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Regio- and stereoselective hydrohalogenation of ynamide components in 1,3-butadiynes with in situ generated HX

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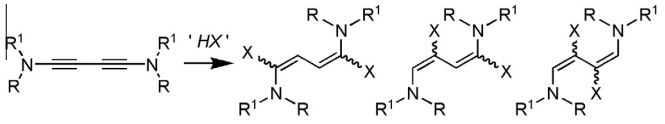
ABSTRACT

A simple protocol for regio-, and stereoselective hydrohalogenation of ynamide moieties in 1,3-butadiyne structures is described. The facile approach enables exact *syn*-addition of HX to the diyne components, giving just single isomer of the corresponding dienes and enynes.

1,3-Dienes are clearly important building blocks in organic synthesis.[1] Structural 1,3-diene components are frequently found in bioactive natural products[2] and pharmaceutically interesting molecules.[3–5] They are also capable of participating in a wide range of complexity-generating transformations[1] (e.g., cycloadditions,[6] 1,2- and 1,4-additions,[7] and cycloisomerizations[8]). From the synthetic point of view, functionalized 1,3-dienes bearing multi-heteroatom substituents are versatile variants of 1,3-dienes.[9] Among them 1,3-dienes directly-joining to halogen and nitrogen atoms at their vinyl positions can be especially useful (Scheme 1). Because halovinyls 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,[10–12] and moreover the enamide substructures serve as a novel type of nucleophiles in stereoselective C—C and C—N bond forming reactions.[13] Thus, such hybrid butadienes combined with halovinyl and enamide are potentially instructive toward the synthesized nitrogen-containing complex molecules.[14] Despite the utility of such hybrid butadienes, their synthetic availability still remains a challenge, because of the inherent difficulty in regio- and stereoselective hydrohalogenation of 1,3-diynes.[15] As shown in Scheme 1, the stoichiometric addition of hydrogen halide (HX) to buta-1,3-diyne-1,4-diamine moiety is one way to prepare the dihalobuta-1,3-diene-1,4-diamine skeleton; however, the generation and transfer of hygroscopic and gaseous HX are inconvenient and difficult to perform.[16–18] 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,[19] and actually Scheme 1 can permit ten products as 1,3-butadienes.

The prototype protocol for efficient hydrohalogenation of alkynes without using gaseous HX was developed by Ishii and coworkers in 1990[20]: mixing of chlorotrimethylsilane, sodium iodide, and water generates in situ HI, and addition of the HI to alkynes produced α-vinyl halides. And continuous efforts have aimed to refine this initial method;[21,22] for example, halotrimethylsilane,[21] MgX_2,[14] and HF-SbF_5,[23] each-mediated in situ generation of HX converted alkynes into variedly functionalized halovinyls. However, to the best of our knowledge, any trial for hydrohalogenation of 1,3-diynes employing in situ generated HX is not performed.

On the other hand, we recently reported simple syntheses of α-haloenamides as a single isomer in gram-scale using in situ generated HX.[24] The in situ HX (X = I, Br) was generated from mixing of 1 M halotrimethylsilane (TMSX) in CH_2Cl_2 and water, and added to ynamide in nearly quantitative yields with perfect regio- and stereoselectivity. The method completes the reaction within 1 h



Scheme 1. Hydrohalogenation of buta-1,3-diyne-1,4-diamine moiety.

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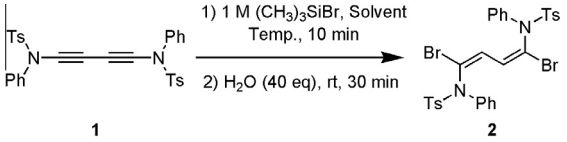


Scheme 2. Synthesis of **2** from **1** (Ts = *p*-toluenesulfonyl).

under routine conditions, and showed extensive substrate compatibility, giving novel compounds of not only varied α-haloenamides but also 1-(1-halovinyl)-1*H*-indoles and (1-iodovinyl)arenes.

In this Letter, as shown in Scheme 2, we describe a regio- and stereoselective hydrohalogenation of buta-1,3-diyne-1,4-diamine moiety (like **1**) with in situ generated HX, which yields *N*,*N*′-(1*E*,3*E*)-1,4-dihalobuta-1,3-diene-1,4-diyl skeleton (like **2**) as a single isomer. Thus, the protocol provides a simple access to novel 1,3-butadiene directly-joining to the halogen and nitrogen atoms at their vinyl positions.

At the onset of our study, we focused on the reactivity of **1**[25] for hydrobromination, based on our previous report.[24] The mixture of **1** and 1 M TMSBr was stirred at −78 °C for 10 min, then water was added, and the reaction was allowed to warm to ambient temperature. After workup and purification, the product was isolated through silica gel column chromatography without decomposition, and both ^{1}H and ^{13}C NMR analyses revealed to be a single isomer. The molecular structure of **2** was determined by crystallographic analysis as shown in Figure 1,[26] disclosing its stereochemistry as a *N*,*N*′-((1*E*,3*E*)-1,4-dibromobuta-1,3-diene-1,4-diyl)bis(4-methyl-*N*-phenylbenzenesulfonamide).

As summarized in Table 1, the reactivity of **1** conducted via Scheme 2 was evaluated. For entries 1–4, the amounts of TMSBr were surveyed: more than 3.2 equiv were needed for consumption of the starting **1**. The enyne-type product that undergoes one-sided hydrohalogenation of the triple bonds was not observed through entries 1–4. For entries 5–7, the yields in acetone, toluene, and THF resulted in 60%, 52%, and 24%, respectively; they were not more than 68% in entry 3. For entries 8, the hydrohalogenation in CH_2Cl_2 at −78 °C suitably proceeded in up to 72% yield along with disappearance of **1**. The attempt at −78 °C was successful presumably due to control over the sharp reactivity of TMSBr. For entry 9, water was mixed in advance to the solvent of CH_2Cl_2, and the comparable yield of **2** to entry 8 was attained. For entry 10, this protocol was amenable to scale up; 1.1 g of **2** was obtained in 79% yield.

Scheme 3 illustrates different halotrimethylsilyl patterns tested. Like TMSBr, TMSI generated in situ HI, and the HI nicely added to the triple bonds of **1** to yield iodide **3** in 71%. Unfortunately in the same condition TMSCl did not activate **1** at all. Then, several approaches were attempted, and finally the employment of aqueous NH_4Cl in the mixed solvent of CH_2Cl_2 and CH_3CN achieved the formation of chloride **4** as a single isomer in acceptable yield of 65%. It was confirmed that the hydrochlorination never occurred under only aqueous NH_4Cl.[27] The increase of ionic chloride in the system would enhance the addition reaction to produce **4**. Dihalide **3** and **4** were stable at ambient temperature under argon atmosphere at least for 1 month with no appreciable decomposition.

With the viable conditions for synthesizing **2** in hand (Table 1, entries 8 and 10), starting materials of buta-1,3-diyne-1,4-diamines having allyl and *p*-tolyl groups[28] underwent this hydrohalogenation, and its resultant products are listed in Table 2 as **5a**, **5b**, **6a**, and **6b**. These products are also afforded as single isomers in up to 79% yield. The type of these halovinyls is an excellent candidate for use in transition metal-mediated reactions such as an example (Scheme 4): **5a** underwent the cross-coupling with trimethylsilyl acetylene.[29] The starting **5a** had two bromines as reaction sites, and both reacted thoroughly along with forming conjugated bisenyne framework of **7** in 69% yield.

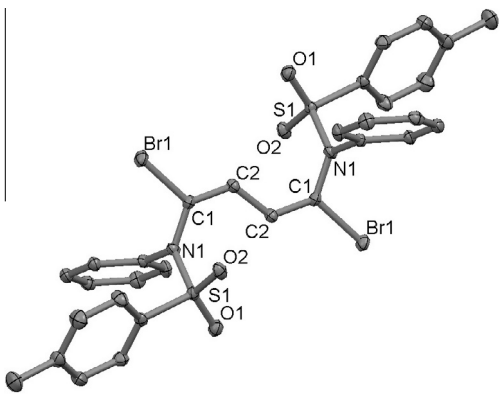
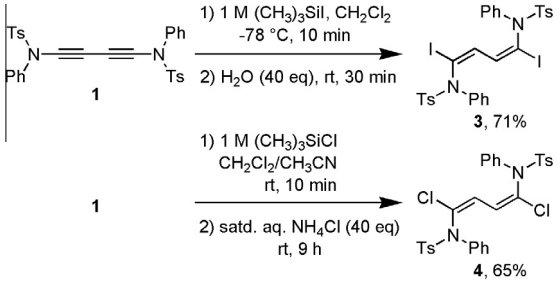


Figure 1. ORTEP drawing of **2** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected lengths (Å): C(1)–C(2) = 1.339, C(1)–Br(1) = 1.919, C(1)–N(1) = 1.394, C(2)–C(2) = 1.454.

Table 1
Evaluation of the reactivity of **1** conducted via Scheme 2[a]

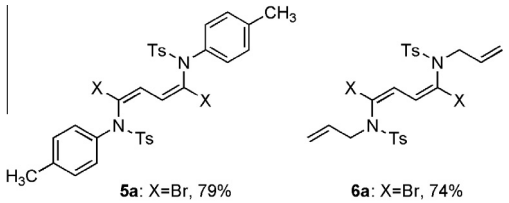
Entry	TMSBr (equiv)	Solvent	Temp (°C)	Yield (%)	
				1	**2**
1	1.2	CH_2Cl_2	0	28	44
2	2.4	CH_2Cl_2	0	12	60
3	3.2	CH_2Cl_2	0	2	68
4	4.0	CH_2Cl_2	0	2	64
5[b]	3.2	Acetone	rt	4	60
6[b]	3.2	Toluene	rt	28	52
7[b]	3.2	THF	rt	72	24
8	3.2	CH_2Cl_2	−78	0	72
9	3.2	CH_2Cl_2/H_2O (8% v/v)	−78	0	69
10[c]	3.2	CH_2Cl_2	−78	0	79

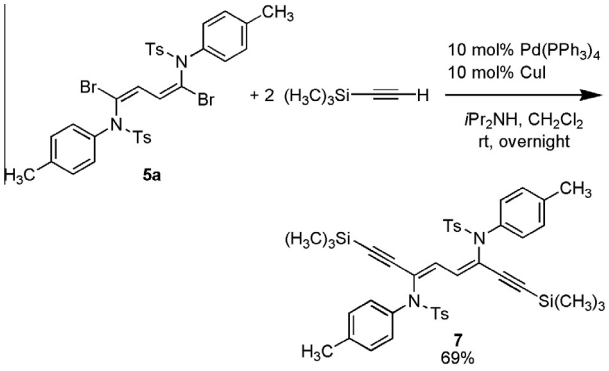
[a] Reaction conditions: **1** (135 mg, 0.25 mmol), solvent (10 mL), 1 M $(CH_3)_3SiBr$ in CH_2Cl_2, H_2O (10 mmol).
[b] The starting **1** did not dissolve at 0 °C; thus the reactions at rt were carried out.
[c] The reaction was performed in eight times scale; **1** (2 mmol), 80 mL of CH_2Cl_2, 80 mmol of H_2O. The product **2** was afforded in 1.1 g.



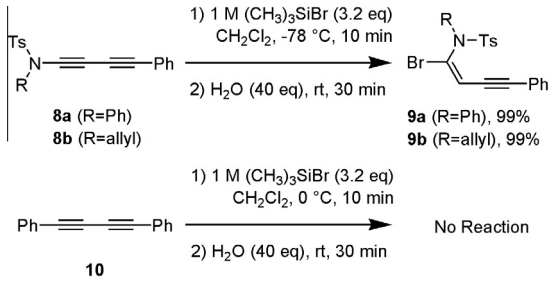
Scheme 3. Hydroiodation and hydrochlorination of **1** to give **3** and **4**.

Table 2
Synthesis of 1,3-dienens **5a**, **5b**, **6a**, and **6b**





Scheme 4. Synthesis of **7** from **5a** via Sonogashira reaction.

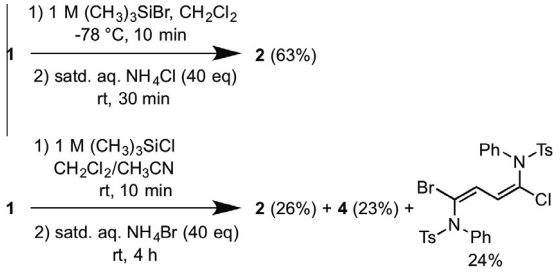


Scheme 5. Effect of the regio-, and stereoselective hydrobromination on **8a**, **8b**, and **10**.

To amplify this hydrohalogenation method, the unsymmetrically structured 1,3-diynes[30] **8a** and **8b** in Scheme 5 were prepared, because they were tested on the regio-, and stereoselective hydrobromination. Actually, the clean conversion of **8a** into **9a** was smoothly achieved in 99% yield[31]: one-sided alkyne of ynamide **8a** underwent the hydrobromination, and the other triple bond remained totally unreacted. Similar selective hydrobromination for the allyl **8b** proceeded to afford **9b** in 99% yield. On the other hand, no reaction was observed on the hydrobromination of **10**. The electronic bias in the triple bond of ynamide moiety proved to be important for straightforward preparation of well-defined enyne components in **9a** and **9b**.

The mechanism resulting in high stereochemical control to derive predominantly *syn*-adducts is not yet fully known; however, some points of the reaction process would be estimated. TMSX initially reacts with water to generate in situ HX. The HX would be active species because the yields at entries 8 and 9 in Table 1 were nearly equal regardless of addition of water in advance or not. Then, the HX regio- and stereoselectively adds to the triple bond of ynamide structure: according to the nature of the keteniminium resonance form, halogen automatically unites with the α-carbon. The addition mode might be partially or fully ionic mechanism because the use of aqueous NH_4Cl dramatically improved the hydrochlorination in Scheme 3. Actually, the hydrobromination in Scheme 5 occurred only in the strongly polarized ynamide triple bond. In addition, Scheme 6 exemplified different ionic combinations of TMSBr/NH_4Cl and TMSCl/NH_4Br: the former yielded only **2** in 63%, and the latter outputted mixtures of **2** in 26%, **4** in 23%, and the corresponding chlorobromide in 24% yield. This suggests that chloride ion derived from TMSCl would be less reactive toward **1** than bromide ion. Yet the reason for just stereoselective *syn*-addition is unclear: TMSX could be involved in some way for the stereochemical outcome.[27,32]

In conclusion, we have developed a simple protocol for the synthesis of *N*,*N*′-(1*E*,3*E*)-1,4-dihalobuta-1,3-diene-1,4-diyl



Scheme 6. Effect of aqueous NH_4Cl and NH_4Br on the hydrohalogenations.

molecules from buta-1,3-diyne-1,4-diamine moieties. The in situ generated HX from halotrimethylsilane and water adds to the alkynes in *syn*-mode, resulting in regio-, and stereoselective installation of halogen and hydrogen atom. In addition, similar selective hydrobromination for the unsymmetrical 1,3-diyne was achieved. This method completes the reactions quickly under the routine conditions, and was amenable to gram-scale. We hope this procedure finds widespread use in organic synthesis.

Acknowledgments

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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.2014.02.028.

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26. *Crystal data of* ***2***: Triclinic, space group $P1$, colorless, $a = 7.0069(6)$ Å, $b = 9.1341(8)$ Å, $c = 11.7012(9)$ Å, $\alpha = 94.481(3)°$, $\beta = 100.231(3)°$, $\gamma = 96.954(3)°$, $V = 727.75(10)$ Å^3, $Z = 1$, $T = -180$ °C, $d_{calcd} = 1.603$ g cm^{-3}, μ(Mo, Kα) = 2.975 mm^{-1}, $R_1 = 0.0357$, $wR_2 = 0.0996$, GOF = 1.158.
27. TMSX would work as a Lewis acid: TMSBr and TMSI are stronger Lewis acids than TMSCl, and may activate **1** efficiently.
28. We tried to prepare other 1,3-butadiynes as starting materials that possess *N*-benzyl tosylamide *N*-methyl tosylamide, and *N*-(4-cyanophenyl) tosylamide; however, unfortunately, these were not successfully isolated.
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31. Compound **9a** was converted into the corresponding olefin using *tert*-BuLi for lithium-halogen exchange, and the (*Z*)-olefin was obtained in 67% yield with typical coupling constant $J = 9.7$ Hz for *cis*-form: in brief, the compound **9a** was in (*E*)-fashion.
32. We have carried out some mechanistic studies with NMR experiments; however, unfortunately, no proof of halosilylation of the starting alkynes was not observed and the addition of HX was too fast to pursuit the reaction intermediates.