SYNTHESIS OF POLYFLUORINATED ALKYNES, NOVEL BUILDING BLOCKS FOR FLUOROUS CHEMISTRY

Tomáš Bříza[1], Jaroslav Kvíčala[2],*, and Oldřich Paleta[3]

Department of Organic Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail: [1] *ftor@seznam.cz,* [2] *kvicalaj@vscht.cz,* [3] *paletao@vscht.cz*

Ethynyldimethylphenylsilane (**2**) was lithiated with butyllithium and reacted with (perfluorohexyl)ethyl triflate (**1**) to afford silylated 4-(perfluorohexyl)butyne **3**, which was deprotected with potassium fluoride to give 4-(perfluorohexyl)butyne **4**. Lithiation of fluoroalkyne **4** with butyllithium followed by the addition of polyfluoroalkyl triflate **1** furnished bis(perfluorohexyl)butyne **5** in a moderate yield. Polyfluoroalkylated alkynes **3**, **4** and **5** are perspective building blocks for fluorous chemistry, the sufficient nucleophilic properties of which are preserved by one or two ethylene spacers between the triple bond and perfluoroalkyl group(s).

Keywords: Fluorous ligands; Acetylenes; Alkynes; Acetylides; Polyfluoroalkyl groups; Fluorophilic; Nucleophilic substitutions; Lithiations.

Alkynes are widely used building blocks in synthetic organic chemistry. Cyclizations of alkynes to aromatic or superaromatic compounds are central to their applications. Among others, alkynes can be employed in Diels–Alder reactions yielding cyclohexadienes[1], in reactions with zirconacyclopentanes forming zirconacyclopentenes and subsequently cyclopentadienes[2], in cyclotrimerization reactions affording arenes[3] and with *arachno*-decaborane yielding *closo*-1,2-carboranes[4].

During the last decade, attempts to minimize the environmental impact of industrial processes in accord with the "green chemistry" concept have led to the development of fluorous biphase catalysis (FBC), which employs polyfluorinated ligands as a part of fluorophilic homogeneous catalysts. These catalysts can be extracted after reaction into a perfluorinated solvent phase immiscible with the organic phase containing products[5–8]. The original FBC concept has gradually broadened its scope into a number of reactions, isolation and combinatorial techniques known as fluorous chemistry[9].

As fluorous ligands, polyfluorinated phosphanes have been used predominantly[9–12]. Although cyclopentadienes rank among the most common ligands employed in organometallic chemistry[13], surprisingly little attention has been paid to the preparation of fluorous cyclopentadienes. First such ligands synthesized were cyclopentadienes substituted with a perfluoroalkyl chain, which proved to be poor ligands due to the lack of a spacer insulating the cyclopentadiene ring from the electron-attracting perfluoroalkyl chain[14,15]. Cyclopentadienes containing one polyfluorinated ring with such spacer displayed insufficient fluorophilic properties due to low fluorine content, which should exceed 60% [16]. The attempts to prepare perfluoroalkylated tetramethylcyclopentadienes, in which the attached methyl groups would balance electronic properties of perfluorinated chain, did not improve substantially their complexing ability[17].

We therefore concentrated on the preparation of cyclopentadienes substituted with two polyfluoroalkyl groups. As our first attempts to prepare them by a radical addition of perfluoroalkyl iodides to divinylcyclopentadienediols failed due to an unexpected side-reaction[18], we synthesized bis(polyfluoroalkyl)cyclopentadienes[19,20] with sufficient complexing and fluorophilic properties[21] by the stepwise nucleophilic substitution of polyfluoroalkyl triflates with cyclopentadienide anions. The main drawback of this approach was that both polyfluorinated cyclopentadienes and their complexes were formed as mixtures of regioisomers.

As cyclopentadienes can be synthesized from alkynes on the basis of zirconocene chemistry[2], we started our research in this area by the preparation of fluorinated alkynes.

In contrast to hexafluorobut-2-yne, which is a common ligand used in organometallic chemistry[22,23], no organometallic complexes using polyfluorinated alkynes have been reported. The preparations of alkynes possessing one perfluoroalkyl group has been reviewed[22] and well developed. On the other hand, the procedures reporting the preparation of alkynes substituted with fluoroalkyl chains separated from the triple bond by an insulating spacer or by two fluorinated groups are severely limited. Thus, among several methods for the preparation of perfluoroalkylated terminal alkynes, the Burton's approach[24] based on an exhaustive chlorination and a subsequent dehalogenation of commercially available (perfluoroalkyl)ethenes seems to be the most general. The internal alkynes containing one alkyl and one perfluoroalkyl group can be synthesized by a one step procedure from perfluoroalkyl iodides and 1-bromoalk-1-ynes[25]. Another general methodology for the preparation of internal alkynes that deserves attention is coupling of alkynylstannanes with perfluoroalkyl iodides catalyzed by

Pd(0) catalysts[26]. The only published general synthesis of bis(perfluoro-alkyl)ethynes employs radical addition of perfluoroalkyl iodide to (per-fluoroalkyl)ethyne followed by dehydrohalogenation[27]. Analogously, there are only sole reports dealing with the preparation of internal alkynes containing the perfluoroalkyl group separated from the triple bond by a methylene[28] or ethylene[29] spacer. Both methods use the coupling reactions catalyzed by copper or palladium. No preparations of the terminal alkynes with one polyfluoroalkylated chain or internal alkynes with two such groups have been reported. In the patent[30], 4-(perfluoroalkyl)but-1-ynes are mentioned but, except for a general methodology, no details on their preparation and properties are given.

We wish to report here a novel preparation of fluorous alkynes with triple bond insulated from one or two electron-acceptor perfluorinated groups by the ethylene spacer(s), which is based on fluorous building blocks recently developed by us[19], polyfluoroalkyl triflates.

EXPERIMENTAL

Temperature data were uncorrected. NMR spectra were recorded with a Varian GeminiPlus 300 HC spectrometer, ^{1}H NMR spectra at 300.1 MHz using tetramethylsilane as an internal standard, ^{13}C NMR spectra at 75.5 MHz using tetramethylsilane as the internal standard and ^{19}F NMR spectra at 282.4 MHz using chlorotrifluoromethane as the internal standard with upfield values designed negative. The chemical shifts, δ, are given in ppm, the coupling constants, J, in Hz. FTIR spectra (ν in cm^{-1}) were recorded with a FT-IR Nicolet 740 instrument in CHCl$_3$. GC-MS analysis was performed with a Micromass Autospec Ultima instrument using 60 m capillary column (stationary phase C Vax).

All manipulations and reactions with organometallic reagents were performed under dry inert atmosphere in an oven-dried aparatuses. Dichlorodimethylsilane, bromobenzene, triflic anhydride, ethynylmagnesium bromide (0.5 M solution in THF) and butyllithium (2.5 M solution in hexanes) were purchased from Aldrich. Concentrations of ethenylmagnesium bromide and butyllithium solutions were estimated prior to use by titration[31]. 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctan-1-ol was kindly gifted by Elf Atochem. Diethyl ether was dried over sodium benzophenone ketyl and distilled prior to use. Potassium fluoride was predried by heating in a dish by a burner, finely grinded and dried at 200 °C *in vacuo* for 12 h, followed by cooling under dry inert atmosphere.

3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl triflate (**1**) was prepared according to ref.[19], chlorodimethylphenylsilane according to ref.[32] Ethynyldimethylphenylsilane (**2**) was synthesized according to ref.[33] in a 90% yield.

1-(Dimethylphenylsilyl)-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodec-1-yne (**3**)

A 25-ml flask equipped with a magnetic stirbar was charged with ethynyldimethyl-phenylsilane (**2**; 6.00 g, 37.4 mmol) and diethyl ether (20 ml). After cooling the mixture to –78 °C, butyllithium solution (16.5 ml, 2.63 g, 41.1 mmol) was slowly added with a syringe.

The mixture was then allowed to warm to laboratory temperature while stirring for about 20 min. Another 500-ml flask equipped with a magnetic stirbar and reflux condenser fitted with septum was charged with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl triflate (**1**; 14.3 g, 28.8 mmol) and diethyl ether (150 ml). Solutions in both flasks were cooled to –10 °C and the content of the first flask was transferred to the second flask with a capillary. After the addition was completed, the mixture was refluxed for 3 h. After cooling, the mixture was extracted with water (100 ml). The water layer was separated and extracted with diethyl ether (3 × 50 ml). Combined organic layers were dried with anhydrous magnesium sulfate, the drying agent was filtered off and the solvent was removed on a vacuum rotary evaporator. From the residue, unreacted ethynylsilane **2** and fluorotriflate **1** were distilled off (fraction boiling at 50–80 °C/200 Pa, colorless liquid). The product, silylated fluoroalkyne **3**, was isolated as the main fraction (6.1 g, 42%, b.p. 106–115 °C/200 Pa, colorless liquid). ^{1}H NMR (300.1 MHz, CDCl$_3$): 0.41 s, 6 H; 2.40 m, 2 H; 2.60 t, 2 H, $^3J_{HH}$ = 7.15; 7.39 m, 3 H; 7.62 m, 2 H. ^{13}C NMR (100.6 MHz, CDCl$_3$): –1.0 s, 2 C; 12.0 s, 1 C; 30.6 t, 1 C, $^2J_{CF}$ = 21.2; 84.4 s, 1 C; 104.8 s, 1 C; 108.2–120.9 bm, 6 C; 127.9 s, 1 C; 129.4 s, 2 C; 133.6 s, 2 C; 137.0 s, 1 C. ^{19}F NMR (376.5 MHz, CDCl$_3$): –81.3 t, 3 F, $^3J_{FF}$ = 10.5; –115.7 t, 2 F, $^3J_{FF}$ = 15.4; –122.4 m, 2 F; –123.3 m, 2 F; –124.1 m, 2 F; –126.6 m, 2 F. IR (CHCl$_3$): 3073, 2964, 2928, 2186, 1430, 1238, 1145, 1118, 1074. For C$_{18}$H$_{15}$F$_{13}$Si (506.3) calculated: 42.70% C, 2.96% H; found: 42.30% C, 3.14% H.

5,5,6,6,7,7,8,8,9,9,10,10,10-Tridecafluorodec-1-yne (**4**)

A 250-ml flask equipped with a reflux condenser was charged with silylated polyfluorodecyne **3** (12.2 g, 24.0 mmol), methanol (150 ml) and anhydrous potassium fluoride (4.20 g, 72.3 mmol). The reaction mixture was then refluxed for 2 h. After cooling to room temperature, the mixture was diluted with water (100 ml). Aqueous layer was separated and extracted with pentane (2 × 50 ml). Combined organic layers were dried with anhydrous magnesium sulfate and drying agent was filtered. The solvents were carefully removed on a vacuum rotary evaporator (40 °C/80 kPa). Deprotected fluorodecyne **4** was isolated by fraction distillation of the residue (4.5 g, 50%, b.p. 126–129 °C/70 kPa, colorless liquid). ^{1}H NMR (300.1 MHz, CDCl$_3$): 2.02 t, 1 H, $^3J_{HH}$ = 2.48; 2.36 m, 2 H; 2.52 m, 2 H. ^{13}C NMR (100.6 MHz, CDCl$_3$): 10.6 s, 1 C; 30.5 t, 1 C, $^2J_{CF}$ = 21.2; 69.7 s, 1 C; 80.8 s, 1 C; 108.2–120.9 bm, 6 C. ^{19}F NMR (376.5 MHz, CDCl$_3$): –81.3 t, 3 F, $^3J_{FF}$ = 10.5; –115.7 t, 2 F, $^3J_{FF}$ = 15.4; –122.4 m, 2 F; –123.3 m, 2 F; –124.1 m, 2 F; –126.6 m, 2 F. IR (CHCl$_3$): 3320, 2964, 1451, 1241, 1146, 1113, 1075. GC-MS (EI, *m/z*): 372 (4, M$^+$), 134 (5), 133 (5) 131 (5), 104 (52), 103 (100), 83 (21), 77 (8), 69 (14), 57 (5), 53 (28), 51 (7), 39 (37), 27 (5). Satisfactory elemental analysis could not be obtained due to high volatility of the product.

1,1,1,2,2,3,3,4,4,5,5,6,6,13,13,14,14,15,15,16,16,17,17,18,18,18-Hexacosafluorooctadec-9-yne (**5**)

A 100-ml flask equipped with a magnetic stirbar and septum was charged with polyfluorodecyne **4** (2.95 g, 7.90 mmol) and diethyl ether (20 ml). The mixture was cooled to –78 °C and butyllithium solution (3.2 ml, 0.52 g, 8.1 mmol) was dropwise added to it with a syringe, followed by stirring for 30 min. Polyfluoroalkyl triflate **1** (4.8 g, 9.7 mmol) was dissolved in diethyl ether (15 ml) and this solution was dropwise added to the reaction mixture while cooling to –78 °C and stirring. The mixture was then stirred at room temperature for 25 min and then refluxed for 1 h. Salts were removed by a column chromatography (silica

gel, short column 5 × 8 cm, eluent pentane). Solvents were removed on a vacuum rotary evaporator. Product, bis(polyfluoroalkylated) alkyne **5**, was obtained by vacuum distillation of the residue (2.56 g, 45.0%, b.p. 135–140 °C/400 Pa, colorless liquid). ^{1}H NMR (300.1 MHz, CDCl$_3$): 2.31 m, 4 H; 2.47 t, 4 H, $^3J_{HH}$ = 8.25. ^{13}C NMR (100.6 MHz, CDCl$_3$): 10.7 s, 2 C; 30.7 t, 2 C, $^2J_{CF}$ = 21.2; 78.2 s, 2 C; 108.2–120.9 bm, 12 C. ^{19}F NMR (376.5 MHz, CDCl$_3$): –81.3 t, 3 F, $^3J_{FF}$ = 10.5; –115.7 t, 2 F, $^3J_{FF}$ = 15.4; –122.4 m, 2 F; –123.3 m, 2 F; –124.1 m, 2 F; –126.6 m, 2 F. IR (CHCl$_3$): 2953, 2936, 1452, 1239, 1145, 1121, 1074. For C$_{18}$H$_8$F$_{26}$ (718.2) calculated: 30.10% C, 1.12% H; found: 30.33% C, 1.00% H.

RESULTS AND DISCUSSION

Initially, we attempted to synthesize the first target compound, terminal polyfluorinated alkyne **4**, directly from ethynylsodium, ethynyllithium or ethynylmagnesium bromide using 2-(perfluorohexyl)ethyl iodide or 2-(perfluorohexyl)ethyl triflate (**1**) as the corresponding electrophiles. Although we employed a wide variety of the reaction conditions including highly solvating solvents such as DMPU, we did not achieve higher yields of the desired product than few percent. An analogous series of experiments was accomplished using ethynyltrimethylsilane-based organometallic compounds, but the increase in the yield was negligible. We suspect that both types of acetylides displayed unsufficient nucleophility in the reaction with polyfluorinated triflates, which are poor electrophiles. We therefore changed our strategy and turned our attention to coupling reactions in analogy to the published preparation of polyfluorinated phenylacetylenes[29]. Coupling of tributylethynylstannane with 2-(perfluorohexyl)ethyl iodide catalyzed by tetrakis(triphenylphosphine)palladium did not afford any desired product. We also tried to use some other transition metal catalysts, but without any substantial improvement.

Our first step forwards came when we tried to replace the trimethylsilyl group protecting the starting alkyne with dimethylphenylsilyl group. The reaction of this silyl chloride with commercial ethynylmagnesium bromide according to a published procedure[33] afforded ethynyldimethylphenylsilane (**2**) in a good yield. Surprisingly, in contrast to experiments with acetylene or (trimethylsilyl)acetylene-based organometallic compounds, lithiation of this ethynylsilane followed by the reaction of the corresponding ethynyllithium with polyfluoroalkyl triflate **1** yielded the target (polyfluoroalkyl)ethyne **3** in moderate yield (Scheme 1). In analogy to our previous experiments with 2-(perfluoroalkyl)ethyl triflates and analogous iodides[19], 2-(perfluorohexyl)ethyl iodide displayed negligible reactivity in the reaction with lithiated alkyne **2**.
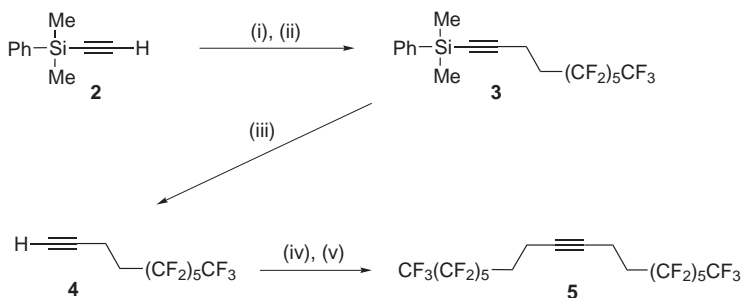
(i) BuLi, Et$_2$O, –78 °C to r.t., 20 min; (ii) CF$_3$(CF$_2$)$_5$C$_2$H$_4$OTf (**1**), –10 °C to reflux, 3 h, 42%;
(iii) KF, MeOH, reflux, 2 h, 50%; (iv) BuLi, Et$_2$O, –78 °C, 30 min; (v) CF$_3$(CF$_2$)$_5$C$_2$H$_4$OTf (**1**),
–78 °C to r.t., 25 min, then reflux, 45%

Scheme 1

The deprotection of dimethylphenylsilyl group was accomplished with a moderate yield according to a published general procedure[34] by stirring the silylated alkyne **3** with anhydrous KF in methanol (Scheme 1). Attempts to employ other fluorine sources as TBAF or Gingras reagent (tetrabutyl-ammonium difluorotriphenylstannate) did not improve the yield of de-protection. Due to high volatility of the unprotected polyfluoroalkyne **4**, special precaution had to be applied to minimize losses of the product **4** in the course of its isolation. Complete removal of solvents required careful short-path fractional distillation.

In contrast to numerous failures in the preparation of polyfluorinated terminal alkyne **4**, lithiation of fluoroalkyne **4** with BuLi followed by the reaction with polyfluoroalkyl triflate **1** afforded bis(polyfluoroalkyl)acetylene **5** in moderate yield (Scheme 1). Again, polyfluoroalkyl iodides proved to be unreactive under identical conditions.

We synthesized the first terminal alkyne substituted with one per-fluorinated group separated from the triple bond by the ethylene spacer, as well as the first internal alkyne substituted with two such (perfluoro-alkyl)ethyl groups, thus preserving electron-rich properties of alkynes essential for their cyclization reactions catalyzed by transition metal complexes. The key compounds for their preparation are ethynyldi-methylphenylsilane (**2**) and 2-(perfluorohexyl)ethyl triflate (**1**). All alkynes prepared (**3**–**5**) are perspective fluorophilic building blocks for fluorous chemistry.

REFERENCES

1. Hilt G., Korn T. J.: *Tetrahedron Lett.* **2001**, *42*, 2783.
2. Takahashi T., Sun W.-H., Xi C., Kotora M.: *Chem. Commun.* **1997**, 2069.
3. Schore N. E.: *Chem. Rev. (Washington, D. C.)* **1988**, *88*, 1081.
4. Hawthorne M. F.: *Acc. Chem. Res.* **1973**, *6*, 110.
5. Horváth I. T., Rábai J.: *Science* **1994**, *266*, 72.
6. Horváth I. T.: *Acc. Chem. Res.* **1998**, *31*, 641.
7. Hope E. G., Stuart A. M.: *J. Fluorine Chem.* **1999**, *100*, 75.
8. Fish R. H.: *Chem. Eur. J.* **1999**, *5*, 1677.
9. Alvey L. J., Rutherford D., Juliette J. J. J., Gladysz J.: *J. Org. Chem.* **1998**, *63*, 6302.
10. Bhattacharyya P., Gudmunsen D., Hope E. G., Kemmitt R. D. W., Paige A. M., Stuart J.: *J. Chem. Soc., Perkin Trans. 1* **1997**, 3609.
11. Kainz S., Luo Z., Curran D. P., Leitner W.: *Synthesis* **1998**, 1425.
12. Richter B., Spek A. L., van Koten G., Deelman B.-J.: *J. Am. Chem. Soc.* **2000**, *122*, 3945.
13. Keenan M. J. in: *Cyclopentadiene and Dicyclopentadiene* (J. I. Kroschwitz and M. Howe-Grant, Eds), Kirk–Othmer Encyclopedia of Chemical Technology, 4th ed., Vol. 7, p. 859. John Wiley, Chichester 1993.
14. Herrera V., de Rege P. J. F., Horváth I. T., Le Husebo T., Hughes R. P.: *Inorg. Chem. Commun.* **1998**, *1*, 197.
15. Hughes R. P., Trujillo H. A.: *Organometallics* **1996**, *15*, 286.
16. Kiss L. E., Kövesdi I., Rábai J.: *J. Fluorine Chem.* **2001**, *108*, 95.
17. Čermák J., Auerová K., Nguyen H. T. T., Blechta V., Vojtíšek P., Kvíčala J.: *Collect. Czech. Chem. Commun.* **2001**, *66*, 382.
18. Kvíčala J., Bříza T., Paleta O., Čermák J.: *Collect. Czech. Chem. Commun.* **2002**, *67*, 1345.
19. Bříza T., Kvíčala J., Mysík P., Paleta O., Čermák J.: *Synlett* **2001**, 685.
20. Bříza T., Kvíčala J., Paleta O., Čermák J.: *Tetrahedron* **2002**, *58*, 3841.
21. Kvíčala J., Bříza T., Paleta O., Čermák J.: *Tetrahedron* **2002**, *58*, 3847.
22. Turbanova E. S., Petrov A. A.: *Usp. Khim.* **1991**, *60*, 1005.
23. Mague J. T.: *J. Organomet. Chem.* **1988**, *351*, 215.
24. Burton D. J., Spawn T. D.: *J. Fluorine Chem.* **1988**, *38*, 119.
25. Sanchez V., Greiner J.: *J. Fluorine Chem.* **1994**, *68*, 79.
26. Matsubara S., Mitani M., Utimoto K.: *Tetrahedron Lett.* **1987**, *28*, 5857.
27. Sanchez V., Greiner J.: *Tetrahedron Lett.* **1993**, *34*, 2931.
28. Hung M.-H.: *Tetrahedron Lett.* **1990**, *31*, 3703.
29. Shimizu R., Fuchikami T.: *Tetrahedron Lett.* **1996**, *37*, 8405.
30. Von Werner K., Weiss K.: Eur. Pat. Appl. EP 483722 (1992); *Chem. Abstr.* **1992**, *117*, 112254.
31. Furniss B. S., Hammford A. J., Smith P. W. G., Tatchell A. R.: *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., pp. 443, 535. Wiley, New York 1991.
32. Eaborn C., Jones K. L., Lickiss P. D.: *J. Organomet. Chem.* **1994**, *466*, 35.
33. Fleming I., Takaki K., Thomas A. P.: *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269.
34. Borzilleri R. M., Weinreb S. M., Parvez M.: *J. Am. Chem. Soc.* **1995**, *117*, 10905.