Mild Stereoselective Hydrohalogenation Leading to (*Z*)-Halopropenamides at Room Temperature

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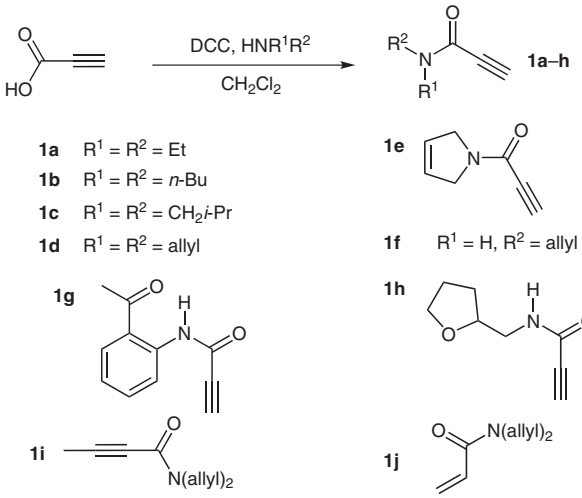
Abstract: Hydroiodination of 2-propynamides leading stereoselectively to (*Z*)-iodopropenamides was achieved under mild conditions at room temperature by the combined use of zinc iodide and *tert*-butyl iodide. Similarly, the use of zinc bromide in the presence of *tert*-butyl bromide enabled the synthesis of (*Z*)-bromopropenamides. (*Z*)-Halopropenoic esters were also prepared in high yields.

Key words: hydrohalogenation, (*Z*)-halopropenamides, (*Z*)-halopropenoic esters, *tert*-butyl halide, zinc halide

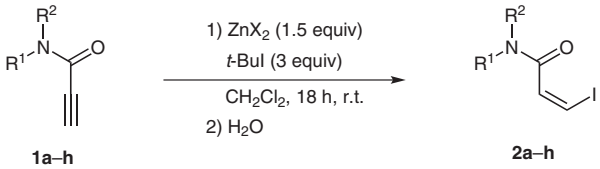
3-Iodo- and 3-bromopropenamides have proved to be valuable building blocks in organic synthesis. Owing to the presence of three functional groups, these compounds have been involved in several types of important organic reactions, including palladium-mediated coupling processes,[1] asymmetric Heck cyclization,[2] intramolecular Diels–Alder reactions,[3] copper-mediated C–N bond formation leading to enamides,[4] and polar cyclization leading to 4,5-dehydropiperidine-2,6-diones.[5]



Scheme 1

To the best of our knowledge, among the different ways[6] to obtain 3-iodo- or 3-bromopropenamides, only two methodologies are based on direct hydrohalogenation of 3-propynamides. The combined use of cerium salts, halotrimethylsilanes and sodium iodide affords a mixture of *Z*- and *E*-isomers.[7] Ma et al.[8] reported the stereospecific hydrohalogenation of 2-propynoic acid and its derivatives mediated by LiI in acetic acid at 90 °C.[9] It is noteworthy that tertiary 3-propynamides were transformed in the corresponding halo compounds in lower yields than primary and secondary ones.

Table 1 Hydroiodination of 3-Propynamide in the Presence of *tert*-Butyl Iodide and Zinc Halide



Entry	Substrate **1**	ZnX_2	Product **2**	Yield (%)
1	**1a**	$ZnBr_2$	**2a**	65
2	**1a**	$ZnCl_2$	**2a**	58
3	**1a**	ZnI_2	**2a**	63
4	**1a**	ZnI_2	**2a**	73 (in THF)
5	**1a**	ZnI_2	**2a**	97 (in MeCN)
6	**1c**	$ZnBr_2$	**2c**	94
7	**1c**	ZnI_2	**2c**	82
8	**1d**	ZnI_2	**2d**	87
9	**1d**	$ZnBr_2$	**2d**	81
10	**1b**	$ZnBr_2$	**2b**	91
11	**1e**	ZnI_2	**2e**	46
12	**1f**	ZnI_2	**2f**	93
13	**1g**	ZnI_2	**2g**	78
14	**1h**	ZnI_2	**2h**	91

During the course of our studies on the use of diethylzinc as mediator in atom-transfer radical addition–cyclization reaction leading to α-alkylidene-γ-lactams,[10] we found out by accident that the couple ZnX_2/*t*-BuX (X = Br, I) could be used to perform the hydrohalogenation of 3-propynamides. We report in this letter the investigation of this mild and stereospecific methodology that leads to

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(*Z*)-3-iodo- and 3-bromopropenamides in high yields at room temperature.

Secondary and tertiary 3-propynamides **1a–h** were prepared by coupling propiolic acid and various amines with DCC (Scheme 1).

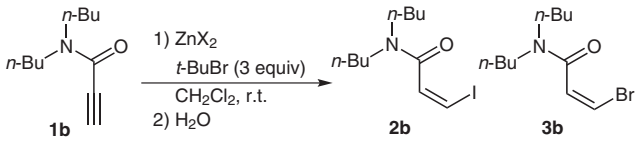
In the presence of 3 equivalents of *tert*-butyl iodide[11] and 1.5 equivalents of zinc halide in dichloromethane at room temperature, **1a** was selectively transformed into diethylamino-*(Z)*-3-iodopropenamide (Table 1, entries 1–3). The *E*-isomer was not detected. The reaction could be conducted also in THF or acetonitrile (entries 4, 5). Conversely to alkynyl sulfoxides,[12] propynamides did not react with zinc halides in the absence of *tert*-butyl iodide at room temperature.[13] Good yields were obtained with secondary propynamides **1f–h** (entries 12–14) and tertiary propynamides **1a–d**[14] (entries 5–10). The reaction of **1e** with ZnI_2/*t*-BuI gave the expected product in lower yield (entry 11), but the stereoselectivity was still high (no trace of *E*-isomer was detected in ^{1}H NMR spectrum of the crude reaction mixture).

The reaction is compatible with functional groups like carbon–carbon double bonds (entries 8, 11, 12), ketones (entry 13), ethers (entry 14), and also propargylic and benzylic esters (Scheme 5). Acetals were degraded under these experimental conditions.

The procedure is chemoselective. Whereas disubstituted alkynamide **1i** or *N*,*N*-diallylacrylamide **1j** (Scheme 1) led to the corresponding iodides under Ma's conditions at 90 °C, these substrates were found to be unreactive under our experimental conditions at room temperature. Refluxing in acetonitrile was necessary in order to convert them into the expected iodides.

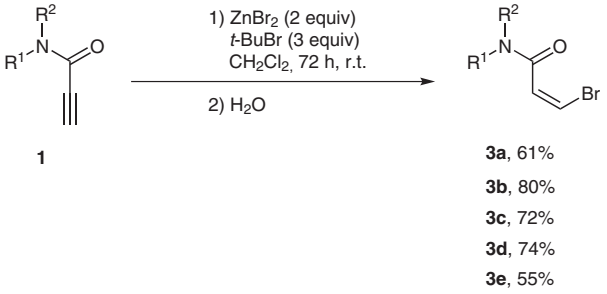
Other Lewis acids were tested in the presence of *tert*-butyl iodide and **1a**. No reaction occurred when using $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$, or $Yb(OTf)_3$.

3-Bromopropenamides were prepared by replacing *tert*-butyl iodide with *tert*-butyl bromide (Scheme 2). In the presence of 2 equivalents of zinc iodide the only product was vinylic iodide **2b**. No trace of the desired bromide was detected. Moving to zinc bromide enabled the synthesis of **3b** in 80% yield. However, the reaction was slower and 72 hours were needed to reach completion at room temperature.



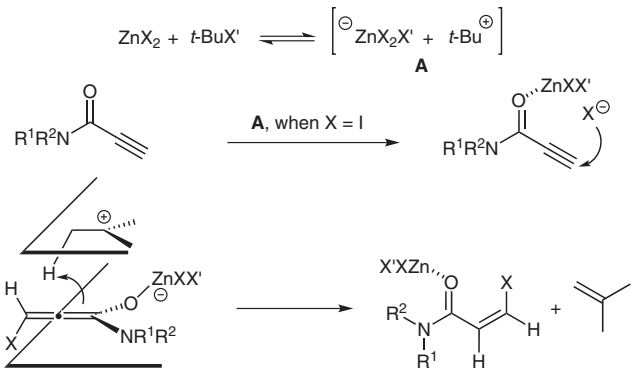
Scheme 2 Hydroiodination vs. hydrobromination in the presence of *tert*-butyl bromide depending on the nature of the zinc halide

As reported in Scheme 3, stereoselective hydrobromination of 3-propynamides **1a–e** could be achieved by mixing the substrate with 3 equivalents of *tert*-butyl bromide and 2 equivalents of zinc bromide at room temperature for 3 days.



Scheme 3 Hydrobromination in the presence of *tert*-butyl bromide and zinc bromide

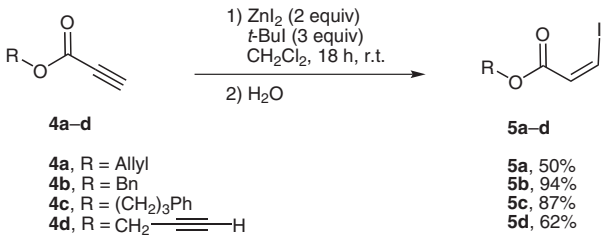
Owing to the previously noted functional groups compatibility, the reaction does not involve in situ formation of HX. It is likely to involve the reversible formation of a loose ion pair via heterolysis of the carbon–halogen bond (Scheme 4). The anionic zinc species delivers the most nucleophilic halide that undergoes conjugate addition to the activated substrate. *tert*-Butyl cation protonates the intermediate allenoate.[15] Approach of *tert*-butyl cation from the less hindered face of the double bond explains the selective formation of the (*Z*)-vinylic iodide.



Scheme 4 Proposed mechanism

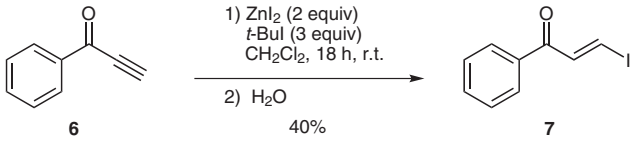
Quenching the reaction with D_2O led to no incorporation of deuterium. Two olefinic protons were characterized in the ^{1}H NMR spectrum,[16] which implied that water was not the proton donor.

The methodology was also suitable to convert 3-propynoic esters into 3-iodopropenoates (Scheme 5). Allylic, benzylic, and propiolic esters could be used without decomposition or degradation of the substrate. Zinc iodide turned out to be the best candidate in this case.[17] It was noted that no trace of the diiodo compound, observed under Ma's conditions (i.e., LiI/AcOH-mediated hydroiodination)[8a] was detected.



Scheme 5 Hydroiodination of propiolic esters

Finally, 1-phenylprop-2-yn-1-one was tested as substrate (Scheme 6). In this case the reaction led exclusively to the *E*-isomer. However, the yield was rather low. It is known from previous work that in this case the *Z*-isomer is slowly converted into the *E*-isomer on standing at 35 °C.[8b]



Scheme 6 Hydroiodination of 1-phenylprop-2-yn-1-one

In conclusion, we have shown that the couple zinc halide and *tert*-butyl halide could be used to prepare stereoselectively (*Z*)-halopropenamides under very mild conditions. High yields were obtained at room temperature whatever the substitution of the amide. This mild methodology, also suitable to prepare 3-halopropenoates, offers an alternative to the most commonly used procedures.

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(9) The reactions were generally performed at 90 °C over 22–48 h. At 70 °C lower yields were obtained (see ref. 8b).

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(11) Using only 2 equivalents of *tert*-butyl iodide led to lower yields.

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(13) This might be correlated to the relative basicity of amides and sulfoxides.

(14) **(*Z*)-*N*,*N*-Diallyl-3-iodoacrylamide(2d); Typical Procedure**
To a solution of *N*,*N*-diallyl-3-propynamide (50 mg, 0.335 mmol) in CH_2Cl_2 (1.7 mL) were added *t*-BuI (200 μL, 1.67 mmol, 3 equiv) and ZnI_2 (214 mg, 0.67 mmol, 2 equiv) at r.t. After 18 h, H_2O (5 mL) was added, and the reaction mixture was extracted twice with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtered, and concentrated under reduce pressure. Flash chromatography on SiO_2 (100% pentane then 100% Et_2O) afforded **2d** (81 mg, 0.293 mmol, 87%). ^1H NMR (300 MHz): δ = 3.85 (br d, *J* = 5.1 Hz, 2 H), 4.05 (br d, *J* = 5.9 Hz, 2 H), 5.11–5.28 (m, 4 H), 5.68–5.89 (m, 2 H), 6.85 (d, *J* = 8.8 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 1 H). ^{13}C NMR (75 MHz): δ = 47.4 (CH_2), 49.9 (CH_2), 87.6 (=CHI), 117.9 (=CH_2), 118.4 (=CH_2), 132.9 (=CH), 133.1 (=CH), 134.5 (=CH), 167.1 (C=O). HRMS: *m/z* calcd for $C_9H_{12}NOI$ $[MH]^+$: 278.0036; found: 278.0035.

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(16) Owing to complexation of the product to zinc salts, the olefinic protons are more deshielded in the crude reaction mixture – before aqueous treatment – than in the pure isolated product **2d** (δ = 7.0 ppm and 7.4 ppm with a coupling constant equal to 9.1 Hz: 6.85 ppm and 7.10 ppm with a coupling constant equal to 8.8 Hz, respectively).

(17) Using zinc bromide led to degradation of benzylic and propargylic esters.