ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 5, pp. 800–804. © Pleiades Publishing, Ltd., 2017.
Original Russian Text © A.G. Lyapunova, A.S. D'yachenko, N.A. Danilkina, 2017, published in Zhurnal Organicheskoi Khimii, 2017, Vol. 53, No. 5, pp. 783–786.

SHORT COMMUNICATIONS

Potassium Fluoride for *One-Pot* Desilylation and the Sonogashira Coupling of Ethynylsilanes and Buta-1,3-diynylsilanes

A. G. Lyapunova, A. S. D'yachenko, and N. A. Danilkina*

St. Petersburg State University, Universitetskaya nab. 7/9, St. Petersburg, 199034 Russia
**e-mail: n.danilkina@spbu.ru*

Received February 15, 2017

Abstract – Opportunities were outlined for application of available KF as a source of fluoride ions and a base in desilylation/the Sonogashira coupling reactions under conditions of a one-pot process.

DOI: 10.1134/S1070428017050268

The Sonogashira (Sonogashira–Hagihara) reaction is a general synthetic method for the generation of a new *sp*-sp^2 C–C bond from terminal acetylenes and halo derivatives or triflates of arenes, hetarenes, or alkenes [1, 2]. Ethynylsilane derivatives also may be substrates for *sp*-sp^2 cross-coupling [3]. This modification of the Sonogashira reaction makes it possible to avoid the stage of the protective group R_3Si removal as well as to utilize more stable R_3Si-substituted derivatives instead of terminal acetylenes. Depending on the conditions of the ethynylsilanes cross-coupling this reaction can proceed either by mechanism of the Hiyama reaction [4], the *sila*-Sonogashira [5], or via desilylation and the Sonogashira coupling under the conditions of a *one-pot* process [6].

We recently developed a general approach to the synthesis of enediynes antibiotics analogs fused to heterocycles based on the succession of the Sonogashira coupling of *ortho*-functionalized iodoarenes with diacetylene derivatives, electrophilic cyclization of the obtained diacetylenes, and the second Sonogashira reaction of iodoethynylheterocycles with monoacetylene compounds [7–11]. Therewith in both stages of the introduction of ethynyl fragments we showed the efficiency of desilylation and cross-coupling in the *one-pot* process [8–11].

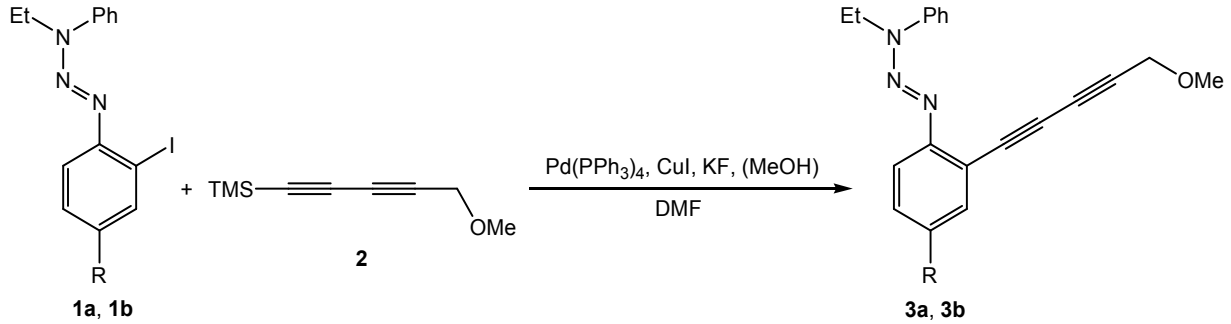
In the presence of an allylethynyl fragment in the initial TMS-acetylene or iodide the best results were obtained using potassium fluoride as a desilylating agent [8, 10], and the application of potassium carbonate resulted in the isomerization of the double bond in the allyl substituent to the internal position [8]. Moreover, in some cases the cross-coupling in the presence of KF does not require addition of a base and can occur at slight heating (40°C) both in the presence and in the absence of a proton source [10].

Few examples describe the application of KF in similar transformations [12, 13], or only as a base in the Sonogashira reaction involving terminal acetylenes [14]. In this study we evaluated the opportunities of the application of cheap and available KF as a source of fluoride ions and a base in desilylation/the Sonogashira coupling under *one-pot* conditions, and also only as a base in the Sonogashira reaction with substrates requiring mild cross-coupling conditions.

Br- and COOEt-substituted iodoaryltriazenes **1a** and **1b**, and 3-iodo-2-methoxymethylethynylbenzo[*b*]-thiophene **4** were chosen as substrates. 5-Methoxypenta-1,3-diyn-1-yltrimethylsilane **2** and trimethyl-[3-(3,4,5-trimethoxyphenyl)prop-1-ynyl]silane **5a** were used as initial acetylene compounds in the *one-pot* reaction of desilylation/the Sonogashira coupling, and 3-*tert*-butylsulfanylprop-1-yne **5b** and *N*-benzylbut-1-yn-1-amine **5c** were utilized as terminal acetylenes. These reactions can be of interest as intermediate stages in the synthesis of cinnoline derivatives by the Richter reaction [15, 16], as well as for the preparation of macrocyclic enediynes fused to a benzothiophene scaffold [17].

The desilylation/cross-coupling under *one-pot* conditions of bromoiodotriazene **1a** with diacetylene **2**

Scheme 1.



R = Br (**a**), COOEt (**b**).

was performed in anhydrous DMF in the presence of potassium fluoride (5 equiv) and methanol (10 equiv) at room temperature in order to avoid the possible bromine substitution (Scheme 1).

Under these conditions the reaction occurred chemoselectively with the substitution of only the iodine atom affording the target diacetylene **3a** in a good yield (67%). At replacing the bromine atom for the ethoxycarbonyl group the target compound **3b** was isolated in only 50% yield despite the reaction temperature increase to 40°C. However, the removal of methanol from the reaction mixture resulted in the increase in the yield of compound **3b** to 75%. It is presumable that in the absence of methanol the cross-coupling proceeds through the formation of a penta-coordinated $FSiR_3$-butadiyne with its subsequent transformation into copper acetylenide.

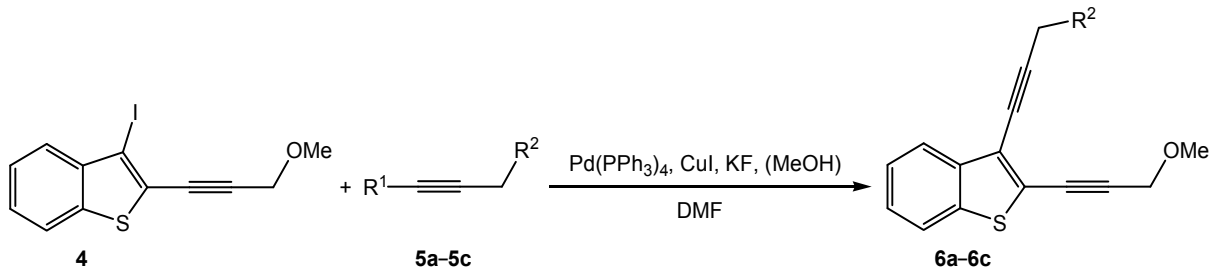
Benzothiophene **4** was brought in cross-coupling reactions both with TMS-protected (3,4,5-trimethoxybenzyl)acetylene **5a** and terminal *S*- and *N*-containing acetylenes **5b** and **5c** (Scheme 2).

The reaction with TMS-trimethoxybenzylacetylene **5a** was carried out in the presence of methanol and KF that provided the target enediyne **6a** in a high yield (90%). On introducing in the system an additional base, diisopropanolamine that has been very effective in the preparation of a number of enediynes in the condensation with benzothiophene [8] the yield of endiyne **6a** decreases to 43%.

The application of potassium fluoride as a base also proved to be successful in the synthesis of *tert*-butylsulfanyl-substituted acetylene **6b** and *N*-benzyl derivative **6c**. Both enediynes were obtained in good yields: **6b** (85%), **6c** (79%). The replacement of KF for diisopropylamine often used as base in the Sonogashira reaction [2] negatively affected the preparation of endiyne **6b** resulting in the formation of an intractable products mixture.

Hence potassium fluoride in the environment of anhydrous DMF provides a possibility to perform the reaction sequence of desilylation and the Sonogashira coupling under the conditions of *one-pot* process both with mono- and diacetylenes in the presence as well as in the absence of hydrogen donors. On top of that the application of potassium fluoride as a base in the medium of anhydrous DMF makes it possible to carry out the Sonogashira cross-coupling with acetylene substrates containing divers heteroatoms and

Scheme 2.



R^1 = TMS, R^2 = 3,4,5-$(CH_3O)_3C_6H_2$ (**a**); R^1 = H, R^2 = S-*t*-Bu (**b**); R^1 = H, R^2 = CH_2NHBn (**c**).

functional groups. Mild conditions, tolerance of functional groups, and also the availability and cheapness of potassium fluoride as compared to organic fluorides (TASF, TBAF) should favor a wide application of this procedure to the synthesis of functionalized mono- and polyacetylene compounds.

Compounds 3a, 3b, and 6a–6c. General procedure. To a solution of 1 equiv of iodoarene in anhydrous DMF (*c* 0.1 mol L^{-1}) was added while stirring 5 mol % of $Pd(PPh_3)_4$, 10–15 mol % of CuI, and 5–8 equiv of KF. The reaction mixture was degassed and thrice flushed with argon. Then to the reaction mixture was added 10 equiv of methanol (if indicated) and a solution of 1.3–2.3 equiv of alkyne or TMS-alkyne in 1 mL of anhydrous DMF. The reaction mixture was stirred at room temperature or at 40°C. The reaction progress was monitored by TLC. On completion of the reaction the mixture was poured in a saturated aqueous solution of NH_4Cl, extracted with ethyl acetate, combined organic fractions were washed with saturated water solutions of NH_4Cl and NaCl and dried with anhydrous Na_2SO_4. The solvent was removed in a vacuum. The reaction product was purified by column chromatography.

1-[2-(5-Methoxypenta-1,3-diyn-1-yl)-4-bromophenyl]-3-phenyl-3-ethyltriaz-1-ene (3a) was obtained with addition of methanol from 0.215 g (0.5 mmol) of triazene **1a** and 0.108 g (0.65 mmol) of TMS-diacetylene **2** using 0.145 g (2.5 mmol) of KF and 15 mol % of CuI. Reaction time 2 h at room temperature. Eluent petroleum ether–ethyl acetate, 10 : 1. Yield 0.134 g (67%), yellow-orange oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 t (3H, *J* 7.0 Hz), 3.43 s (3H), 4.27 s (2H), 4.37 q (2H, *J* 7.0 Hz), 7.14–7.18 m (1H), 7.36–7.51 m (6H), 7.67 d (1H, *J* 1.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 10.8, 41.0, 57.8, 60.4, 71.3, 75.0, 78.5, 79.7, 117.2, 118.8, 119.1, 119.3, 124.2, 129.3, 133.0, 136.2, 143.9, 152.3. Found *m/z* 418.0591 $[M + Na]^+$. $C_{20}H_{18}BrN_3ONa$. Calculated *m/z* 418.0525.

Ethyl 3-(5-methoxypenta-1,3-diyn-1-yl)-4-(3-phenyl-3-ethyltriaz-1-enyl]benzoate (3b). *a*. It was obtained with addition of methanol from 0.212 g (0.5 mmol) of triazene **1b** and 0.108 g (0.65 mmol) of TMS-diacetylene **2** using 0.145 g (2.5 mmol) of KF and 15 mol % of CuI. The reaction mixture was stirred at room temperature for 1 h, then additionally more 0.083 g (0.5 mmol) of TMS-diacetylene **2** was introduced and the stirring was continued for 15 h. Eluent petroleum ether–ethyl acetate, 10 : 1. Yield 0.097 g (50%), yellow-orange oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.36–1.43 m (6H), 3.43 s (3H), 4.27 s (2H), 4.34–4.45 m (4H), 7.19 t (1H, *J* 7.3 Hz), 7.37–7.45 m (2H), 7.47–7.53 m (2H), 7.59 d (1H, *J* 8.6 Hz), 8.00 d.d (1H, *J* 8.6, 2.0 Hz), 8.24 d (1H, *J* 1.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 10.8, 14.3, 41.3, 57.8, 60.5, 61.1, 71.4, 75.7, 77.9, 79.3, 117.3, 117.5, 117.8, 124.5, 127.8, 129.4, 131.0, 135.7, 143.8, 156.2, 165.6. Found *m/z* 496.0780 $[M + Ag]^+$. $C_{23}H_{23}AgN_3O_3$. Calculated *m/z* 496.0785.

b. It was obtained without addition of methanol from 0.423 g (1 mmol) of triazene **1b** and 0.251 g (1.51 mmol) of TMS-diacetylene **2** using 0.290 g (5 mmol) of KF and 15 mol % of CuI. The reaction mixture was stirred at room temperature for 1 h, then additionally more 0.083 g (0.5 mmol) of TMS-diacetylene **2** was introduced and the stirring was continued for 2 h. Yield 0.292 g (75%).

2-(3-Methoxyprop-1-yn-1-yl)-3-[3-(3,4,5-trimethoxyphenyl)prop-1-yn-1-yl]benzo[*b*]thiophene (6a). *a*. It was obtained with addition of methanol from 0.566 g (1.73 mmol) of 3-iodobenzothiophene **4** and 0.624 g (2.24 mmol) of TMS-acetylene **5a** using 0.5 g (8.65 mmol) of KF and 10 mol % of CuI. Reaction time 20 h at 40°C. Eluent cyclohexane–ethyl acetate, 5 : 1. Yield 0.63 g (90%), light brown powder, mp 78–79°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.44 s (3H), 3.85 s (3H), 3.88 s (6H), 3.94 s (2H), 4.40 s (2H), 6.73 s (2H), 7.37–7.45 m (2H), 7.70–7.77 m (1H), 7.85–7.93 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 26.5, 56.3, 57.9, 60.7, 61.0, 76.2, 79.6, 94.7, 94.9, 105.2, 122.3, 123.49, 123.51, 125.0, 125.2, 126.4, 132.2, 137.0, 138.6, 139.0, 153.5. Mass spectrum, *m/z* (I_{rel}, %): 406 (100) $[M]^+$, 375 (20) $[M - OMe]^+$, 344 (10) $[M - 2OMe]^+$, 277 (80), 246 (26), 201 (30). Found *m/z* 406.1232 $[M]^+$. $C_{24}H_{22}O_4S$. Calculated *m/z* 406.1233.

b. It was obtained with addition of methanol and 1-(2-hydroxypropylamino)propan-2-ol (diisopropanolamine) from 0.106 g (0.32 mmol) of 3-iodobenzothiophene **4** and 0.180 g (0.65 mmol) of TMS-acetylene **5a** using 0.094 g (1.62 mmol) of KF, 15 mol % of CuI, and 0.172 g (1.29 mmol) of diisopropanolamine. Reaction time 13 h at 40°C. Eluent cyclohexane–ethyl acetate, 10 : 1, then 5 : 1. Yield 0.056 g (43%).

2-(3-Methoxyprop-1-yn-1-yl)-3-(3-*tert*-butylsulfanylprop-1-yn-1-yl)benzo[*b*]thiophene (6b) was obtained from 0.99 g (3.02 mmol) of 3-iodobenzothiophene

4 and 0.773 g (6.04 mmol) of terminal acetylene **5b** using 1.40 g (24.1 mmol) of KF, 15 mol % of CuI, and with addition of 0.08 g (0.3 mmol, 10 mol %) of PPh_3. The reaction mixture was stirred for 21 h at 40°C, introducing additionally 0.192 g (1.5 mmol) of acetylene **5b** and heating at 40°C for 25 h. Eluent cyclohexane–ethyl acetate, 25 : 1, then 10 : 1. Yield 0.85 g (85%), yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.46 s (9H), 3.50 s (3H), 3.65 s (2H), 4.43 s (2H), 7.35–7.45 m (2H), 7.67–7.75 m (1H), 7.83–7.89 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.0, 31.1, 43.6, 57.9, 60.7, 75.6, 79.5, 94.4, 94.9, 122.2, 123.3, 123.6, 125.2 (2C), 126.4, 138.5, 138.9. Mass spectrum, *m/z* (I_{rel}, %): 328 (75) $[M]^+$, 239 (100) $[M - t\text{-BuS}]^+$, 209 (78), 195 (33), 152 (15), 69 (18). Found *m/z* 328.0949 $[M]^+$. $C_{19}H_{20}OS_2$. Calculated *m/z* 328.0950.

***N*-Benzyl-4-{2-(3-methoxyprop-1-yn-1-yl)-benzo-[*b*]thiophen-3-yl}but-3-yn-1-amine (6c)** was obtained from 0.098 g (0.3 mmol) of 3-iodobenzothiophene **4** and 0.09 g (0.6 mmol) of terminal acetylene **5c** using 0.139 g (2.4 mmol) of KF, 15 mol % of CuI, and with addition of 0.008 g (0.03 mmol, 10 mol %) of PPh_3. Reaction time 4 h at 40°C. Eluent petroleum ether–ethyl acetate, 2 : 1. Yield 0.085 g (79%), orange oily substance. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.71 t (2H, CH_2, *J* 6.5 Hz), 2.86 t (overlapped with H_2O signal) (2H, CH_2), 3.33 s (3H, OCH_3), 3.81 s (2H, CH_2), 4.30 s (2H, CH_2), 7.12–7.19 m (1H), 7.20–7.29 m (2H), 7.31–7.37 m (2H), 7.38–7.44 m (2H), 7.76–7.81 m (1H), 7.81–7.86 m (1H) (NH signal overlapped with H_2O signal). ^{13}C NMR spectrum (acetone-d_6), δ, ppm: 20.5, 47.7, 52.9, 56.8, 59.7, 74.0, 78.6, 95.4, 96.4, 122.4, 123.2, 123.6, 124.2, 125.4, 126.63, 126.64, 128.0, 128.2, 138.2, 138.6, 141.0. Found *m/z* 360.1406 $[M + H]^+$. $C_{23}H_{22}NOS$. Calculated *m/z* 360.1417.

Melting points were measured in open capillaries on an apparatus Stuart SMP50. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance III 400 (400 and 100 MHz), as internal references served the signals of residual protons (^{1}H) and carbon atoms (^{13}C) of deuterated solvents. Mass spectra of compounds **6a** and **6b** were taken on an instrument Finnigan MAT 90 with a direct admission of the sample, ionizing electrons energy 70 eV, of compounds **3a**, **3b**, and **6c**, on a mass spectrometer Bruker MicroTOF using electrospray ionization and registration of positive ions. Reaction progress was monitored by TLC on Macherey-Nagel (Silica gel 60, F254) plates, development under UV irradiation or with alkaline $KMnO_4$ solution. For preparative chromatography silica gel Macherey-Nagel (Silica gel 60, 230–400 mesh) was used. Initial compounds **1a**, **b** [16], **2**, **4** [17], **5a** [18], and **5c** [19] were prepared by known methods. Compound **5b** was obtained by the general procedure for 3-alkylsulfanylprop-1-ynes [20].

ACKNOWLEDGMENTS

The study was carried out under the financial support of Saint-Petersburg State University (12.40.537.2017) and Russian Foundation for Basic Research (grant no. 17-03-00910) on the equipment of resource centers of the Saint-Petersburg State University (Magnetic Resonance Research Centre, Chemical Analysis and Materials Research Centre, Chemistry Educational Centre).

The authors are grateful to Candidate of Chemical Sciences V.N. Mikhailov for the help in preparing the manuscript.

REFERENCES

1. Sonogashira, K., Tohda, Y., and Hagihara, N., *Tetrahedron Lett*., 1975, vol. 16, p. 4467.
2. Thomas, A.M., Sujatha, A., and Anilkumar, G., *RSC Adv*., 2014, vol. 4, p. 21688.
3. Schaub, T.A., Kivala, M., *Metal-Catalyzed Cross-Coupling Reactions and More*, de Meijere, A., Bräse, S., and Oestreich, M., Eds., Weinheim: Wiley-VCH, 2014, p. 731.
4. Hatanaka, Y. and Hiyama, T., *J. Org. Chem*., 1988, vol. 53, p. 918.
5. Nishihara, Y., Ikegashira, K., Mori, A., and Hiyama, T., *Chem. Lett*., 1997, vol. 12, p. 1233.
6. Halbes, U., Bertus, P., and Pale, P., *Tetrahedron Lett*., 2001, vol. 42, p. 8641.
7. Danilkina, N.A., Bräse, S., and Balova, I.A., *Synlett*., 2011, p. 517.
8. Danilkina, N.A., Kulyashova, A.E., Khlebnikov, A.F., Bräse, S., and Balova, I.A., *J. Org. Chem*., 2014, vol. 79, p. 9018.
9. Danilkina, N., Nieger, M., Selivanov, S., Bräse, S., and Balova, I., *Eur. J. Org. Chem*., 2012, p. 5660.
10. Danilkina, N.A., Lyapunova, A.G., Khlebnikov, A.F., Starova, G.L., Bräse, S., and Balova, I.A., *J. Org. Chem*., 2015, vol. 80, p. 5546.
11. Danilkina, N.A., Gurskaya, L.Y., Vasilyev, A.V., and Balova, I.A., *Eur. J. Org. Chem*., 2016, p. 739.
12. Kinashi, N., Sakaguchi, K., Katsumura, S., and Shinada, T., *Tetrahedron Lett*., 2016, vol. 57, p. 129.

13. Ishikawa, T., Seto, M., Banno, H., Kawakita, Y., Oorui, M., Taniguchi, T., Ohta, Y., Tamura, T., Nakayama, A., Miki, H., Kamiguchi, H., Tanaka, T., Habuka, N., Sogabe, S., Yano, J., Aertgeerts, K., and Kamiyama, K., *J. Med. Chem*., 2011, vol. 54, p. 8030.
14. Hosseinzadeh, R., Mohadjerani, M., Tavakoli, R., and Alikarami, M., *Synth. Commun*., 2010, vol. 40, p. 282.
15. Vinogradova, O.V., Sorokoumov, V.N., Vasilevskii, S.F., and Balova, I.A., *Russ. Chem. Bull*., 2008, vol. 57, p. 1725. doi 10.1007/s11172-008-0228-z
16. Danilkina, N.A., Vlasov, P.S., Vodianik, S.M., Kruchinin, A.A., Vlasov, Y.G., and Balova, I.A., *Beilst. J. Org. Chem*., 2015, vol. 11, p. 373.
17. Lyapunova, A.G., Danilkina, N.A., Khlebnikov, A.F., Köberle, B., Bräse, S., and Balova, I.A., *Eur. J. Org. Chem*., 2016, p. 4842.
18. Imperio, D., Pirali, T., Galli, U., Pagliai, F., Cafici, L., Canonico, P.L., Sorba, G., Genazzani, A.A., and Tron, G.C., *Bioorg. Med. Chem*., 2007, vol. 15, p. 6748. doi 10.1016/j.bmc.2007.08.020
19. Hess, W. and Burton, J.W., *Chem. Eur. J*., 2010, vol. 16, p. 12303.
20. Zheng, R., Wang, Y., and Zhang, L., *Tetrahedron Lett*., 2015, vol. 56, p. 3144.