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Regio- and stereospecific synthesis of (*E*)-α-iodoenamide moieties from ynamides through iodotrimethylsilane-mediated hydroiodation

Akihiro H. Sato, Kazuhiro Ohashi, Tetsuo Iwasawa *

Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University Otsu, Shiga 520-2194, Japan

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ABSTRACT

A facile approach to (*E*)-α-haloenamide moieties from ynamides using bromo- or iodotrimethylsilane is described. The simple protocol enables a regio- and stereospecific hydrohalogenation of the triple bond in gram-scale and provides a general entry for synthesis of novel enamide analogues.

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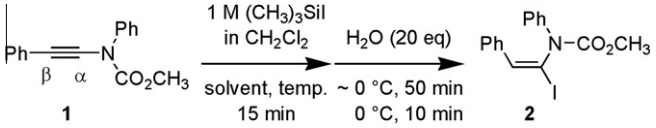
Enamides are basic building blocks in organic synthesis.[1–3] Structural enamide components are frequently found in natural products,[4,5] and they recently have emerged as a novel type of useful nucleophiles in stereoselective C–C and C–N bond-forming reactions.[6] From the synthetic point of view, haloenamides are versatile variants of enamides. Iodoenamides are especially useful, as they are readily converted into various functional groups by halogen–metal exchange and are significant for carbon–carbon bond forming reactions by way of transition-metal catalyzed cross-coupling reactions.[7–9] Thus, the weakly bonded iodide and electron-rich olefin are highly reactive and potentially useful toward the synthesized nitrogen-containing complex molecules.[10,11] Despite the utility of iodoenamides, their synthetic availability still remains a challenge, because of the inherent difficulty in regio- and stereoselective hydrohalogenation.[12] The stoichiometric addition of hydrogen iodide (HI) to ynamide is one way to prepare iodoenamides; however the hygroscopic and gaseous HI is inconvenient, and this method often results in poor regio- and stereochemical control, and separation of the resultant isomeric mixtures is laborious.[13]

The pioneering work for efficient synthesis of iodoenamide from ynamide via addition of HI was reported by Hsung and coworkers in 2003:[14] the in situ generation of HI from MgI_2 and H_2O afforded α-iodoenamides with good selectivities of *E*/*Z* ratios. The outcome of stereoselective addition is dictated by the polarization of the triple bond caused by nitrogen.[15] According to the nature of the keteniminium resonance form, the iodine automatically unites with the α-carbon.[16] There is still room for improvement in reaction efficiency, especially in terms of its scale and purity;[17] the prototype system worked using only 0.1 mmol of starting alkynes and giving the products with *E*/*Z* mixtures.

Herein we report a completely regio- and stereospecific synthesis[18] of (*E*)-α-iodoenamides from ynamides using in situ generated HI (Scheme 1). The in situ HI was generated from iodotrimethylsilane (TMSI) and H_2O,[19,20] and quickly added to ynamide in nearly quantitative yields, exclusively giving single isomer. The method is compatible with a variety of reaction conditions and is applicable to hydrobromination utilizing TMSBr. Thus, the protocol provides simple access to (*E*)-α-haloenamide moieties.

To initiate our search, we focused on TMSI-mediated hydroiodation of **1**[21] (Scheme 1), based on our previous report.[19] The mixture of **1** and TMSI[22] was stirred at −78 °C for 15 min, and water was added, and the reaction was allowed to warm to 0 °C. After usual workup and purification, the product was isolated without decomposition and identified as (*E*)-α-iodoenamide **2** according to an authentic sample.[23–25]

As summarized in Table 1, the reactivity of **1** conducted via Scheme 1 was evaluated.[26] More than 1.5 equiv of TMSI was



Scheme 1. Synthesis of **2** from **1** via iodotrimethylsilane-mediated hydroiodation.

* Corresponding author. Tel.: +81 77 543 7461; fax: +81 77 543 7483.
E-mail address: iwasawa@rins.ryukoku.ac.jp (T. Iwasawa).

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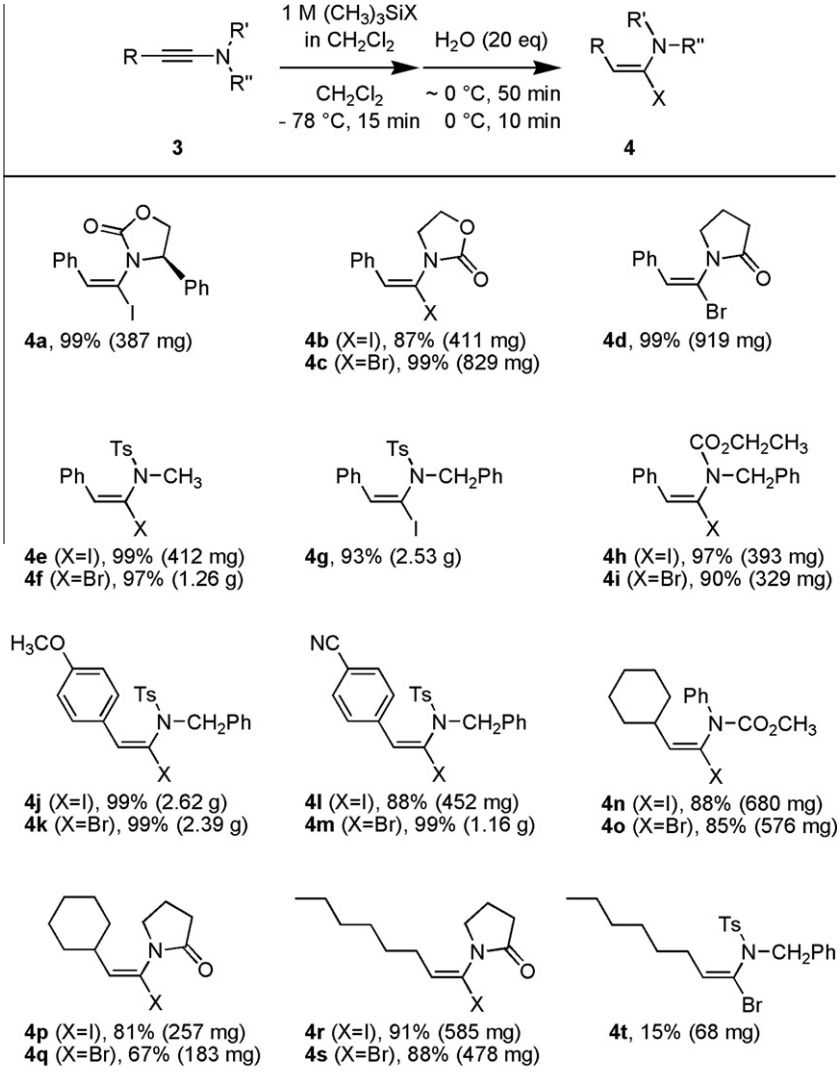
Table 1
Evaluation of the reactivity of 1 conducted via Scheme 1[a]

Entry	TMSI (equiv)	Temp (°C)	Solvent	Yield[b] (%)
1[c]	1.2	−78	CH_2Cl_2	77
2	1.5	−78	CH_2Cl_2	98
3	2.0	−78	CH_2Cl_2	99
4	2.0	−20	CH_2Cl_2	98
5	2.0	0	CH_2Cl_2	85
6	2.0	25	CH_2Cl_2	71
7[d]	2.0	−78	CH_2Cl_2	80
8	2.0	−78	Toluene	98
9	2.0	−78	Hexane	99
10	2.0	−78	CH_3CN	99
11	2.0	−78	THF	65
12	2.0	−78	Cyclopentyl methyl ether	63
13	2.0	−78	CH_2Cl_2/H_2O (4% v/v)	94
14[e]	2.0	−78	CH_2Cl_2	95
15[f]	2.0	−78	CH_2Cl_2	99
16[g]	2.0	−78	CH_2Cl_2	28[h]

[a] Reaction conditions: **1** (1 mmol), solvent (8 mL), 1 M $(CH_3)_3SiI$ in CH_2Cl_2, H_2O (20 mmol).
[b] Isolated yields after column chromatography.
[c] 23% of **1** was recovered.
[d] 1 mL of CH_2Cl_2 was used.
[e] CH_3OH was added instead of H_2O.
[f] $(CH_3)_3SiBr$ was used instead of $(CH_3)_3SiI$.
[g] $(CH_3)_3SiCl$ was used instead of $(CH_3)_3SiI$.
[h] Determined by ^1H NMR.

needed for completion (entries 1–3), and low temperature was favorable (entries 3–6). The concentration was increased in entry 7 (1.0 mL CH_2Cl_2), however, the yield decreased to 80%. Other solvents of toluene, hexane, acetonitrile were successful to give high yields (entries 8–10). THF and cyclopentyl methyl ether gave only acceptable yield of **2** (entries 11–12). For entry 13, addition of H_2O to the solvent in advance gave 94% yield. For entries 15 and 16, $(CH_3)_3SiBr$ and $(CH_3)_3SiCl$ were used instead of TMSI; the corresponding (*E*)-α-haloenamide was yielded in 99% and 28%, respectively. The respective bond energies of Si–Cl, Si–Br, and Si–I are 113, 96, and 77 kcal/mol:[27] the obstinate bond of Si–Cl would be difficult to activate. It is worth noting that any (*Z*)- or β-isomer of **2** was not observed on NMR spectra and TLC analyses from entry 1 through entry 16.

Next, the substrate generality with respect to the ynamides was investigated, and the results are summarized in Scheme 2. [28] Evans auxiliary **4a**[14] was successfully obtained in 99% yield without any isomers. Application of Hsung's method gave mixtures of *E*:*Z* = 88:12.[29] Iodide **4b** immediately decomposed after the isolation: on the other hand, bromide **4c** and **4d** were stable even in neat form, presumably due to the stronger bond energy. Similar stabilities of the vinyl halides were observed in **4e**, **4f**, **4p**, and **4q**, although **4j** and **4k** were both fragile oil. The carbamate, sulfonamide, and amide groups are accepted for the hydroiodation



Scheme 2. The substrate scope of ynamides under the reaction conditions of **3** (1 equiv), solvent (8 mL/mmol of 3), and 1 M $(CH_3)_3SiX$ in CH_2Cl_2 (2 equiv).

(**4a–4i**), and the transformation also worked well in the presence of functional groups such as OMe and CN (**4j–4m**). The reactions at gram-scale successfully performed in **4f**, **4g**, **4j**, **4k**, and **4m**. The synthesis of **4n–4s** derived from aliphatic alkynes proceeded very well, although **4t** decomposed in the process of column chromatography: at the present time it is difficult to predict which products of (*E*)-α-haloenamides are inclined to decompose. Notably, all the enamides were observed as single isomers even in crude states, and any *E*/*Z* isomeric mixtures were not obtained.

The mechanism for the resulting in perfect stereochemical control to produce only (*E*)-adducts is not yet fully known. Deuterioiodation of **1** was carried out with D_2O, and the deuterium was thoroughly incorporated for H of **2** as we expected. The result indicates that this reaction does not follow a stepwise path. Possible chelation[30] of the silicon atom with the nitrogen atom and/or the oxygen atom of the electron-withdrawing group would provide concerted *syn*-addition of HI toward the triple bond.[14,15,31]

In conclusion, commercially available TMSI and TMSBr were found to convert ynamides into (*E*)-α-haloenamides in high yields along with the perfect regio- and stereochemical outcomes. The method completes the reaction quickly under routine conditions, and was readily amenable to scale-up. This approach showed excellent substrate compatibility, and afforded a wide variety of new (*E*)-α-haloenamides. The synthetic utility of the products is clear and we hope this reliable methodology finds widespread use in organic synthesis. Application and mechanistic elucidation are ongoing for further development of this reaction and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.101.

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22. Preparation of 1 M TMSI in CH_2Cl_2, see Supplementary data.
23. We prepared the authentic compound of (*E*)-α-fashioned **2** according to the Ref. 14, and confirmed that its ^1H NMR and ^{13}C NMR were identical to compound **2** derived from our method. Elemental analysis also showed good match as described in Ref. 26.
24. Compound **2** derived from our method was converted to the corresponding olefin using *tert*-BuLi for lithium–halogen exchange, and the (*Z*)-olefin was obtained in 39% yield with typical coupling constants $J = 9.1$ Hz for *cis*-form. In brief, the compound **2** was formed in (*E*)-fashion.
25. Similar identification of the stereochemistry in the case of **4a** was also ensured; we prepared the authentic sample of (*E*)-α-fashioned **4a** according to Hsung's method in Ref. 14, and its spectroscopic data was the identical to that of **4a** derived from our procedure.
26. *Representative procedure for (E)-α-haloenamide moieties,* for **2** (Table 1, entry 3): To a solution of **1** (1 mmol) in anhydrous CH_2Cl_2 (8 mL) at −78 °C was added TMSI (1 M in CH_2Cl_2) dropwise over 5 min. After 15 min stirring, H_2O (20 mmol) was added, and the mixture was allowed to warm to 0 °C over 50 min, and followed by additional stirring for 10 min. The reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate, stirred for 30 min, and allowed to warm to ambient temperature. To the mixture was added CH_2Cl_2, and organic phases were washed with brine, and then dried over Na_2SO_4, and concentrated to give a crude product. Purification by silica gel column chromatography afforded 375 mg of **2** in 99% yield as yellow viscous materials. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 10H), 7.17 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 142.2, 139.1, 135.2, 129.1, 129.02, 129.00, 127.7, 126.9, 124.5, 95.0, 54.0. MS (EI) *m*/*z*: 252 ($[M-I]^+$), 193 ($[M-I-CO_2CH_3]^+$). IR (neat): 3063, 2953, 1713 (C=O), 1622 (C=C), 1592 cm^{-1}. Anal. Calcd for $C_{16}H_{14}INO_2$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.66; H, 3.70; N, 3.76.
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29. We actually attempted the hydroiodation of **4a** under the Hsung's condition according to Ref. 14.
30. A competitive reaction using a mixture of **3a** (1 mmol) and **3g** (1 mmol) was performed under the condition of CH_2Cl_2 (8 mL), 1 M TMSI (1.5 equiv). Unexpectedly, the hydroiodation occurred in **3g** predominantly: 0.97 mmol of **4g** and 0.03 mmol of **4a** were yielded, and 0.03 mmol of **3g** and 0.97 mmol of **3a** were unreacted. This indicates that the different ability in chelation of silicon with oxygen between **3a** and **3g** might regulate the activity of reagent system.
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