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A stereoselective synthesis of α-halo vinyl sulfides and their applications in organic synthesis†

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Abstract—α-Halo vinyl sulfides have been synthesized stereoselectively via the addition of the in situ generated hydrogen halide to acetylenic thioether. α-Halo vinyl sulfides are versatile substrates that can undergo many important transformations.

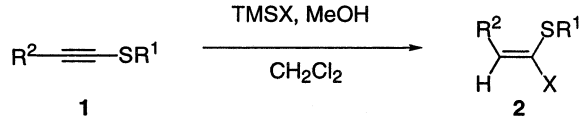
α-Halo vinyl sulfides are an important group of compounds with wide applications in organic synthesis.[1] Many procedures for the preparation of α-halo vinyl sulfides have been developed.[2] Among them, the regioselective addition of hydrogen halide (HCl, HBr, HI) to acetylenic sulfides was the most simple and efficient.[2a] Although the regioselectivity of the addition of hydrogen halide to acetylenic sulfides was excellent, it often resulted in the formation of both *Z*- and *E*-isomers due to use of excess aqueous hydrogen halide (37% HCl, 48% HBr, or 51% HI) or saturated gaseous HX in benzene. Moreover, separation of the *Z*- and *E*-isomers was often quite difficult. Therefore, a new procedure is needed for the stereoselective synthesis of α-halo vinyl sulfides.

Recently we have discovered that hydrogen halide generated in situ (by reaction of trimethylsilyl halide with anhydrous methanol) can add to acetylenic ethers at low temperature in a completely regio- and stereoselective manner with nearly quantitative yields.[3] This prompted us to investigate the possibility of the application of this methodology for the stereoselective synthesis of α-halo vinyl sulfides.

We found that hydrogen halide generated in situ by addition of 0.99 equiv. of trimethylsilyl halide[4] to a solution of 1.0 equiv. of acetylenic thioether[5] and 0.99 equiv. of MeOH in CH_2Cl_2 at low temperature gave α-halo vinyl sulfides with superior regio- and stereoselectivity (Scheme 1). The yield was nearly quantitative. Since traces of the starting material acetylenic sulfide **5** did not interfere with the subsequent reaction, and the only side product, MeOTMS, could be evaporated easily, neither work up nor column chromatography was necessary.

Table 1 summarized the preparation of a variety of α-halo vinyl sulfides using our procedure.[6] Controlling the reaction temperature was crucial to achieve high stereoselectivity for both α-bromo and α-iodo vinyl sulfides. If the reaction temperature was too high, a substantial amount of the *Z*-isomer would be formed along with the *E*-isomer. In the case of HCl, a higher temperature (25°C) and 2 equiv. of reagents were needed to drive the reaction to completion (Table 1, entry 3).

A typical procedure used in the stereoselective synthesis of α-halo vinyl sulfides follows: To a solution of acetylenic thioether (1 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added anhydrous methanol (0.99 mmol) followed by slow addition of TMSBr (0.99 mmol) under nitrogen at the temperature indicated. The reaction mixture was stirred at that temperature for about 1 h, and then was allowed to warm up to 25°C. After removal of the solvent and the side product (MeOTMS) by rotary evaporation, the product can be used without any further purification.



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Scheme 1.

Keywords: α-halo vinyl sulfide; acetylenic thioether.

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† Synthesis via α-halo vinyl ethers **3**.

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Table 1. A stersoselective synthesis of α-halo vinyl sulfides

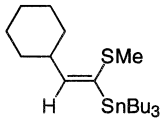
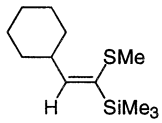
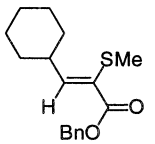
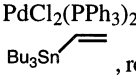
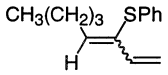
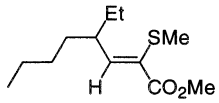
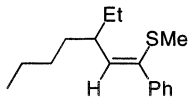
Entry	Substrates	Conditions[a]	Products[b]	Yield
1	$CH_3(CH_2)_3$—≡—SPh **3**	Method A	$CH_3(CH_2)_3$ SPh / H Br **4** E:Z>20:1	99%
2	**3**	Method B	$CH_3(CH_2)_3$ SPh / H I **5**	99%[c]
3	**3**	TMSCl(2eq) MeOH(2eq) CH_2Cl_2, 25°C, 12hr	$CH_3(CH_2)_3$ SPh / H Cl **6**	99%[c]
4	$CH_3(CH_2)_6$—≡—SMe **7**	Method A	$CH_3(CH_2)_6$ SMe / H Br **8** E:Z>33:1	99%
5	**7**	Method B	$CH_3(CH_2)_6$ SMe / H I **9** E:Z=15:1	99%
6	Et, —≡—SMe **10**	Method A	Et, SMe / H Br **11**	99%[c]
7	**10**	Method B	Et, SMe / H I **12**	99%[c]
8	$PhCH_2CH_2$—≡—SMe **13**	Method A	$PhCH_2CH_2$ SMe / H Br **14** E:Z=19:1	99%
9	**13**	Method B	$PhCH_2CH_2$ SMe / H I **15** E:Z=11:1	99%
10	—≡—SMe **16**	Method A	SMe / H Br **17**	96%[c]
11	**16**	Method B	SMe / H I **18** E:Z>20:1	99%

[a] All reactions were run in CH_2Cl_2. [b] The geometry of double bonds were determined by NOESY spectra. The E/Z ratios were measured by integration of well-resolved signals in the ^1H NMR. [c] The minor isomer was not detected by NMR. Method A: TMSBr (0.99 equiv), MeOH (0.99 equiv), -40°C, 1 h; Method B: TMSI (0.99 equiv), MeOH (0.99 equiv), -78°C, 1 h.

The applications of α-halo vinyl sulfides in organic synthesis were summarized in Table 2. Compounds **19**, **20**, and **21** (Table 2, entries 1–3) were synthesized via α-alkylthio vinyllithium intermediates which were prepared by the treatment of α-halo vinyl sulfides with *t*-BuLi at −78°C.[7] All reactions afforded excellent yields with the retention of the stereochemistry of the double bond.

α-Halo vinyl sulfides can also undergo many important transformations catalyzed by transition metals like palladium and nickel. In the presence of a catalytic

Table 2. Application of α-halo vinyl sulfides in organic synthesis

Entry	Substrates[a]	Conditions	Products[a]	Yield[b]
1	**17**	1) *t*-BuLi, THF, -78 °C, 30 min 2) Bu_3SnCl, -78 °C, 15 min	 **19**	89%
2	**17**	1) *t*-BuLi, THF, -78 °C, 30 min 2) TMSCl, -78 °C, 15 min	 **20**	86%
3	**17**	1) *t*-BuLi, THF, -78 °C, 30 min 2) $ClCO_2Bn$, -78 °C, 15 min	 **21**	91%
4	**4**	$PdCl_2(PPh_3)_2$, CH_3CN,  , reflux,	 **22** Z:E=1:1	92%
5	**11**	$Pd(OAc)_2$, PPh_3, Et_3N, CO, MeOH, DMF, 70 °C	 **23**	91%
6	**11**	$NiCl_2dppp_2$, PhMgBr, 25 °C, benzene	 **24**	88%

a. The geometry of double bonds were determined by NOE or NOESY spectra. b. All yields are isolated yields.

amount of $PdCl_2(PPh_3)_2$, α-bromo vinyl sulfide **4** underwent Stille coupling[8] with tributylvinyltin to provide 1,3-diene **22** in excellent yield (Table 2, entry 4). Palladium (0)-catalyzed carbonylation[9] between α-bromo vinyl sulfide **11** and CO in the presence of methanol gave compound **23** in 91% yield with complete retention of the stereochemistry of the double bond (Table 2, entry 5). α-Halo vinyl sulfides also coupled with Grignard reagents catalyzed by an organonickel catalyst. Compound **11** reacted with PhMgBr in the presence of a catalytic amount of $NiCl_2dppp_2$ to give **24** in 88% (Table 2, entry 6).[10]

In conclusion, we have successfully developed a highly regio- and stereoselective synthesis of α-halo vinyl sulfides. We have demonstrated that α-halo vinyl sulfides are highly versatile substrates that can undergo many important transformations. Application of these methodologies to the total synthesis of natural products is underway, and will be reported in due course.

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