Stereoselective hydrohalogenation of alkynoic acids and their esters in ionic liquids

José Salazar*, Francys Fernández, Jelem Restrepo and Simón E. López

Departamento de Química, Universidad Simón Bolívar, Valle de Sartenejas, Baruta, Caracas 1080-A, Apartado 89000, Venezuela

A novel procedure is described for the hydrohalogenation of alkynoic acids and their esters using *N*-alkylpyridinium ionic liquids. Hydrohalogenating agents were prepared by mixing *N*-alkylpyridinium halides with an equimolar amount of trifluoroacetic acid. The corresponding halogenated alkenes were obtained in good yields with high diastereoselectivity.

Keywords: hydrohalogenation, ionic liquids, alkynoic acids, *N*-alkylpyridinium

1-Functionalised 3-haloalk-2-enes are important classes of compounds for organic synthesis. For example, 3-halopropenoic acids and their derivatives have proved to be valuable intermediates owing to the presence of three functional groups, *i.e.*, the carbonyl group, the conjugated carbon–carbon double bond, and the C–X bond.[1] Due to the great attention to transition-metal-catalysed sp^2–sp^2 or sp–sp^2 carbon–carbon bond formation during the last 25 years, this type of compound is of vital importance as they are in widespread use as starting materials for such reactions. Palladium-catalysed cross coupling of vinyl bromides or iodides[2] with vinyl or acetylide organometallic reagents[3] permits the easy preparation of diene or enyne compounds which are important synthetic intermediates[4] and their structural features are present in numerous natural products.[5]

Among the most important preparation procedures for the synthesis of functionalised 3-haloalk-2-enes is the hydrohalogenation of alkynes. Several methods have been published for this reaction. These include: the preparation of 2-bromoalk-1-enes starting from terminal alkynes by reaction with a dichloromethane solution of hydrogen bromide in tetraethylammonium bromide;[6] hydrobromination or hydroiodination of terminal alkynes using hydrogen bromide or acetyl iodide and alumina;[7] employing a BI_3-*N,N*-diethylaniline complex in acetic acid;[8] forming vinyl iodides from terminal alkynes using a mixture of iodine, triethylsilane and $CuO.HBF_4$ in dichloromethane at low temperature;[9] the use of sodium iodide and trimethylsilane chloride in water for the stereoselective preparation of alkenyl iodides;[10] the formation of *E/Z* mixtures of 3-halopropeanoate esters from the corresponding 2-propiolates and aqueous mixtures of HI or HBr;[11] stereospecific reaction of 2-propiolate esters or propynoic acids with lithium halides in acetic acid yielding the corresponding (*Z*)-3-halopropenoates or (*Z*)-3-halopropenoic acids;[12] *Z/E* mixtures of 3-halopropen-2-ones from 3-propyn-2-ones and lithium halides in acetic acid at room temperature;[12c] 3-chloroalkenoic acids, esters and amides from alk-2-ynoic acids by treatment with thionyl chloride or oxalyl chloride and dimethylformamide followed by quenching with water, alcohols or amines.[13,14] The above mentioned methodologies, however, suffer from some disadvantages such as the use of hazardous hydrogen halides, dangerous chlorinated reagents, volatile solvents and large work-up procedures; many of those problems should be avoided by the use of "green" systems, such as that exemplified by reactions performed in ionic liquids. A widespread interest in ionic liquids has emerged,[15] basically due to their unique properties, such as lack of measurable vapour pressure and good thermal stability, which make them a possibly environmentally benign alternative to volatile solvents. These properties have led to a variety of successful applications, ranging from industrial[16] to green chemistry.[17] Alkylpyridinium salts are well documented ionic liquids;[18] the combination of an alkylpyridinium bromide with bromine, for example, generates a useful-ionic liquid-brominating agent.[19] The latter is a good example of an ionic liquid which integrates the function of solvent and reagent. Trying to combine those useful advantages turned our attention to the development of a new hydrohalogenating methodology based on alkylpyridinium ionic liquids. The addition of trifluoroacetic acid to the corresponding alkylpyridinium halide generates HX-equivalent hydrohalogenating mixtures which were efficiently used as new solvent-reagent systems for the hydrohalogenation of different alkynoic acids and esters (see Table 1).[20] Good yields were obtained and only the corresponding *Z*-diastereoisomer was detected in all the studied cases. As can be seen, the method could be applied even for the hydrochlorination of an alkynoic ester (**2j**), a difficult task to achieve in high yield and stereoselectivity for most alkynes.[21] An *in situ* generation of the hydrohalogenating agent in the reaction avoids the preparation and transfer of hydrogen halide reagents, which are both highly hygroscopic and gaseous, and make the reaction difficult to handle and perform stoichiometrically.[21a] Many hydrohalogenation procedures still require an aqueous work-up, which generates environmentally toxic hydrogen halides, a task avoided in this new non-aqueous work-up methodology. Also, the procedure permits the easy preparation of deuterium-labelled compounds (**2b**, **2f**) if deuterated trifluoroacetic acid is employed.

In conclusion, this report represents a new, stereoselective and high-yielding methodology for the hydrohalogenation of alkynoic acids and their esters. The low cost of the hydrohalogenating mixtures, containing only simple alkylpyridinium ionic liquids and trifluoroacetic acid, make this an affordable, attractive and simple procedure for the hydrohalogenation of other organic compounds, a study which is ongoing in our research group and will be published elsewhere.

Experimental

Melting points were determined in a Fischer-Johns micro hot-stage apparatus and are uncorrected. NMR spectra were obtained on a JEOL Eclipse Plus spectrometer in deuterated chloroform, operating at 400 MHz (^1H, internal standard TMS). The IR spectra were recorded as liquid films using an FT-IR Nicolet Magna Spectrometer. Mass spectra (GC-MS) were recorded using a gas chromatograph Hewlet Packard 5890 Series I coupled to a mass detector (EI, 60 eV) Hewlett Packard 5917 A. Microanalyses of synthesised compounds were performed by Atlantic Microlab Inc. (Norcross, GA, USA); results fell in the range of ± 0.4% of the required theoretical values. Silica gel plates ALUGRAM® SIL G/UV254 (Macherey-Nagel GmbH & Co., Germany) were used for TLC testing. Reagents were obtained from Aldrich (Milwaukee, MI, USA) or Merck (Darmstadt, Germany) and used without further purification.

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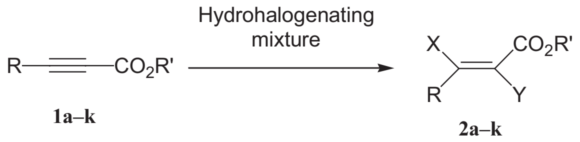
* Correspondent. E-mail: jsalazar@usb.ve

Table 1 Hydrohalogenation of alkynoic acids (esters) using different ionic liquid hydrohalogenating mixtures



Compound	R	R′	X	Y	Hydrohalogenating mixture (equiv)	Time/h	Temp/°C	Yield/%	Ref.*
2a	H	Et	Br	H	*n*BuPy$^+$Br$^-$/CF$_3$CO$_2$H (1)	4	70	77	12a
2b	H	Et	Br	D	*n*BuPy$^+$Br$^-$/CF$_3$CO$_2$D (1)	4	70	61	23
2c	Ph	Et	Br	H	*n*BuPy$^+$Br$^-$/CF$_3$CO$_2$H (3)	12	80	74	24
2d	CO$_2$Me	Me	Br	H	*n*BuPy$^+$Br$^-$/CF$_3$CO$_2$H (1)	4	60	85	25
2e	H	Et	I	H	*n*BuPy$^+$I$^-$/CF$_3$CO$_2$H (1)	8	25	68	12c
2f	H	Et	I	D	*n*BuPy$^+$I$^-$/CF$_3$CO$_2$D (1)	8	25	65	–
2g	Ph	Et	I	H	*n*BuPy$^+$I$^-$/CF$_3$CO$_2$H (3)	12	80	97	12e
2h	CO$_2$Me	Me	I	H	*n*BuPy$^+$I$^-$/CF$_3$CO$_2$H (1)	6	60	82	26
2i	CO$_2$H	H	I	H	*n*BuPy$^+$I$^-$/CF$_3$CO$_2$H(1)	6	60	76	26
2j	H	Et	Cl	H	*n*HexPy$^+$Cl$^-$/CF$_3$CO$_2$H (2)	12	60	85	12a
2k	CH$_3$	H	I	H	*n*BuPyr$^+$I$^-$/CF$_3$CO$_2$H(1.5)	12	60	80	27

^{a}Compounds were isolated in pure isomeric form after work-up. Their physical and spectroscopical data were identical with those reported in the references given.

Procedure for the preparation of hydrohalogenating mixtures: The *N*-alkylpyridinium salt[22] (ionic liquid, 8 mmol) was gently warmed until it melted and was then mixed thoroughly with trifluoroacetic or deuterated trifluoroacetic acid (8 mmol). The mixture was vigarously stirred until one phase was formed and then cooled to room temperature.

Procedure for the hydrohalogenation of alkynoic acids and their esters: The alkynoic acid or ester (1 mmol) was mixed with the hydrohalogenating mixture and stirred at the indicated ratios, temperatures and times (see Table 1). The reaction mixture was then cooled to room temperature, extracted with diethyl ether (3 × 10 ml), the extract passed through a silica-gel-charcoal column and the solvent evaporated to give the corresponding compound (**2a–k**). Spectroscopic and physical data corresponded to reported compounds (see Table 1).

Typical examples

Ethyl Z-3-bromopropenoate (**2a**): Colourless oil. Yield: 77%; IR (cm^{-1}): 1730; ^{1}H NMR: δ 6.93 (d, 1H, $J = 8.4$ Hz, CH), 6.55 (d, 1H, $J = 8.4$ Hz, CH), 4.16 (q, 2H, $J = 7.0$ Hz, CH$_2$), 1.24 (t, 3H, $J = 7.0$ Hz, CH$_3$); ^{13}C NMR: δ 163.9, 124.5, 122.0, 60.7, 14.1. MS: *m/z* 150 and 152 (1 : 1, [M–29]$^+$).

Ethyl Z-3-iodo-2-deuteriopropenoate (**2f**): Colourless oil. Yield: 65%; IR (cm^{-1}): 1735; ^{1}H NMR: δ 7.39 (s, 1H CH), 4.16 (q, 2H, $J = 7.3$ Hz, CH$_2$), 1.25 (t, 3H, $J = 7.3$ Hz, CH$_3$); ^{13}C NMR: δ 164.5, 129.9 (t, 1C, $J = 26.4$ Hz, CD), 94.9, 60.8, 14.3 Anal. Calcd. for $C_5H_6DIO_2$: C 26.45%, H 3.10%; found: C 26.6%, H 3.2%.

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