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

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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 electronrich 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 regioand 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 MgI₂ and H₂O 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 nat-

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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ure 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 synthesis¹⁸ of (*E*)- α -iodoenamides from ynamides using in situ generated HI (Scheme 1). The in situ HI was generated from iodotrimethylsilane (TMSI) and H₂O,^{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 $\mathbf{1}^{21}$ (Scheme 1), based on our previous report.¹⁹ The mixture of **1** and TMSI²² was stirred at $-78 \,^{\circ}$ 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

$$\begin{array}{c} \begin{array}{c} Ph \\ Ph \\ \hline \beta \\ \alpha \end{array} \begin{array}{c} Ph \\ CO_2CH_3 \end{array} \\ \begin{array}{c} 1 \\ 1 \end{array} \begin{array}{c} 1 \\ \hline n \\ CO_2CH_3 \end{array} \begin{array}{c} 1 \\ \hline n \\ solvent, temp. \end{array} \begin{array}{c} 1 \\ \hline n \\ column \\ red \\ \hline red \\ red \\ red \\ \hline red \\ re$$

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



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| Table I | | |
|------------|--|--|
| Evaluation | of the reactivity of 1 conducted via Scheme 1 ^a | |

| Evaluation of the reactivity of r conducted via benchie r | | | | | | | | |
|---|-----------------|--------------|-----------|--|------------------------|--|--|--|
| | Entry | TMSI (equiv) | Temp (°C) | Solvent | Yield ^b (%) | | | |
| | 1 ^c | 1.2 | -78 | CH ₂ Cl ₂ | 77 | | | |
| | 2 | 1.5 | -78 | CH ₂ Cl ₂ | 98 | | | |
| | 3 | 2.0 | -78 | CH ₂ Cl ₂ | 99 | | | |
| | 4 | 2.0 | -20 | CH ₂ Cl ₂ | 98 | | | |
| | 5 | 2.0 | 0 | CH ₂ Cl ₂ | 85 | | | |
| | 6 | 2.0 | 25 | CH ₂ Cl ₂ | 71 | | | |
| | 7 ^d | 2.0 | -78 | CH ₂ Cl ₂ | 80 | | | |
| | 8 | 2.0 | -78 | Toluene | 98 | | | |
| | 9 | 2.0 | -78 | Hexane | 99 | | | |
| | 10 | 2.0 | -78 | CH ₃ CN | 99 | | | |
| | 11 | 2.0 | -78 | THF | 65 | | | |
| | 12 | 2.0 | -78 | Cyclopentyl methyl ether | 63 | | | |
| | 13 | 2.0 | -78 | CH ₂ Cl ₂ /H ₂ O (4% v/v) | 94 | | | |
| | 14 ^e | 2.0 | -78 | CH ₂ Cl 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)₃Sil in CH_2Cl_2 , H_2O (20 mmol).

- ^b Isolated yields after column chromatography.
- ^c 23% of **1** was recovered.
- ^d 1 mL of CH₂Cl₂ was used.
- ^e CH₃OH was added instead of H_2O .
- f (CH₃)₃SiBr was used instead of (CH₃)₃SiI.
- ^g (CH₃)₃SiCl was used instead of (CH₃)₃SiI.
- ^h Determined by ¹H NMR.
- 5

needed for completion (entries 1–3), and low temperature was favorable (entries 3–6). The concentration was increased in entry 7 (1.0 mL CH₂Cl₂), 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 H₂O to the solvent in advance gave 94% yield. For entries 15 and 16, $(CH_3)_3$ SiBr and $(CH_3)_3$ SiCl 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 (CH₃)₃SiX in CH₂Cl₂ (2 equiv).

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(**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 D₂O, 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 chelation³⁰ 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.

References and notes

- (a) Larock, R. C. Comprehensive Organic Transformations: A Guide to Functional Group Preparations; Wiley-VCH: New York, 1999; (b) Rappoport, Z. The Chemistry of Enamines. In The Chemistry of Functional Groups; New York: John Wiley and Sons, 1994.
- (a) Shen, R.; Porco, J. A., Jr. Org. Lett. 2000, 2, 1333; (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. Org. Lett. 2003, 5, 3667.
- For reviews on enamides, see: (a) Dehli, J. R.; Legros, J.; Bolm, C. Chem. Commun. 2005, 973; (b) Whitesell, J. K.; Whitesell, M. A. Synthesis 1983, 517; (c) Hickmott, P. W. Tetrahedron 1975, 1982, 38; (d) Hickmott, P. W. Tetrahedron 1982, 38, 3363; (e) Lenz, G. R. Synthesis 1978, 489.
- (a) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. J. Antibiot. **1998**, 51, 14; (b) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. J. Antibiot. **1998**, 51, 1075; (c) Yet, L. Chem. Rev. **2003**, 103, 4283.
- For examples on synthesis of enamides, see: (a) Anthoni, U.; Bock, K.; Chevolot, L.; Larson, C.; Nielsen, P. H.; Christophersen, C. J. Org. Chem. **1987**, *52*, 5638; (b) Lin, X.; Weinreb, S. M. Tetrahedron. Lett. **2001**, *42*, 2631; (c) Pinder, J. L.; Weinreb, S. M. Tetrahedron. Lett. **2003**, *44*, 4141; (d) Nakamura, R.; Tanino, K.; Miyashita, M. Org. Lett. **2003**, *5*, 3583; (e) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. Org. Lett. **2004**, *6*, 27; (f) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. Angew. Chem., Int. Ed. **2005**, *44*, 3714; (g) Nishikawa, T.; Kajii, S.; Isobe, M. Synlett **2004**, 2025; (h) Sum, C.; Camp, J. E.; Weinreb, S. M. Org. Lett. **2006**, *8*, 1779; (i) Palimkar, S. S.; Uenishi, J. Org. Lett. **2010**, *12*, 4160.
- 6. Matsubara, R.; Kobayashi, S. Acc. Chem. Res. 2008, 41, 292. and references therein.
- (a) Brandsma, L.; Verkruijsse, H. Preparative Polar Organometallic Chemistry 1; Springer: Berlin, 1987; (b) Wakefield, B. J. Organolithium Methods; Academic

Press: London; (c) Brandsma, L. Preparative Polar Organometallic Chemistry 2; Springer: Berlin, 1990; (d) Schlosser, M. In Organometallics in Synthesis A Manual; Schlosser, M., Ed., 2nd ed.; Wiley: Chichester, UK, 2002; pp 1–352.

- (a) Neumann, H.; Seebach, D. Chem. Ber. 1978, 111, 2785; (b) Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. J. Org. Chem. 1976, 41, 3947.
- . Galli, C.; Rappoport, Z. Acc. Chem. Res. 2003, 36, 580.
- (a) Funk, R. L.; Hentley, R. J. *Tetrahedron Lett.* **2011**, *52*, 6671; (b) Heffernan, S.; Carbery, D. R. *Tetrahedron Lett.* **2012**, *53*, 5180.
- (a) Yu, Z. Jin, Z. J. Am. Chem. Soc 2000, 122, 9840; (b) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. J. Am. Chem. Soc. 2009, 131, 16678.
- (a) Reddy, Ch. K.; Periasamy, M. Tetrahedron Lett. **1919**, 1990, 31; (b) Stewart, L. J.; Gray, D.; Pagni, R. N.; Kabalka, G. W. Tetrahedron Lett. **1987**, 28, 4497; (c) Stone, H.; Schecher, H. Org. Syn. Coll. **1963**, 4, 543.
- (a) Kropp, P. J.; Craword, S. D. J. Org. Chem. 1994, 59, 3102; (b) Hudrlik, P. F.;
 Kulkarni, A. K.; Jain, S.; Hudrlik, A. M. Tetrahedron 1983, 39, 877; (c) Griesbaum,
 K.; El-Abed, M. Chem. Ber. 2001, 1973, 106.
- Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. Org. Lett. 2003, 5, 1547.
- (a) Compain, G.; Jouvin, K.; Martin-Mingot, A.; Evano, G.; Marrot, J.; Thibaudeau, S. Chem. Commun. **2012**, 48, 5196; (b) Evano, G.; Coste, A.; Jouvin, K. Angew. Chem., Int. Ed. **2010**, 49, 2840; (c) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Chem. Rev. **2010**, *110*, 5064; (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, P. R. Synlett **2003**, 1379.
- 16. Sanapo, G. F.; Daoust, B. Tetrahedron Lett. **2008**, 49, 4196. 17. Novori R Angew Chem Int Ed **2002** 41, 2008
- Noyori, R. Angew. Chem., Int. Ed. 2002, 41, 2008.
 The regioelectivity of the products in this paper is different from the previous report (Ref. 19) in which addition of HI to ethynylarenes using TMSI-H₂O custom professional study and study the product. In the above monitored is a study of the product.
- system preferentially gave *anti*-style products. In the above-mentioned meaning, we used the word 'specific' as a sense of 'ynamide-specific'.
- 19. Sato, A. H.; Mihara, S.; Iwasawa, T. Tetrahedron Lett. 2012, 53, 3585.
- 20. Kamiya, N.; Chikami, Y.; Ishii, Y. Synlett **1990**, 675.
- (a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. Org. Lett. 2004, 6, 1151; (b) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. J. Org. Chem. 2006, 71, 4170.
- 22. Preparation of 1 M TMSI in CH₂Cl₂, 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 ¹³C 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 CH₂Cl₂ (8 mL) at -78 °C was added TMSI (1 M in CH₂Cl₂) dropwise over 5 min. After 15 min stirring, H₂O (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 CH₂Cl₂, and organic phases were washed with brine, and then dried over Na₂SO₄, 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, CDCl₃) δ 7.38–7.28 (m, 10H), 7.17 (s, 1H), 3.74 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) 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 (El) *m/z*: 252 ([M–I]⁺), 193 ([M–I–CO₂CH₃]⁺). IR (neat): 3063, 2953, 1713 (C=O), 1622 (C=C), 1592 cm⁻¹. Anal. Calcd for C₁₆H₁₄INO₂: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.66; H, 3.70; N, 3.76.
- (a) Walsh, R. Acc. Chem. Res. 1981, 14, 246; (b) Doncaster, A. M.; Walsh, R. J. Phys. Chem. 1979, 83, 3037.
- Full spectroscopic data for all new compounds in Scheme 2 of ¹H NMR, ¹³C NMR, MS, IR, and Elemental analyses were listed in Supplementary data.
- 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 CH₂Cl₂ (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.
- The alternative to the concerted way is synchronous mechanism, see: (a) Fishcer, J.; Steglich, W. Angew. Chem., Int. Ed. 1979, 18, 167; (b) Bearpark, M.; Bernardi, F.; Olivucci, M.; Robb, M. A. J. Am. Chem. Soc. 1990, 112, 1732.