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SIMPLE ONE-POT PREPARATION OF SOME HIGHLY ELECTROPHILIC HALOACETYLENES

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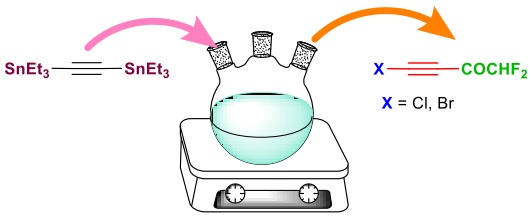
Abstract

Preparation of some *bis*(trialkylstannyl)acetylenes from the corresponding trialkylstannyl chlorides was improved. The tin reagents interact with reactive acid chlorides and bromides to afford intermediate 1-acyl-2-trialkylstannylacetylenes in quantitative yields. The subsequent halogenation performed as a one-pot procedure gives the target 1-acyl-2-haloacetylenes in high yields and provides an effective recycling of the expensive starting trialkylstannyl chlorides.



Key words: *bis*(trialkylstannyl)acetylenes, acid chlorides, one-pot halogenation, trialkylstannyl chlorides, recycling.

Introduction

The chemistry of alkynes is one of the most interesting and rapidly growing fields of organic synthesis [1–4]. Among acetylenes, the halogenated alkynes are of particular importance owing to their wide range of transformations and, therefore, high synthetic potential [5]. They are frequently used in a variety of electrophilic alkynylations [6], the Diels–Alder cycloaddition [7], and cross-coupling reactions [8]. Snider *et al*. [9] described [2+2]-cycloaddition of methyl chloropropiolate with alkenes catalyzed by $EtAlCl_2$. Previously we have investigated the synthesis of haloalkynes activated by extremely strong trifluoroacetyl, ethyl oxalyl and polyfluorinated alkyl oxalyl electron-withdrawing groups [10–12]. Apart from the possibility to enter the Diels–Alder reaction, these alkynes possess a unique ability to form [2+2]-cycloadducts with simple alkenes under mild conditions. The resulting cyclobutenes contain a *β*-haloenone core and represent versatile reagents for heterocyclizations [13–15]. Currently, there are numerous approaches for the preparation of haloalkynes [5] but the only known route for the synthesis of such enormously electrophilic alkynes **C** always includes three stages starting from trimethyltin chloride, which initially is converted into *bis*(trimethylstannyl)acetylene **A** [10–12]. The last one is acylated with one of the reactive acid chlorides or anhydrides to afford stannylated alkynones **B**, which, in turn, are subjected to the halogenation to form target haloalkynes **C** (Fig. 1).

The most significant drawback of this approach is a mandatory use of two equivalents of an expensive trimethyltin chloride, which cannot be recycled and is irretrievably lost. Moreover, products **B** containing an oxalic core may partly decompose under vacuum distillation that sharply decreases the yields and purity of the target compounds.

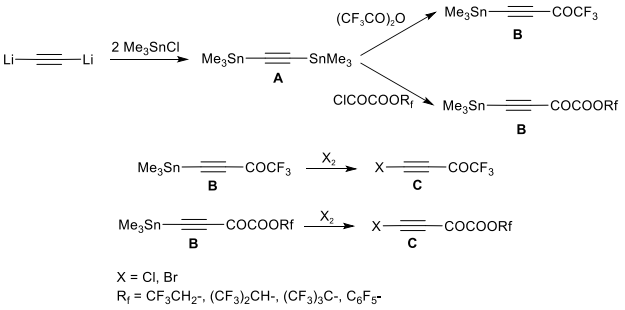
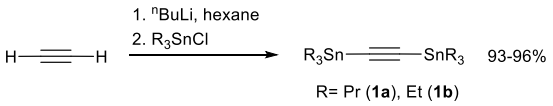


Figure 1. Previously described synthesis of highly electrophilic haloalkynes [8–10].

Herein, we describe the short preparative synthesis of some highly electrophilic acetylenes and recycling of the expensive staring materials in very high yields. Moreover, the protocol developed allows one to avoid the separation of unstable intermediates and significantly enhances the availability of the valuable target alkynes.

Results and discussion

At first, the preparation of *bis*(tripropylstannyl)acetylene **1a** and *bis*(triethylstannyl)acetylene **1b** from tripropyltin or triethyltin chloride, acetylene, and butyllithium was significantly improved. It was found that the reaction in hexane facilitates simplified isolation of target products **1a**,**b** and increases their yields up to almost quantitative ones (Scheme 1). It should be noted that **1a**,**b** are more stable upon storage and are much easier to handle, comparing with compound **A**. Earlier these compounds were obtained by different approaches in moderate yields [16].



Scheme 1. Improved synthesis of *bis*(trialkylstannyl)acetylenes.

Next, the interaction of **1a** with polyfluorinated alkyl oxalyl chlorides or methyl oxalyl chloride has been thoroughly explored. It was stated that the reaction proceeds smoothly at 25 °C and is completed within 24 h in the case of the polyfluorinated derivatives or 72 h for methyl oxalyl chloride. According to the ^{13}C NMR spectroscopic data, after this period, the conversion of **1a** reaches 100% and the only products of these transformations are monoacylated alkynes **2a**–**d** and tripropyltin chloride whereas *bis*-acylated alkynes are not formed even in trace amounts (Scheme 2).

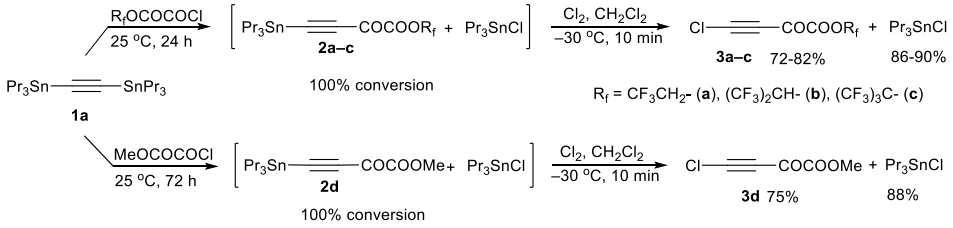
Since the acylation of **1a** with reactive acid chlorides is a very clear reaction, we decided to perform the chlorination of intermediate monoacylated alkynes **2a**–**d** as a one-pot process without their isolation. It turned out that the chlorination proceeds very quickly even at –35 °C to form target alkynes **3a**–**d** in good yields (Scheme 2, protocol A). Another important feature of these transformations is an effective recycling of valuable Pr_3SnCl which is formed at both stages of the conversion. After two consecutive distillations, 90% of starting Pr_3SnCl was recovered and used again for the preparation of alkyne **1a**.

Compound **1b** also reacts easily with polyfluorinated alkyl oxalyl chlorides and methyl oxalyl chloride; however, it is not recommended to use it for the synthesis of haloalkynes **3a**–**d** due to the proximity of boiling points of **3a**–**d** and Et_3SnCl, which hinders their separation and sharply decreases the yields of the target products.

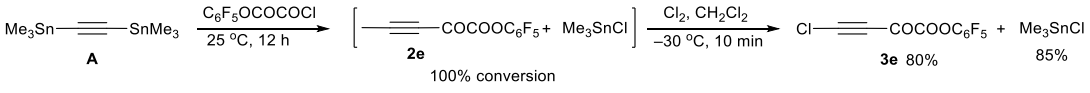
Pentafluorophenyl ester of 4-chloro-2-oxobut-3-ynoic acid **3f** was synthesized similarly, starting from compound **A** instead of **1a** since Me_3SnCl, forming at both stages of the transformation, can be separated from target product **3f** by distillation much more easily than Pr_3SnCl. Importantly, the recycling of Me_3SnCl in this case was also quite successful (Scheme 3, protocol B).

Interestingly, the chlorination of **2a**–**e** does not require a precise dosage of chlorine. Usually we used 20–40% excess of Cl_2; however, in one of the experiments almost a double excess of chlorine was introduced due to inaccurate calculation, and this surprisingly did not affect the yield of the target product. When the reaction mixture was allowed to heat up to the ambient temperature, the evolution of HCl was observed. Therefore, the excess of chlorine is consumed in the chlorination of CH_2Cl_2 at the temperatures above 0 °C and does not react with a C≡C bond of **3a**–**e** and R_3SnCl (R = Pr, Me).

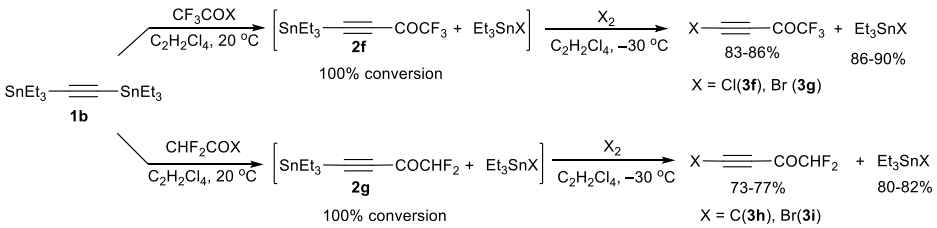
Moreover, it was found that the reactions of **1b** with trifluoro- and difluoroacetic acid chlorides and bromides proceed clearly and rapidly at 20 °C, resulting in intermediate stannylated alkynones **2f**,**g**. The latter were further halogenated directly after the acylation completion in a one-pot procedure to afford halogenated trifluoroacetyl acetylenes **3f**,**g** and previously unknown difluoroacetyl acetylenes **3h**,**i** in good yields (Scheme 4, protocol B). Interestingly, compound **1a** gives noticeably worse results in these processes. Since target products **3f**–**i** have relatively low boiling points, symmetric tetrachloroethane proved to be the solvent of choice for this transformation. Its boiling point (146 °C) allowed us to isolate easily **3f**–**i** and to recover E_3SnCl (bp: 207 °C) in high yields. Obviously, the acylation of **1a** with acid chlorides requires the further chlorination of intermediates **2**, whereas the use of acid bromides requires the further bromination.



Scheme 2, protocol A. One-pot preparation of polyfluorinated and methyl esters of 4-chloro-2-oxobut-3-ynoic acid. An effective recycling of tripropyltin chloride.



Scheme 3, protocol B. One-pot preparation of pentafluorophenyl ester of 4-chloro-2-oxobut-3-ynoic acid. An effective recycling of trimethylin chloride.



Scheme 4, protocol C. One-pot preparation of halogenated trifluoroacetyl- and difluoroacetyl acetylenes. An effective recycling of triethyltin chloride and bromide.

Therefore, the developed methods (one-pot protocols A, B, and C) significantly improve the preparation of highly electrophilic haloalkynes previously described by us and some new representatives of these derivatives. Importantly, this new approach allows for effective recycling of the expensive starting materials (Pr_3SnCl, Et_3SnCl, Me_3SnCl) and their subsequent use in the same sequence of transformations.

Experimental section

General remarks

The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AMX 400 spectrometer at 400, 100, 376.5 MHz, respectively. The chemical shifts are reported in ppm relative to TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F). The IR spectra were registered on a Bruker IFS 25 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Trialkyltin chlorides were prepared by heating the corresponding tetraalkyltins with $SnCl_4$ [17]. Polyfluorinated alkyl oxalyl chlorides [12], trifluoroacetyl chloride [18], trifluoroacetyl bromide [18], difluoroacetyl chloride [18], difluoroacetyl bromide [19], and *bis*(trimethylstannyl)acetylene [11] were synthesized according to the previously described methods. Methyl oxalyl chloride was purchased from Sigma Aldrich. All manipulations with *bis*(trialkylstannyl)acetylenes were carried out in an argon atmosphere, though the contact with air within several seconds is not critical. Dichloromethane and tetrachloroethane were distilled prior to use over P_2O_5. The chlorine gas was dried by passing through concentrated H_2SO_4 and condensed in a measuring test tube cooled with dry ice.

Syntheses

Bis(tripropylstannyl)acetylene (1a) and bis(triethylstannyl)acetylene (1b). To a vigorously stirred solution of BuLi (1.0 N, 0.80 mol) in hexane (800 mL) at –35 °C, a strong stream of acetylene was introduced until the absorption of the gas has stopped (detected with a gas counter at the system output). The reaction mixture was refluxed for 1 h and then cooled to 0 °C. A solution of tripropyltin chloride or triethyltin chloride (0.85 mol) in hexane (200 mL) was added in one portion to the stirred suspension of lithium acetylide. The mixture was refluxed and stirred additionally for 1 h and then left under an argon atmosphere at 20 °C overnight. The most part of the clear solution was decanted from lithium chloride; the precipitate was diluted with hexane and filtered off. The combined hexane solution was concentrated, and the residue obtained was distilled under vacuum to afford 193.14 g (93%) of **1a** as a mobile colorless liquid. Bp: 152–153 °C (0.4 Torr), lit. [14] 136–137 °C (0.1 Torr), 181–187 °C (1.5 Torr). A similar procedure afforded 167.12 g (96%) of **1b** as a mobile colorless liquid. Bp: 120–121 °C (0.4 Torr), lit. [14] 114–115 °C (0.18 Torr), 131–134 °C (1.5 Torr). The ^1H and ^{13}C NMR spectroscopic data of **1a,b** were in accordance with those described earlier [14].

One-pot general preparation of haloalkynes 3a–d (protocol A, Scheme 2). Alkyne **1a** (51.92 g, 0.10 mol) was mixed with the corresponding polyfluorinated alkyl oxalyl chloride $R_fOCOCOCl$ (0.12 mol) or methyl oxalyl chloride (0.20 mol) (Scheme 2), and the reaction mixture was left under an argon atmosphere at 25 °C for 24 h (in the case of **3a**–**c**) or 96 h (in the case of **3d**). The excess of acid chloride was removed under vacuum. The dark residue obtained was diluted with CH_2Cl_2 (120 mL). The stirred resulting solution was cooled to –35 °C, and the chlorine gas was gradually passed into it through a cannula from a measuring test tube containing 8.50–10.00 g (0.12–0.15 mol, 5.50–6.50 mL) of cooled liquid chlorine. The gas passing was controlled (occasional cooling of the tube) in such a rate to maintain the temperature of the reaction mixture below –25 °C. The solvent was removed under vacuum. The residue obtained was fractionated on a Vigreux column, collecting two wide-range fractions 50–70 °C (10 Torr) and 115–130 °C (10 Torr). Each of these fractions was repeatedly distilled to afford haloalkynes **3a**–**d** and recover pure Pr_3SnCl, 48.69–50.96 g (86–90%). Bp: 118–120 °C (10 Torr). The boiling points and spectroscopic data of **3a**–**c** were in good agreement with the literature data [10].

4-Chloro-2-oxo-but-3-ynoic acid 2,2,2-trifluoro-ethyl ester 3a. Colorless liquid, yield: 16.52 g (77%). Bp: 62–63 °C (10 Torr).

4-Chloro-2-oxo-but-3-ynoic acid 2,2,2-trifluoro-1-trifluoromethyl-ethyl ester 3b. Colorless liquid, yield: 23.17 g (82%). Bp: 51–52 °C (10 Torr).

4-Chloro-2-oxo-but-3-ynoic acid 2,2,2-trifluoro-1,1-bis-trifluoromethyl-ethyl ester 3c. Colorless liquid, yield: 28.04 g (80%). Bp: 58–60 °C (10 Torr).

Methyl-4-chloro-2-oxobut-3-ynoate 3d. Colorless liquid, yield: 10.99 g (75%). Bp: 56–57 °C (10 Torr). ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H, CH_3O). ^{13}C NMR ($CDCl_3$): δ 56.8 (CH_3O), 67.9, 80.3 (C≡C), 160.3, 170.7 (C=O, O–C=O). IR (film): ν 2990, 2202, 1788, 1705, 1344, 1363, 1277, 1222, 1210. Anal. Calcd for $C_5H_3ClO_3$: C, 40.96; H, 2.05; Cl, 24.23. Found: C, 41.28; H, 2.29; Cl, 24.05%.

One-pot preparation of 4-chloro-2-oxo-but-3-ynoic acid pentafluorophenyl ester 3e (protocol B, Scheme 3). To a stirred solution of 35.12 g (0.10 mol) of alkyne **A** in CH_2Cl_2 (100 mL), pentafluorophenyl oxalyl chloride (30.20 g, 0.11 mol) was added in one portion at 20 °C. The resulting solution was left at 20 °C for 24 h. The stirred reaction mixture was cooled to –35 °C, and the chlorine gas was gradually passed into it through a cannula from a measuring test tube containing 8.50–10.00 g (0.12–0.15 mol, 5.50–6.50 mL) of cooled liquid chlorine. The solvent was evaporated, and the residue obtained was heated at 30–40 °C (1 Torr) for 1 h, while sublimating Me_3SnCl was collected in a trap cooled with dry ice allocated directly over the solution. The crystalline product was additionally distilled at 150–153 °C to give 33.85 g (85%) of recovered Me_3SnCl. The residual liquid in the reaction flask was distilled to afford 23.84 g (80 %) of compound **3e** as a colorless liquid. Bp: 97–99 °C (1 Torr). The boiling point and spectroscopic data of **3e** were in good agreement with the literature data [10].

One-pot general preparation of haloalkynes 3f–i (protocol C, Scheme 3). To a stirred solution of 43.52 g (0.10 mol) of alkyne **1b** in $C_2H_2Cl_4$ (100 mL), one of acid halides (CF_3COCl, CF_3COBr, CHF_2COCl, CHF_2COBr) (0.13 mol) was added in one portion at –35 °C. The reaction flask was equipped with a dry ice cooled trap used as a condenser to avoid the evaporation of volatile starting products. The stirred mixture was allowed to warm up gradually to 20 °C (6–8 h) and was left overnight in an argon atmosphere. Then, the mixture was stirred at 30–35 °C

(15–20 Torr) for 1 h to remove the excess of acid halides and cooled to –35 °C, after which Cl_2 (8.52 g, 0.12 mol) or Br_2 (16.00 g, 0.10 mol) was introduced gradually into the stirred solution. The reaction mixture was evacuated to 15 Torr at 30–40 °C and the volatile products were collected in a dry ice cooled trap. Their subsequent distillation at atmospheric pressure afforded pure haloalkynes **3f**–**i**. The residue in the flask was subjected to distillation to recover the solvent $C_2H_2Cl_4$ (bp: 52–54 °C (15 Torr)) and 38.58–43.34 g (80–90%) of Et_3SnCl, bp 94–95 °C (15 Torr), or 46.84–49.12 g (82–86%) of Et_3SnBr, bp 108–110 °C (15 Torr).

***4-Chloro-1,1,1-trifluorobut-3-yn-2-on 3f*.** Colorless liquid, yield: 13.46 g (86%). Bp: 64–65 °C. The boiling point and the spectroscopic data of **3f** were in good agreement with the literature data [8].

***4-Bromo-1,1,1-trifluorobut-3-yn-2-on 3g*.** Yellowish liquid, yield: 16.83 g (83%). Bp: 89–90 °C. The boiling point and spectroscopic data of **3g** were in good agreement with the literature data [8].

***4-Chloro-1,1-difluorobut-3-yn-2-on 3h*.** Colorless liquid, yield: 10.66 g (77%). Bp: 86–87 °C. ^{1}H NMR ($CDCl_3$): δ 5.33 (t, 1H, CHF_2, J_{HF} = 50.9 Hz). ^{13}C NMR ($CDCl_3$): δ 62.7, 81.8 (C≡C), 110.5 (t, CF_2, J_{CF} = 252.7 Hz), 176.0 (t, CO, J_{CF} = 30.1 Hz). ^{19}F NMR ($CDCl_3$): δ –124.9 (CF_2). IR (film): ν 1730 (C=O), 2253 (C≡C). Anal. Calcd for C_4HClF_2O: C, 34.66; H, 0.72; Cl, 25.63; F, 27.44. Found: C, 34.90; H, 0.82; Cl, 25.39; F, 27.19%.

***4-Bromo-1,1-difluorobut-3-yn-2-on 3i*.** Colorless liquid, yield: 13.36 g (73%). Bp: 108–110 °C. ^{1}H NMR ($CDCl_3$): δ 5.30 (t, ^{1}H, CHF_2, J_{HF} = 51.1 Hz). ^{13}C NMR ($CDCl_3$): δ 68.0, 74.4 (C≡C), 109.8 (t, CF_2, J_{CF} = 254.5 Hz), 175.3 (t, CO, J_{CF} = 30.8 Hz). ^{19}F NMR ($CDCl_3$): δ –122.7 (CF_2). IR (film): ν 1703 (C=O), 2198 (C≡C). Anal. Calcd for C_4HBrF_2O: C, 26.23; Cl, 19.40; F, 20.77. Found: C, 26.50; Cl, 19.12; F, 20.69%.

Conclusions

Extremely electrophilic halogenacetylenes activated with polyfluoroalkyl oxalyl, pentafluorophenyl oxalyl, methyl oxalyl, trifluoroacetyl, and difluoroacetyl groups were synthesized by the simple and convenient one-pot procedure from the corresponding *bis*(trialkylstannyl)acetylenes. The protocols developed allow for increasing the yields of the target products and effective recycling of the starting valuable trialkylstannyl chlorides. The latter can be repeatedly used in the preparation of *bis*(trialkylstannyl)acetylenes.

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