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Synthesis of 1-haloethenamides from ynamide through halotrimethylsilane-mediated hydrohalogenation

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ABSTRACT

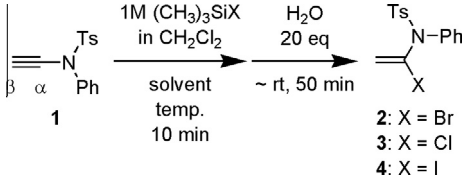
A convenient synthesis of 1-haloethenamides has been achieved by utilizing halotrimethylsilane (TMSX, X = Cl, Br, I) and water. Halotrimethylsilane in 1 M CH_2Cl_2 solution functions as a halogen source of the in situ generated HX, and the HX added to the terminal triple bonds of ynamides in Markovnikov fashion.

Vinyl halides are clearly an important structure in organic synthesis,[1] because of their ability to serve as building blocks in a wide variety of functional group transformations.[2,3] The weakly bonded halogens are highly reactive and incredibly useful toward construction of complex molecules.[4,5] 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.[6,7] From the synthetic point of view, haloenamides[8] are versatile variants of vinyl halides.[9] They are found in natural products,[10] and their intrinsic electron-rich olefin has emerged as a new type of nucleophiles in stereoselective C–C and C–N bond forming reactions.[11] Haloenamide in *exo*-methylene fashion, namely 1-haloethenamide in Scheme 1, is especially useful: the sterically unhindered moiety and N-substituted halovinyl is potentially effective for synthesizing nitrogen-containing complex molecules. Despite the intriguing utility of 1-haloethenamide, their synthetic availability still remains a challenge, because of the inherent difficulty in hydrohalogenation.[12] The stoichiometric addition of hydrogen halide (HX) to terminal alkyne of ynamide is one way to prepare 1-haloethenamides; however, the generation and transfer of hygroscopic and gaseous HX are inconvenient and difficult to perform,[13–15] and the problem associated with this type of reactions lies in the difficulty of the formation of a mixture of stereoisomers and side-products caused by excess of HX.[16] Although an alternative hydrometalation exists, it requires several reaction steps and extra operations.[17]

The pioneering work for efficient synthesis of haloenamides from ynamides via addition of HX was reported by Hsung and co-workers in 2003:[18] the in situ generation of HX from MgX_2 and H_2O afforded α-haloenamides with good selectivities of *E*/*Z* ratios.[19] The outcome of stereoselective addition is dictated by the polarization of the triple bond caused by nitrogen.[20] According to the keteniminium resonance form, the halogen automatically unites with α-carbon;[21] however, any trail for synthesizing 1-haloethenamides was not documented.

On the other hand, we recently reported successful syntheses of α-haloenamides as a single isomer in gram-scale using in situ generated HX.[22] The in situ HX (X = I, Br) was generated from mixing of 1 M halotrimethylsilane (TMSX) in CH_2Cl_2 and 20 equiv of water, and added to ynamide in nearly quantitative yields with perfect regio- and stereoselectivity. The method completes the reaction within 1 h under routine conditions, and showed extensive substrate compatibility, giving novel compounds of not only (1-iodoviny)arenes but also 1-(1-halovinyl)-1*H*-indoles and variedly N-protected α-haloenamides.

In this Letter, we present a synthesis of 1-haloethenamides from ynamides using in situ generated HX (Scheme 1). The



Scheme 1. Syntheses of 1-haloethenamides **2**, **3**, and **4** via hydrohalogenation of **1**.

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in situ HX was generated from 1 M TMSX (X = Cl, Br, I) and 20 equiv of H_2O, and cleanly added to terminal alkyne of ynamide **1** in high yields under a variety of routine reaction conditions. The resultant products were applicable to transition-metal catalyzed reaction.[18c] To the best of our knowledge, so far such a straightforward synthesis of 1-haloenethenamide has not been reported. Thus, it provides simple access to 1-haloethenamide moieties.

Initially, we commenced our investigations with the reaction conditions previously reported for the TMSBr-mediated hydrobromination (Scheme 1).[22] The mixture of **1**[23] and TMSBr[24a] was stirred at −78 °C for 10 min, and water was added, and the reaction was allowed to warm to ambient temperature. After workup, the product **2** was isolated with silica gel column chromatography with typical coupling constant $J = 1.2$ Hz for *exo*-methylene form.[24b]

As summarized in Table 1, the reactivity of **1** conducted via Scheme 1 was evaluated. An appropriate amount of TMSBr proved to be 1.2 equiv for completion at −78 °C (entries 1–3). For entries 4 and 5, ethereal solvents performed better than CH_2Cl_2; highest yielding transformation in entry 5 was achieved under cyclopentyl methyl ether (CPME), and the reaction at 0 °C gave comparable yield with −78 °C (entry 6). For entry 7, acetone also carried out the clean hydrobromination at 0 °C. For entry 8, the reaction under acetonitrile endured to give 93% yield. For entry 9, the yield under toluene was acceptable. It is worth noting that good yields were achieved through the addition of TMSBr prior to water. For entries 1 and 2, the addition of water in advance did not improve the yield very well; that is, the complexation of ynamide and TMSBr would be important for the reaction mechanism. This phenomenon was also observed in the previous report,[22c] and is agreeable with the activation of TMSCl in Table 2.

To further clarify the reactivity of **1** with the in situ HX, chlorotrimethylsilane (TMSCl) and iodotrimethylsilane (TMSI) were tested as halogen sources (Table 2). The reactions with TMSCl under CPME (entries 1 and 2) and THF (entries 3 and 4) smoothly proceeded to give the vinyl chloride **3** in more than 90% yields.[25] For entries 5–7 on hydroiodation with TMSI, high yielding transformations to the vinyl iodide **4** were also achieved in up to 90% yield although the reaction at entry 8 did not work well. To our surprise, the obstinate TMSCl quickly reacted with **1** although it did not react with internal alkynes in the previous report.[22b] As depicted in Table 1, the reaction mechanism emphasizes the importance of complexation between ynamide and TMSX; thus, the sterically unhindered alkyne of **1** tightly coordinates to TMSCl, and readily activates the Si–Cl bond.[22c]

Thus, 1-haloethenamides **2**, **3**, and **4** seemed to be stable during workup and silica gel column chromatography, and were obtained as white solid materials right after purification; however, unfortunately, these gradually decayed to unclear impurities and turned into dark colored stuff even though they were conserved under argon atmosphere at low temperature. Actually, the iodide **4** was quite labile to totally decompose in ca. 2 days along with turning to dark brown solid materials, and the bromide **2** in 10 days after purification was observed to totally decay. Chloride **3** holds against decay, and 70% of the whole did not change into impurities in 1 week.

Preliminary mechanistic investigations were performed through deuteration experiments; H_2O in Scheme 1 was replaced by D_2O, and in situ DBr added to the triple bond of **1** (Table 3). For entries 1 and 2, deuteriobromination under CPME and THF generated (*E*)-**2**-d_1- without (*Z*)-**2**-d_1 in high yields, and the addition mode of DBr was precisely controlled with complete *trans*-selectivity. On the other hand, utilizing diethyl ether, acetone, dichloromethane, and acetonitrile as solvents gave non-negligible amounts of (*Z*)-**2**-d_1 (entries 3–6), and for entry 8 the reaction in acetone at 0 °C underwent hydrobromination strangely in 35% yield of **2** nevertheless dry solvent was used.[26] Thus, we envisaged that the kinetic significance of the protonation step would be probed by the following experiment (entry 9). A blend of D_2O (10 equiv) and H_2O (10 equiv) was used instead of H_2O under

Table 1
Screening of reaction conditions for hydrobromination of **1** conducted via Scheme 1[a]

Entry	TMSBr (equiv)	Solvent	Temp (°C)	Yield[b] (%)
1	2.0	CH_2Cl_2	−78	56
2[c]	2.0	CH_2Cl_2/H_2O (4% v/v)	−78	64
3	1.2	CH_2Cl_2	−78	89
4	1.2	THF	−78	91
5	1.2	Cyclopentyl methyl ether	−78	95
6	1.2	Cyclopentyl methyl ether	0	93
7	1.2	Acetone	0	89
8	1.2	CH_3CN	−20	93
9[d]	1.2	Toluene	0	86

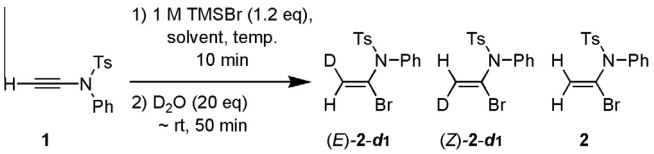
[a] Reaction conditions: **1** (0.5 mmol), solvent (4 mL), 1 M $(CH_3)_3SiBr$ in CH_2Cl_2, H_2O (10 mmol).
[b] Isolated yields after short-plug column chromatography.
[c] 20 equiv of H_2O was blended in advance with 4 mL of CH_2Cl_2.
[d] 6% of unreacted **1** was observed.

Table 2
Hydrochlorination and hydroiodation of **1** conducted via Scheme 1[a]

Entry	Product	Solvent	Temp (°C)	Yield (%)
1	**3**	Cyclopentyl methyl ether	−78	92
2	**3**	Cyclopentyl methyl ether	0	94
3[b]	**3**	THF	−78	90
4	**3**	THF	0	95
5	**4**	Cyclopentyl methyl ether	−78	89
6	**4**	Cyclopentyl methyl ether	0	88
7	**4**	THF	−78	90
8[c]	**4**	THF	0	18

[a] Reaction conditions: 1 (0.5 mmol), solvent (4 mL), 1 M $(CH_3)_3SiX$ in CH_2Cl_2, H_2O (10 mmol).
[b] 6% of unreacted **1** was observed.
[c] 54% of unreacted **1** was observed.

Table 3
Deuteriobromination of **1**[a]



Entry	Solvent	Temp (°C)	Yield[b] (%)		
			(*E*)-**2**-d_1	(*Z*)-**2**-d_1	**2**
1	Cyclopentyl methyl ether	−78	85	0	9
2	THF	−78	92	0	4
3	Diethyl ether	−78	72	18	14
4	Acetone	−78	65	14	8
5	CH_2Cl_2	−78	26	24	14
6	CH_3CN	−20	64	14	16
7	Cyclopentyl methyl ether	0	85	4	9
8	Acetone	0	51	7	35
9[c]	Cyclopentyl methyl ether	−78	21	0	79

[a] Reaction conditions: **1** (0.5 mmol), solvent (4 mL), 1 M $(CH_3)_3SiBr$ in CH_2Cl_2, D_2O (10 mmol).
[b] Determined by ^1H NMR.
[c] Instead of D_2O, a blend of D_2O (10 equiv) and H_2O (10 equiv) was used.

CPME solvent in Scheme 1, which produced **2** as a dominant product (79%) and (*E*)-**2**-d_1 as a minor product (21%). Obviously, the product distribution of **2** and (*E*)-**2**-d_1 was affected by the rate difference of the C–H and C–D formations, indicating that the protonation is the product-determining step.

Whereas 20 equiv of water served as a proton source, methanol mysteriously did not work (Scheme 2). To the mixture of **1** and TMSBr was added 20 equiv of methanol: the target **2** was not observed, and 84% of 4-methyl-*N*-pheynylbenzenesulfonamide was isolated instead. Although the mechanism for dissociating C–N bond of **1** with utilizing methanol is not yet fully known, the molecular water in this reaction system proved to be indispensable for exactly forming 1-haloethenamides.

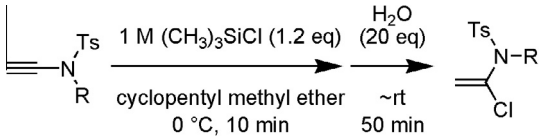
With a viable route to the 1-haloethenamides in hand, we then worked on applying the hydrochlorination to starting *N*-ethynyl tosylamides bearing allyl and *p*-tolyl groups (Table 4). The reactions smoothly proceeded to give the corresponding vinyl chloride **5** and **6** in 95% and 98% yields, respectively. The difference in reactivity between allyl and *p*-tolyl groups was not observed; each smoothly yielded the corresponding product. The products **5** and **6** were isolated as white solid materials that withstood aqueous workup procedures and chromatographic purification on silica gel. As for the stability of **5** and **6**, the allyl **5** was stored at room temperature for 1 week with no appreciable decomposition: however, unfortunately, the chloride **6** began to decay right after isolation, and exhaustive decomposition was observed in ca. 4 h. Although we tried to explore substrate scope for synthesizing other 1-haloethenamides, they were too labile to isolate. The structural motif in 1-haloethenamide, in which exo-methylene incorporated into alpha-haloenamide, would be originally quite fragile.

In view of the situation, we attempted to certify the utility of such an extremely fragile 1-haloethenamide. As shown in Table 5, the synthetic potential was successfully performed by employment of the freshly prepared 1-haloetheneamides. The vinyl halide group is an excellent candidate for use in transition metal mediated reactions such as Sonogashira coupling.[16b] Freshly prepared bromide **2** and iodide **4** underwent the cross-coupling with trimethylsilyl acetylene to yield enyne **7** in 60% and 66% yields, respectively. For entries 3 and 4, each reaction with arylacetylene also proceeded in 74% and 75% yields, respectively. Note that the enyne **7**, **8**, and **9** were stable although the halide **2** and **4** were fragile[27]: thus, the employment of those halides right after isolation was proved to be practicable for Sonogashira reaction.

In conclusion, we have developed a simple procedure for the synthesis of 1-haloethenamides from ynamides employing halotrimethylsilane and water. This reaction is initiated by generation of in situ HX from halotrimethylsilane and water in a wide variety of reaction conditions, and the HX adds to terminal alkynes of ynamides in Markovnikov manner, resulting in regio- and stereoselective installation of H and X atoms. Although the products of 1-haloethenamides were easily broken into impurities, those freshly prepared were fit for use to synthesize the corresponding Sonogashira-coupling adducts of enynes. We hope this protocol serves as a tool for the efficient synthesis of complex amine-substituted molecules.

Scheme 2. Reaction of **1** with TMSBr under addition of methanol.

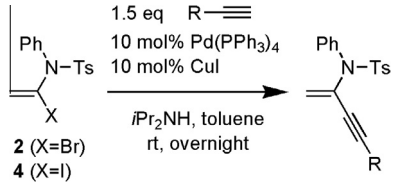
Table 4
Syntheses of 1-chloroethenamides **5** and **6**



R	Product	Yield[a] (%)
$CH_2CH{=}CH_2$	5	95
4-CH_3Ph	6	98

[a] Isolated yields after short-plug column chromatography.

Table 5
Employment of **2** and **4** for synthesizing enynes **7**, **8**, and **9**



Entry	Substrate	R	Product	Yield[a] (%)
1	2	$(CH_3)_3$Si	7	60
2	4	$(CH_3)_3$Si	7	66
3	2	Ph	8	74
4	2	3-ClPh	9	75

[a] Isolated yields after short-plug column chromatography.

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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.2013.11.091.

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24. (a) Preparation of 1 M TMSX in CH_2Cl_2, see Supplementary material.; (b) Representative procedure for synthesizing **2** (Table 1, entry 4): To a solution of **1** (0.5 mmol) in anhydrous CH_2Cl_2 (4 mL) at −78 °C was added TMSBr (1 M in CH_2Cl_2) dropwise over 5 min, and the mixture was stirred for 10 min. Then, H_2O (10 mmol) was added, and the cooling-bath was removed to warm to room temperature. After additional stirring for 50 min, the reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate, and 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 (eluent; hexane/EtOAc = 4/1) afforded **2** in 89% yield (157 mg) as white solid materials. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.38–7.28 (m, 7H), 5.98 (d, J = 1.9 Hz, 1H), 5.68 (d, J = 1.9 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 138.6, 136.3, 129.9, 129.5, 129.0, 128.62, 128.57, 126.0, 122.8, 21.9. MS (DI) m/z: 351 (MH^+), 272 ([MH-Br]$^+$). IR (neat): 3117 (C=C), 3032, 1344 (NSO_2), 1233, 1162 cm^{-1}. HRMS (DI) calcd for $C_{15}H_{14}$(79)$BrNO_2S$ 350.9929, found 350.9913.
25. The difference in reactivity between TMSCl, TMSBr, and TMSI was not observed. Each reagent quickly reacted with **1**.
26. There is likelihood that Lewis acidic TMSBr assisted H-D exchange between acetone and D_2O to give HDO and H_2O, and consequently the yield of **2** increased.
27. Enynes **8** and **9** were obtained in pure form right after column chromatography: their purities decreased to ca. 85% in 1 h although the further decomposition was not observed.