

Hydrohalogenation reaction of electron-deficient allenes*

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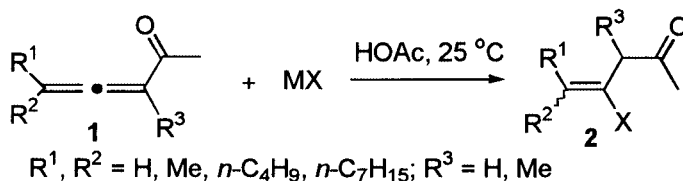
Abstract: The hydrohalogenation reactions of electron-deficient allenes, such as 1,2-allenyl ketones, carboxylic acids, esters, amides, nitriles, sulfoxides, sulfones, and phosphine oxides with MX in HOAc, CF₃COOH–HOAc, CF₃COOH or AlCl₃/H₂O, afforded β-halo-β,γ-unsaturated functionalized alkenes. The regioselectivity of the reaction could be controlled by the reaction conditions.

INTRODUCTION

β-Halo-β,γ-unsaturated functionalized alkenes are classes of compounds with synthetic importance due to the uniquely located carbon–carbon double bonds. During the course of our study of allene chemistry [1], we rationalized from the retrosynthetic analysis that the hydrohalogenation reaction of electron-deficient allenes would be one of the most efficient ways for the synthesis of β-halogen-substituted β,γ-unsaturated products. Since the hydrohalogenation of electron-deficient alkynes afforded α,β-unsaturated functionalized alkenes [2], a challenge encountered here would be the potential migration of the C=C bond from the β,γ-position to the α,β-position, thus affording a synthetically useless mixture of β,γ-unsaturated products and α,β-unsaturated products [3].

HYDROHALOGENATION REACTION OF 1,2-ALLENYL KETONES

The reaction of 3,4-pentadien-2-one with MX (M = Na, Li, X = I, Br, Cl) in acetic acid at 25 °C afforded the corresponding 4-halo-4-penten-2-one with yields ranging from 69 to 82% [4]. Under different reaction conditions, the reaction of 3,4-pentadien-2-one with LiI or NaI afforded a different ratio of β,γ-unsaturated enone/α,β-unsaturated enone. The best results were obtained using MI (M = Na, Li), HOAc (3 N) in tetrahydrofuran (THF) at 0 °C, and the ratio of β,γ-unsaturated enone/α,β-unsaturated enone is 98:2 (Scheme 1) [5].



Scheme 1

The hydroiodination and hydrobromination reactions of 3-alkyl-1,2-allenyl ketones with MX in HOAc at 25 °C yielded *Z*-isomer in high yield (75–93%) with fairly good stereoselectivity (*Z*:*E* > 95:5), although the corresponding hydrochlorination reaction afforded the products *E*-isomer and *Z*-isomer

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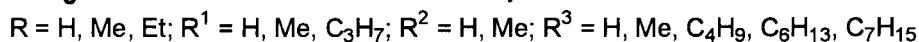
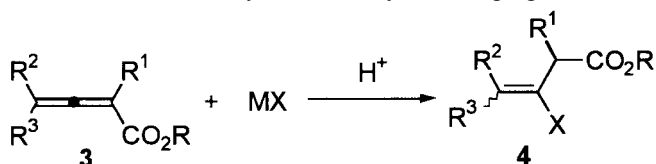
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with *E*-isomer predominating. Hydrohalogenation reaction of 3,3-dimethyl-substituted 1,2-allenyl methyl ketone with MX in acetic acid at 25 °C also went smoothly to afford 4-halo-5-methyl-4-hexen-2-ones in high yields (89–96%). The formation of α,β -unsaturated β -haloenones was not observed [5].

Hydrohalogenation reaction of 1-methyl-1,2-allenyl ketones with NaI in HOAc afforded a mixture of β,γ -unsaturated β -iodoenone and α,β -unsaturated β -iodoenone. However, the reaction in a 1:1 mixture of CF₃COOH and HOAc could afford the β,γ -unsaturated β -iodoenone highly selectively. Under these conditions, 3-alkyl-3,4-pentadien-2-one reacted smoothly with MX to afford the corresponding 4-halo-3-alkyl-4-penten-2-ones in high yields (70–99%) with high selectivity over the α,β -unsaturated enones (> 93:7) [5].

HYDROHALOGENATION REACTION OF 1,2-DIENYL CARBOXYLIC ACIDS AND ESTERS

Reaction of 2,3-butadienoic acid/methyl ester with MX in HOAc at 70 °C afforded the corresponding 3-halo-3-butadienoic acid/methyl ester with yields ranging from 56–92% (Scheme 2) [4].

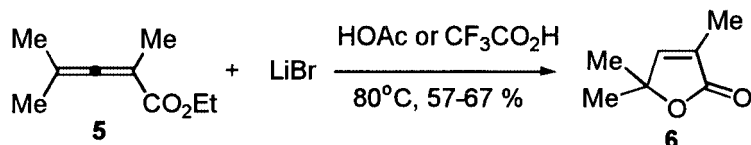


Scheme 2

Hydroiodination reaction of 4-alkyl-substituted 2,3-butadienoic acid with NaI in HOAc at reflux afforded *Z*-isomer of 3-halo-3-alkenoic acid with fairly good stereoselectivity. The corresponding reaction with LiBr·H₂O or LiCl·H₂O afforded a mixture of the products *Z*-isomer and *E*-isomer with lower selectivity. The hydrohalogenation reaction of 2-methyl-2,3-butadienoic acid with MX in CF₃CO₂H afforded the corresponding products with yields from 54–72% (Scheme 3) [6].

The reaction of ethyl 4-alkyl-substituted 2,3-butadienoate with MX in HOAc or CF₃CO₂H went smoothly and afforded the corresponding ethyl 3-halo-3-alkenoate in high yields (82–99%), but the stereoselectivity is not high. Hydrohalogenation reaction of ethyl 2-alkyl-2,3-butadienoate with MX in HOAc afforded a mixture of 2-enoates and 3-enoates in low yields and selectivity slowly. However, when a 1:1 mixture of CF₃CO₂H and HOAc or CF₃CO₂H alone was used as the reaction medium, the hydrohalogenation went smoothly to afford ethyl 3-halo-2-methyl-3-butenates in fairly good yields, and the formation of 2-enoates was not observed. The reaction in CF₃CO₂H was much more efficient than that in CF₃CO₂H–HOAc (1:1) [7].

The reaction of trisubstituted allenates also went smoothly to afford the corresponding products. However, when fully substituted 2,3-dienoate **5** was treated with MX in HOAc, direct cyclization affording butenolide **6** was the only reaction observed [6].

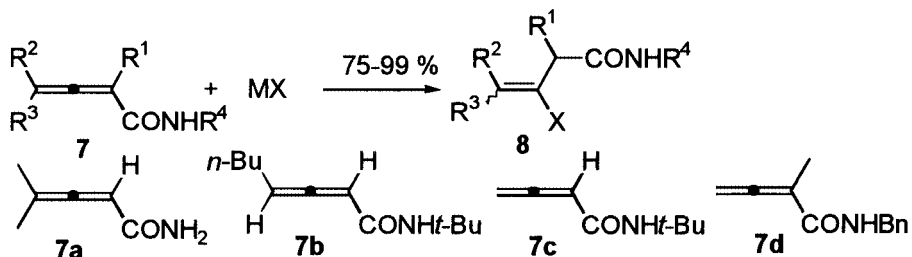


Scheme 3

HYDROHALOGENATION REACTION OF 2,3-DIENAMIDES

Hydrohalogenation reaction of 4-methyl-2,3-pentadienamides **7a**, 2,3-butadienamides **7c**, or 2-methyl-2,3-butadienamides **7d** with MX in HOAc or CF₃CO₂H afforded the corresponding 3-halo-3-enamide

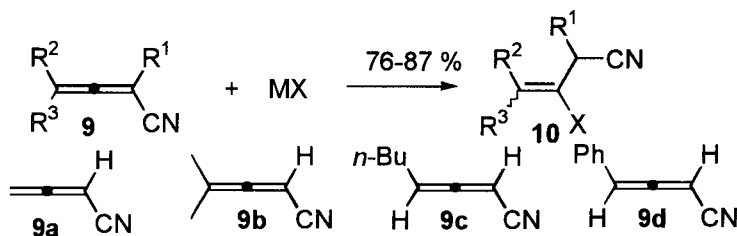
with yields ranging from 75 to 99%. Hydrohalogenation reaction of 2,3-octadienamide **7b** with MX in HOAc or CF₃CO₂H afforded the corresponding 3-halo-3-octenamamide in high yields with low stereoselectivity. But both the *Z*- and *E*-isomers can be separated easily by chromatography on silica gel, providing simple access to both isomers (Scheme 4).



Scheme 4

HYDROHALOGENATION REACTION OF 2,3-DIENENITRILES

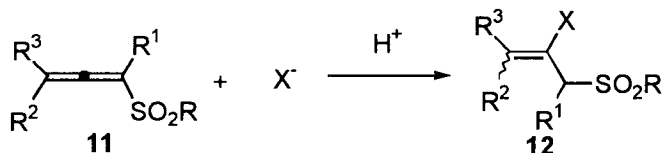
Hydrohalogenation of 2,3-butadienenitrile **9a** with MX in HOAc afforded the corresponding 3-halo-3-butenenitriles with yields ranging from 78 to 87%. However, the hydrohalogenation of 4-methyl-2,3-pentadienenitrile **9b** with MX in HOAc afforded the corresponding 3-halo-4-methyl-3-pentenenitrile in low yield (18–37%). When a 1:1 mixture of CF₃CO₂H and HOAc was used as the reaction medium, the hydrohalogenation went smoothly to afford 3-halo-4-methyl-3-pentenenitrile in fairly good yields (76–80%) and excellent selectivity. The corresponding reactions with 2,3-octadienenitrile **9c** or 4-phenylbutadienenitrile **9d** also went smoothly to afford 4-substituted 3-halo-3-butenenitriles with yields ranging from 37–82% (Scheme 5) [6].



Scheme 5

HYDROHALOGENATION REACTION OF 1,2-ALLENIC SULFONES

Three sets of reaction conditions A, B, and C were established to carry out the hydrohalogenation reactions of 1,2-allenic sulfones **11** with metallic halides (Scheme 6) [8].



R = CH₃, Ph; R¹, R², R³ = H, Me

Conditions A: MX (M = Na or Li), HOAc (solvent).

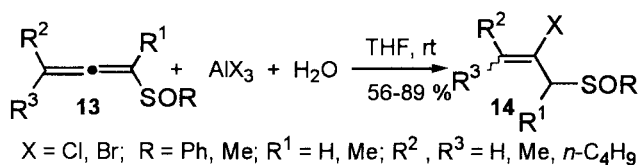
Conditions B: MX (M = Na or Li), HOAc (1 equiv), CH₃CN (solvent).

Conditions C: HX (as the solvent and the reagent).

Scheme 6

HYDROHALOGENATION REACTION OF 1,2-ALLENIC SULFOXIDES

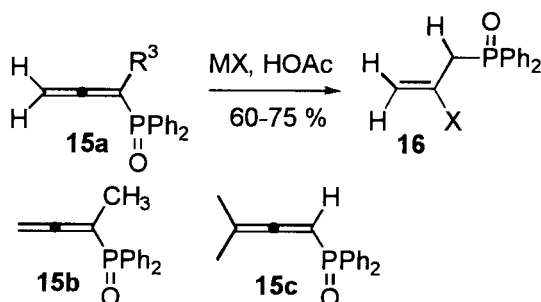
Hydrohalogenation reactions of 1,2-allenic sulfoxides with MX in HOAc failed to provide the expected 2-haloallylic sulfoxides. AlCl₃ was found to show obvious activity, and a certain amount of water promoted this reaction. The ratio of AlCl₃ and H₂O has influence on the speed of this conversion, and the best result is 0.55 equiv of AlCl₃ and 1 equiv of water. Under the standard reaction conditions, hydrohalogenation reactions of 1,2-allenic sulfoxides with AlBr₃ or AlCl₃ afforded the corresponding 2-haloallylic sulfoxides in yields ranging from 56 to 89%. The reaction with AlBr₃ was less efficient than the hydrochlorination reaction with AlCl₃. Hydroiodination can be realized by using a combination of AlCl₃ and NaI. When 4 equiv of NaI and 0.55 equiv of AlCl₃ were used, we did not observe the formation of any hydrochlorination product (Scheme 7) [9].



Scheme 7

HYDROHALOGENATION REACTION OF 1,2-ALLENYL DIPHENYL PHOSPHINE OXIDES

Hydrohalogenation reactions of propadienyl diphenyl phosphine oxide **15a** with MX (M = Na, Li, X = Cl, Br, I) in HOAc afforded 2-halo-2-propenyl diphenyl phosphine oxides in high yields, ranging from 58 to 75%, while the reaction with aqueous HX afforded the products in low yields (31–46%). However, in cases of **15b** and **15c**, the reactivities toward MX in HOAc were low (Scheme 8) [8].



Scheme 8

In conclusion, we have developed a convenient method for the synthesis of β -halo- β,γ -unsaturated functionalized alkenes, such as β -halo- β,γ -unsaturated ketones, carboxylic acids, esters, amides, nitriles, sulfoxides, sulfones, and phosphine oxides. In most cases, the yields are high; the regio- and stereo-selectivities depend on the reaction temperature and the solvent used.

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