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Synthesis of α-Halo-γ-hydroxyenamides by Titanium Tetrahalide Mediated Addition of Aldehydes or Ketones to Ynamides

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Supporting Information

ABSTRACT: α-Chloro- or α-bromo-γ-hydroxyenamides were synthesized by the reaction of an ynamide, titanium tetrahalide, and an aldehyde or a ketone. A γ-hydroxy trisubstituted enamide was prepared stereoselectively by Suzuki coupling of an obtained α-chloro-γ-hydroxyenamide with phenyl boronic acid. Intramolecular cyclization of α-chloro-γ-hydroxyenamide took place to provide a 2,3-dihydrobenzoisothiazole 1,1-dioxide derivative by palladium-catalyzed C−H activation of the tosyl group. Hydrochlorination of ynamides proceeded to give α-chloroenamides by treatment with titanium tetrachloride followed by addition of water.

Ynamides show characteristic reactivities and enable unique bond-forming reactions that lead to the formation of various amine derivatives.[1] A number of reactions have been developed for ynamides. Among them, reactions between ynamides **1** and aldehydes or ketones have been reported to give several classes of compounds depending on the activating agent or catalyst employed (Figure 1). Activation of carbonyl

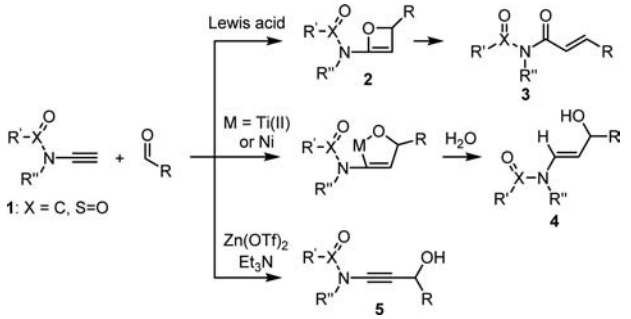

Figure 1. C−C bond formation between ynamide and aldehyde.

compounds with a Lewis acid such as BF_3−Et_2O gave acrylic amides **3** via oxetenes **2** from internal and terminal ynamides.[2] Titanium(II)-mediated[3] or nickel-catalyzed[4] coupling of internal[4] or terminal ynamides with carbonyl compounds afforded γ-hydroxyenamides **4**. $Zn(OTf)_2$-catalyzed addition of terminal ynamides to aldehyde resulted in the production of *N*-substituted propargylic alcohols **5**.[5] In this paper, we report the synthesis of α-halo-γ-hydroxyenamides **6** from ynamides and aldehydes or ketones in the presence of titanium tetrahalide (Figure 2).

The α-halo-γ-hydroxyenamides **6** that were synthesized in this study have two features of α-haloenamides and γ-hydroxyenamides. α-Haloenamides that have been prepared by carbohalogenation[6] or hydrohalogenation[7] of ynamides are

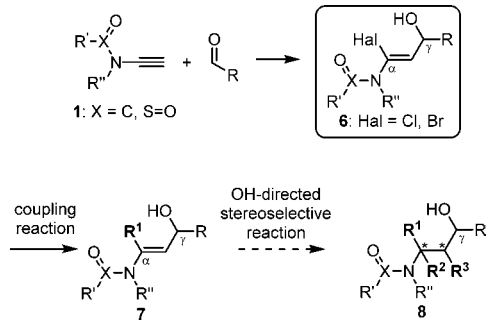

Figure 2. Present study for synthesis of **6** and synthetic utility of **6**.

valuable intermediates for the stereoselective synthesis of amine derivatives. Various groups can be introduced at the α-position of α-haloenamides by palladium-catalyzed coupling reactions,[6,7b] and the so-formed multisubstituted enamides **7** were excellent substrates for the synthesis of amines by stereoselective hydrogenation or cyclopropanation. γ-Hydroxyenamides have also been employed for the stereoselective synthesis of amines by utilizing the γ-hydroxy group as a directing group.[8] Therefore, α-halo-γ-hydroxyenamides are expected to be a versatile intermediate for the stereoselective synthesis of various amines **8**.

Reaction of ynamide **9**[9] with aldehydes was investigated by adding an aldehyde to a mixture of ynamide **9** and $TiCl_4$ at −78 °C (Table 1). Aliphatic aldehydes such as 3-phenylpropanal, isobutyraldehyde, and pivalaldehyde reacted with ynamide to give the corresponding (*E*)-α-chloro-γ-hydroxyenamides **10a**−**c** in 56−78% yields stereoselectively. The stereochemistry of **10b** was unambiguously determined by X-ray crystallography. Although reactions with benzaldehyde gave the corresponding

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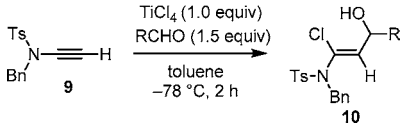
Table 1. Reaction with Aldehydes



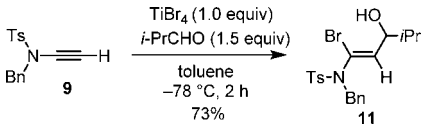
entry	R	10	yield (%)[a]
1	$Ph(CH_2)_2$	**10a**	56
2	*i*Pr	**10b**	87
3	*t*Bu	**10c**	78
4	Ph	**10d**	39
5	$4\text{-}CF_3C_6H_4$	**10e**	56
6	$4\text{-}(MeO_2C)C_6H_4$	**10f**	71
7	$4\text{-}NO_2C_6H_4$	**10g**	75
8[b]	CO_2Et	**10h**	73

[a]Isolated yield. [b]Reaction conditions: ethyl glyoxalate (2 equiv), −78 °C, 15 min.

enamide **10d** in 39% yield, aromatic aldehydes with electron-withdrawing groups such as trifluoromethyl, carbomethoxy, and nitro gave the enamides **10e−g** in good yield (entries 5−7). Ethyl glyoxalate also reacted to afford **10h** in 73% yield (entry 8). Thus, reactions of ynamide **9** with aldehydes gave a different class of compounds than did titanium tetrahalide mediated reactions of arylalkynes with aldehydes[10] or acetals,[11] which gave 1,5-dihalo 1,4-dienes. Reaction of 3-ethynyl-2-oxazolidinone with pentanal in the presence of $TiCl_4$ afforded an unsaturated amide (e.g., **3**) in 21% yield and the corresponding α-chloro-γ-hydroxyenamide, which was unstable during purification by silica gel column chromatography.

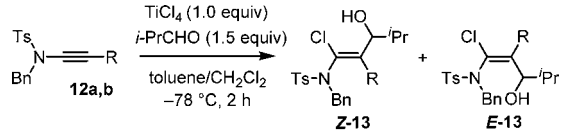
Titanium tetrabromide also mediated the reaction of ynamide **9** and isobutyraldehyde to give α-bromo-γ-hydroxyenamide **11** stereoselectively in 73% yield (Scheme 1). However, the use of titanium tetraiodide gave the corresponding α-iodo-γ-hydroxy enamide in 9% yield.

Scheme 1. Titanium Tetrabromide-Mediated Reaction



Internal ynamides **12a,b** also reacted with isobutyraldehyde to give a 1:1 *E*/*Z* mixture of enamides **13a,b** in 79−81% yields (Scheme 2).

Scheme 2. Reaction of Internal Ynamides 12a,b

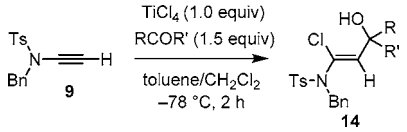


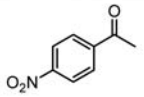
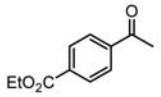
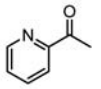
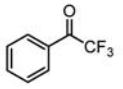
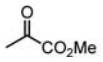
12a: R = Me
12b: R = Et

13a: 81% yield (E/Z = 1:1)
13b: 79% yield (E/Z = 1:1)

Next, the reaction with ketones was investigated (Table 2). As in the case of aldehydes, aromatic ketones bearing electron-withdrawing groups such as nitro and carboethoxy groups reacted with the terminal ynamide **9** smoothly to give enamides **14a,b** in 52−75% yields (entries 1 and 2), whereas reactions of acetophenone and *tert*-butyl methyl ketone gave only trace amounts of desired products. 2-Acetylpyridine and trifluoromethyl phenyl ketone also reacted with ynamide **9** to afford the corresponding enamides **14c,d** in 50−55% yields (entries 3 and 4). Interestingly, reaction of **9** and cyclohexanone which did not have an electron-withdrawing group gave the desired enamide **14e** in 70% yield (entry 5). The reaction of methyl pyruvate gave an enamide **14f** in 85% yield (entry 6).

Table 2. Reaction with Ketones

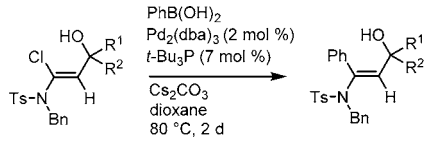


entry	ketone	14	yield (%)[a]
1		**14a**	75
2		**14b**	52
3		**14c**	50
4		**14d**	55
5		**14e**	70
6		**14f**	85

[a]Isolated yield.

Suzuki couplings of α-chloro-γ-hydroxyenamides **10b** and **14e** with phenyl boronic acid were carried out by using $Pd_2(dba)_3$ and *t*-Bu_3P (Scheme 3).[12] The desired trisubstituted enamides **17**, **18** were obtained in 82−62% yields.

Scheme 3. Suzuki Coupling



10b: R^1 = *i*Pr, R^2 = H
14e: R^1, R^2 = -$(CH_2)_5$–

17: R^1 = *i*Pr, R^2 = H (82%)
18: R^1, R^2 = -$(CH_2)_5$– (62%)

Intramolecular direct C−C bond formation between the aromatic ring of the tosyl group and the α-position of the enamide group of **14e** took place by palladium-catalyzed C−H activation (Scheme 4). This is a unique example since many examples of Heck reaction of enamides with a halogenated aromatic ring have been reported.[13]

Hydrohalogenation of alkynes is one of the most fundamental organic reactions, and its regioselecitivity and reaction efficiency have been actively studied in many research groups.[7,14−17] We found that hydrochlorination of the terminal

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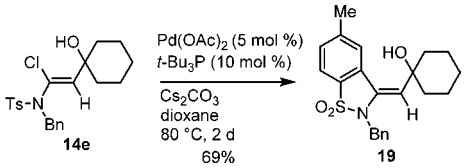
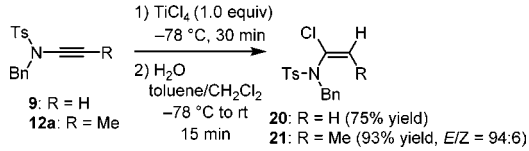
Scheme 4. Palladium-Catalyzed Intramolecular Direct Cyclization



ynamide **9** and the internal ynamide **12a** took place smoothly by treatment with $TiCl_4$, followed by addition of water (Scheme 5).[17] *E*-α-Chloroenamide **21** was formed predominantly from the internal ynamide **12a**. The stereochemistry of **21** was determined by X-ray crystallography.

Scheme 5. Hydrochlorination of Ynamides 9 and 12a



Reactions of ynamide **9** and $TiCl_4$ or $TiBr_4$ were monitored by ^{1}H NMR, and it was found that halotitanation[17] of ynamide **9** with $TiCl_4$ or $TiBr_4$ did not proceed at room temperature. The similar experimental result was reported for the reaction of phenylacetylene and $TiCl_4$.[10,18] Therefore, it was assumed that reactions of ynamides with carbonyl compounds or water proceeded in the presence of titanium tetrahalide. Titanium tetrachloride coordinated to the carbonyl oxgen atom and then ynamide attacked the activated carbonyl compounds. The chloride ion released from the $TiCl_4$–aldehyde complex reacted with the carbocation formed from the ynamide. In the case of terminal yanamide, the chloride ion rapidly reacted from the same face on which aldehyde reacted. On the other hand, more stabilized carbocations from internal ynamides **12a,b** reacted slowly with the chloride ion and nonstereoselectivity was observed.

In conclusion, internal and terminal *N*-alkyl ynsulfonamides react with aldehydes or ketones in the presence of $TiCl_4$ or $TiBr_4$ to give the corresponding α-halo-γ-hydroxyenesulfonamides. Hydrochlorination of ynamides also proceeds by treatment with $TiCl_4$ and H_2O to afford α-chloroenamides. Suzuki coupling of the thus-formed α-chloro-γ-hydroxyenamides was performed by using $Pd_2(dba)_3$ and *t*-Bu_3P. Intramolecular cyclization of α-chloroenamide to the *N*-tosyl group took place smoothly by C–H activation using $Pd(OAc)_2$ and *t*-Bu_3P. Therefore, the present method is useful for the synthesis of versatile α-halo-γ-hydroxyenamides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02526.

Crystallographic data (CIF, CIF)

Experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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