohol is developed. The reaction proceeds via an iodoallene intermediate, which is generated in situ by the reaction of propargylic alcohol with aqueous HI. The iodoallene intermediate is further transformed to an α-iodoenal derivative in good overall yield by oxidation with molecular O_2.

α-Iodoenals and their derivatives have been used widely in organic synthesis as a class of important building blocks.[1] There have been some investigations on the development of synthetic methodologies of these α-iodo-substituted α,β-unsaturated carbonyl compounds.[2] The majority of the synthetic routes to this family of compounds involve key steps based on the halogen exchange of vinyl bromides with iodide ion[2b] or α-iodination of α,β-unsaturated carbonyl compounds.[2g] Considering the limited methods available for their preparation, further development of synthetically useful methodologies for α-iodoenals is highly desirable.

On the other hand, allenes have recently attracted great attention from organic chemists due to their diverse reactivities.[3] Various synthetic methodologies have been developed based on allene chemistry. For example, Ma and co-workers have reported the stereoselective iodohydroxylation of 1,2-allenyl sulfides that generates 2,3-iodohydroxylation products.[4] However, as far as our knowledge is concerned, there have been only a few reports on the reactions of haloallenes.[5] In the course of their investigation of allene iodination, Coulomb and co-workers have reported that 1-(3-iodopropa-1,2-dienyl)benzene is converted into 2-iodo-3-phenylacrylaldehyde by treatment with I_2-MgI_2 and H_2O.[2e] During our recent study, we have found that iodoallenes can be efficiently converted into α-iodoenals under an atmosphere of O_2 at room temperature (Scheme 1).[6]

Since iodoallenes can be easily prepared from propargylic alcohols, we have conceived that this reaction may be useful in the synthesis of α-iodo-substituted α,β-unsaturated aldehydes. Herein we report a one-pot reaction to prepare α-iodoenals from the propargylic alcohols through in situ generation of iodoallenes by the reaction of propargylic alcohols with aqueous HI, followed by the oxidation of the iodoallenes with molecular oxygen (Scheme 2).

Propargylic alcohols could be easily prepared by reaction of aldehydes with a Grignard reagent or lithium acetylide.[7] Having prepared a series of propargylic alcohols, **1a**−**k**, we employed **1a** (Ar = Ph) as the substrate to test the one-pot reaction. Treatment of compound **1a** with aqueous HI in toluene resulted

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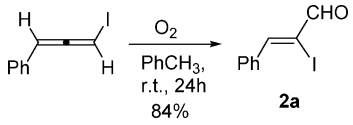
SCHEME 1. Oxidation of Iodoallene



SCHEME 2. One-Pot Synthesis of α-Iodoenals from Propargylic Alcohols

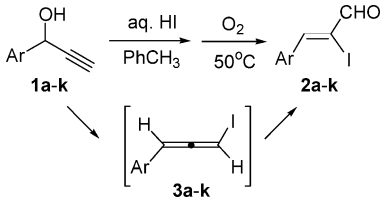


TABLE 1. Effect of Solvent on the One-Pot Synthesis of 2a

entry	solvent	reaction time (h)	yield[a] (%)
1	$PhCH_3$	4	68
2	THF	6	<20
3	CH_3OH	7	25
4	pentane	7	28
5	$ClCH_2CH_2Cl$	4	30
6	neat	4	*b*

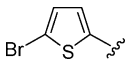
[a] Yields after column chromatographic purification with silica gel. [b] **2a** was not formed. Instead, a small amount of **3a** could be identified in the course of the reaction.

in the formation of iodoallene intermediate **3a**.[8,9] Without separation of **3a**, oxygen was then introduced carefully into the organic phase of the reaction mixture at 50 °C for 4 h. α-Iodoenal **2a** was obtained in 68% isolated yield. The configuration of the C═C bond in **2a** was determined by the NOE study.[10] A trace amount of *trans*-cinnamaldehyde, which was derived from Meyer−Schuster rearrangement,[11] could be detected from the crude products by a ^{1}H NMR study.

To optimize the reaction conditions, we next carefully examined the effect of the solvents on this one-pot reaction. The results are summarized in Table 1. Toluene was found to be the most suitable solvent for this transformation (Table 1, entry 1), whereas a low yield of **2a** was obtained when using a polar solvent such as THF and methanol (entries 2 and 3). Other solvents, such as pentane and $ClCH_2CH_2Cl$, could not improve the yield of the reaction (entries 4 and 5). Interestingly, no α-iodoenal **2a** product was observed when the reaction was carried out without solvent, although iodoallene **3a** intermediate was also formed under this condition (entry 6).

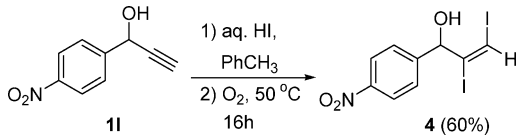
The scope of the reaction under optimized conditions is summarized in Table 2. Various substitutions on the aromatic ring could be tolerated, and the reaction gave moderate to good overall yields of the products **3a**−**k**. It was found that substrates with a phenyl ring bearing an electron-donating group generally gave slightly higher yields (Table 2, entries 2−4), while substrates with an electron-withdrawing substituent on the phenyl ring, such as halogen, gave moderately high yields (entries 5−9). Moreover, it was noted that this approach was also applicable to the substrates bearing heteroaromatic ring substituents (entries 10 and 11). The stereoselectivities were examined by ^{1}H NMR of the crude product. It was found that all the reactions only gave products with *Z* configuration, except the reaction with **1k**, in which a mixture of *Z* and *E* isomers was obtained (entry 11).

TABLE 2. One-Pot Synthesis of α-Iodo-Substituted α,β-Unsaturated Aldehydes 2a−k from Propargylic Alcohols 1a−k

entry	**1a-k,** Ar	reaction time (h)	**2a-k,** yield[a] (%)
1	**1a,** C_6H_5	4	**2a,** 68
2	**1b,** *p*-$CH_3C_6H_4$	4	**2b,** 66
3	**1c,** *o*-$CH_3C_6H_4$	4	**2c,** 70
4	**1d,** *p*-$CH_3OC_6H_4$	2	**2d,** 61
5	**1e,** *p*-FC_6H_4	4	**2e,** 71
6	**1f,** *p*-$C1C_6H_4$	2	**2f,** 53
7	**1g,** *o*-BrC_6H_4	4	**2g,** 58
8	**1h,** *p*-PhC_6H_4	14	**2h,** 54
9	**1i,** *trans*-PhCH=CH-	3	**2i,** 50
10	**1j,** 	1	**2j,** 40
11	**1k,** 	1.5	**2k,** 48[b]

[a] Yields after column chromatographic purification with silica gel. [b] This compound was isolated as a mixture of *E* and *Z* isomers.

SCHEME 3. Reaction of 1l



When a substrate with a strong electron-withdrawing substituent, such as **1l**, was employed in this reaction, no expected α-iodoenal **2l** could be obtained. Instead, the diiodo product **4** was isolated in 60% yield under identical reaction conditions (Scheme 3). This may be attributed to the destabilization effect of the *p*-nitrophenyl group for the generation of propargylic cation, which is assumed an intermediate in the formation of iodoallene. The addition of I_2, which can be generated from iodide through oxidation by O_2, to the triple bond affords the diiodo product **4**.

Besides, it has been noted that this method is also applicable to the alkyl-substituted tertiary propargylic alcohols, albeit with slightly low yields (Scheme 4). For propargylic alcohol **7**, the reaction gave an *E* and *Z* mixture of α-iodoenals with low selectivity. For secondary alcohol, it was observed that the reaction under identical conditions gave a diiodide product.

Because bromoallene could also be generated when propargylic alcohol was treated with aqueous HBr,[8] naturally it was conceivable that this method might be extended to the preparation of α-bromo-substituted α,β-unsaturated aldehydes. When propargylic alcohol **1a** was subjected to aq HBr, followed by treatment with molecular oxygen at 50 °C, the expected α-bromo-substituted α,β-unsaturated aldehyde **9** was indeed

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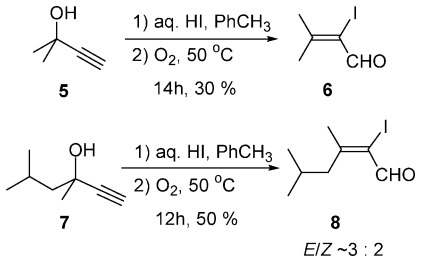
(9) The reaction of **1a** with (TMS)Cl−NaI in CH_3CN between 0 °C and room temperature resulted in a complex mixture; no allene products could be identified.

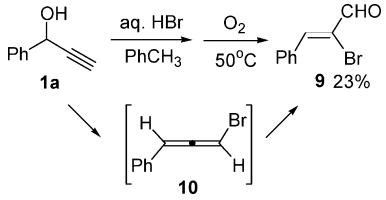
(10) For the details of the NOE experiment, see the Supporting Information.

(11) For a review on Meyer−Schuster rearrangement, see: Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429−438.

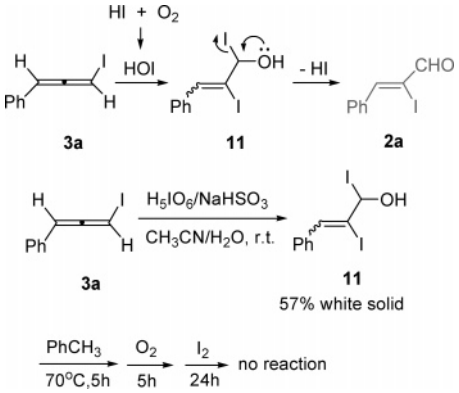
SCHEME 4. Reaction of Alkyl-Substituted Propargylic Alcohol



SCHEME 5. Synthesis of α-Bromoenal



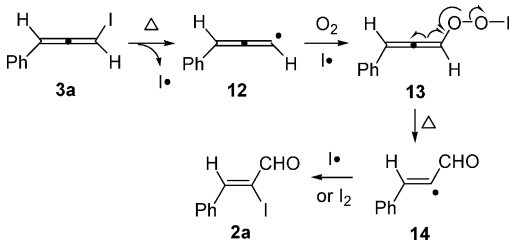
SCHEME 6. Mechanistic Studies



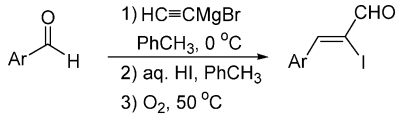
isolated (Scheme 5). However, the yield of **9** was only 23%. The diminished yield could be attributed to the low reactivity of bromoallene intermediate **10**.

A possible reaction mechanism to account for the formation of α-iodoenal is shown in Scheme 6. In the presence of O_2, HI may be oxidized to give hypoiodous acid, HOI.[12] HOI adds to the iodoallene intermediate **3a**, which was generated in situ by the reaction of propargylic alcohol with aqueous HI, to give the diiodide intermediate **11**. Subsequent elimination of HI affords α-iodoenal **2a**. To substantiate this mechanism, we prepared the hypothesized diiodide intermediate **11** according to a literature procedure by the reaction of **3a** with H_5IO_6/$NaHSO_3$ in CH_3CN-H_2O.[12b] Diiodide **11** was found to be a stable compound. When it was heated in toluene at 70 °C for a long time in the presence of O_2 or I_2, no reaction occurred and the starting materials were recovered. To examine whether HOI was generated in our reaction, styrene was subjected to the reaction conditions (aq HI, O_2, 50 °C in $PhCH_3$) since HOI is known to add to an alkene readily.[12b−e] However, no iodohydrin

SCHEME 7. Proposed Mechanism



SCHEME 8. One-Pot Reaction from Aldehydes



15, Ar = C_6H_5 — **2a**, 45%
16, Ar = *p*-$CH_3C_6H_4$ — **2b**, 69%
17, Ar = *p*-FC_6H_4 — **2e**, 60%

product could be identified in this reaction. These experiments obviously do not support the proposed reaction mechanism.

An alternative mechanism involving radical intermediates is then proposed (Scheme 7). Thus, allenyl radical **12** is generated upon heating **3a** in toluene. In the presence of molecular oxygen, iodoperoxide **13** is generated, which is then converted to carbon radical **14** through homolytic cleavage of the O−O bond. Carbon radical **14** is finally trapped by an iodine atom or molecular iodine to afford α-iodoenal **2a**. To prove this radical reaction mechanism, we introduced TEMPO to the system to trap the radical intermediate. The reaction became very sluggish in the presence of TEMPO and resulted in a complex mixture. Addition of Bu_3SnH to the reaction also gave a complex mixture with the formation of a trace amount of cinnamaldehyde. Although these observations seem to favor a radical mechanism, further experiments will be needed to firmly establish the reaction mechanism.[13]

Finally, a one-pot transformation of three-step reactions from aldehydes to α-iodoenals directly was explored. Thus, aldehydes **15**−**17** were treated with ethynylmagnesium bromide in anhydrous toluene at 0 °C. After completion of the addition, the mixture was quenched with aqueous HI, followed by careful introduction of O_2 into the organic phase at 50 °C for several hours. After workup, the α-iodoenals **2a**, **2b**, and **2e** were isolated in 45%, 59%, and 60% overall yields, respectively (Scheme 8). It was again noted that a small amount of Meyer−Schuster rearrangement products was detected in all cases.

In conclusion, we have described an efficient one-pot procedure for the preparation of α-iodo-substituted α, *β*-unsaturated aldehydes from easily available propargylic alcohols by reaction with aqueous HI and molecular O_2. This one-pot transformation provides a convenient, inexpensive, and efficient method for the preparation of various α-iodoenals.

Experimental Section

General Procedure for the One-Pot Synthesis of α-Iodoenals. To a solution of propargyl alcohol (100 mg) in toluene was added aqueous HI (2 mL) at room temperature. After 5 min, O_2 gas was

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(13) One of the reviewers has suggested other pathways that do not involve the departure of the iodide. These pathways provide a rationale for the observed *Z* selectivity of the products. See the Supporting Information. We thank the reviewer for the suggestions on the reaction mechanism.

introduced carefully into the organic phase, and the mixture was stirred for several hours at 50 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solution was extracted with toluene three times, and the combined organic phase was washed with concentrated $Na_2S_2O_3$ and $NaHCO_3$ and then dried over Na_2SO_4. After removal of the solvent under vacuum, the crude product was purified by column chromatography.

Typical Procedure for the Three-Step One-Pot Synthesis of 2a, 2b, and 2e from Aldehydes. Under a nitrogen atmosphere, ethynylmagnesium bromide (1 mmol) was added via syringe to a solution of aldehyde (0.5 mmol) in dry toluene (6 mL) at 0 °C. After the resulting solution was stirred for 10 min, aqueous HI (5 mL) was introduced at the same temperature. Then O_2 was introduced carefully to the organic phase, and the mixture was stirred for several hours at 50 °C. The progress of the reaction was monitored by TLC. The resulting solution was extracted with toluene three times, and the combined organic phase was washed with concentrated $Na_2S_2O_3$ and $NaHCO_3$ and then dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the crude product was purified by column chromatography.

Data for (*Z*)-2-iodo-3-phenylacrylaldehyde (2a):[2b] yield 68%; IR (neat) 1686, 1591 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.54 (m, 3H), 8.00−8.04 (m, 2H), 8.11 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.8, 128.6, 130.4, 131.6, 134.0, 155.8, 189.0; EI-MS (*m/z*, relative intensity) 258 (M^+, 100), 131 (31).

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Supporting Information Available: Characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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