Available online at www.sciencedirect.com

ScienceDirect

*Mendeleev Commun.*, 2023, **33**, 491–493

Mendeleev Communications

# Visible light-induced thiocyanation of *gem*-difluorinated phosphonium salts

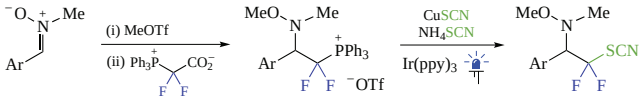
**Gregory A. Lozhkin,[a,b] Alexey L. Trifonov[a] and Alexander D. Dilman*[a]**

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: dilman@ioc.ac.ru*

[b] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2023.06.016

***gem*-Difluorinated phosphonium salts were generated from nitrones by methylation and reaction with (triphenylphosphonio)difluoroacetate. The phosphonium salts were subjected to visible light-induced phosphonium–thiocyanate exchange in the presence of ammonium thiocyanate, copper thiocyanate, and an iridium photocatalyst. The sequence of the reactions was performed in one pot affording thiocyanates attached to the difluoromethylene fragment.**

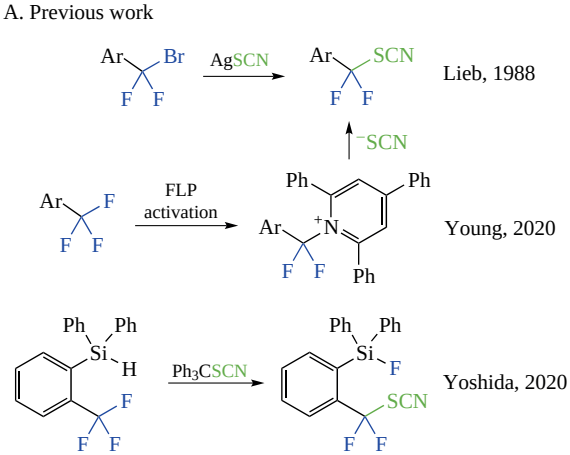



*Keywords*: radicals, nitrones, organofluorine compounds, thiocyanates, phosphonium salts, photochemical reactions.

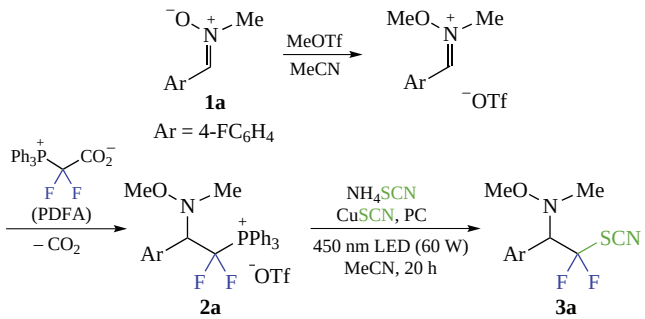
A fluorinated fragment directly bonded to a sulfur atom is a common pattern found in numerous bioactive molecules including approved drugs and agrochemicals.[1–3] Accordingly, methodology for the synthesis of fluorinated organosulfur compounds both as final targets and as reagents has gained great attention.[4–14] Thiocyanates constitute an important class of compounds,[15,16] which are interesting for medicinal chemistry[17–19] and, at the same time, serving as valuable building blocks for the synthesis of variety of products.[20–25] Despite the rapid growth of thiocyanation reactions,[20–25] only few compounds containing the $CF_2SCN$ fragment were isolated and fully characterized. The existing approaches towards this fragment rely on benzylic halogen substitution[26–28] (Scheme 1, part A). Moreover, due to the ambident nature of thiocyanate anion, mixtures of thiocyanate and isothiocyanate products were obtained.[27]

Recently, we have reported that *gem*-difluorinated phosphonium salts could be generated from various electrophilic species and difluorinated phosphorus ylide[29–33] (see Scheme 1, part B). The carbon–phosphorus bond of phosphonium salts readily undergoes cleavage under photoredox conditions,[32–38] and we have exploited this property to effect substitution of the phosphonium fragment by halide anions.[39] Herein, we report that this strategy can be applied for the synthesis of the $CF_2SCN$ fragment. As electrophilic component, *N*-methoxyiminium salts formed from methylation of nitrones were considered (part C).

Nitrone **1a** was selected as a model substrate, and its transformation into difluorinated thiocyanate **3a** was evaluated (Scheme 2, Table 1). First, nitrone **1a** (0.5 mmol) was converted into *gem*-difluorinated phosphonium salt **2a** by methylation using methyl triflate followed by reaction with difluorinated phosphobetaine reagent, (triphenylphosphonio)difluoroacetate (PDFA),[40] in acetonitrile. Intermediate salt **2a** was formed




**Scheme 1**




**Scheme 2**

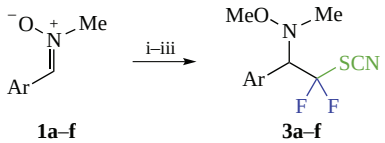
**Table 1** Optimization of intermediate phosphonium salt **2a** conversion into difluoro thiocyanate **3a**.[a]

| Entry | $NH_4SCN$ (equiv.) | CuSCN (equiv.) | *T*/°C | PC | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2.0 | – | 20 | – | <1 |
| 2 | 2.0 | 0.25 | 20 | – | 31 |
| 3 | 2.0 | 1.0 | 20 | – | 60 |
| 4 | 2.0 | 1.0 | 5 | – | 63 |
| 5[c] | 2.0 | 1.0 | 5 | – | 35 |
| 6 | 1.3 | 1.0 | 5 | – | 63 |
| 7 | 1.3 | 1.0 | 5 | $Ir(ppy)_3$ | 70 |
| **8**[d] | **1.3** | **1.0** | **5** | **$Ir(ppy)_3$** | **60 (56[e])** |
| 9[f] | 1.3 | 0.25 | 5 | $Ir(ppy)_3$ | 18 |

[a] Conditions: i, **1a** (0.5 mmol), MeOTf (1.05 equiv.), MeCN (0.5 M) at 0 → 20 °C, 30 min; ii, PDFA (1.3 equiv.), 52 °C, 2 h. [b] Determined by $^{19}F$ NMR with internal standard ($PhCF_3$). [c] 400 nm LED. [d] 2 mmol scale. [e] Isolated yield. [f] Phenanthroline (25 mol%) was added.

quantitatively, and in the reaction mixture it was characterized by NMR spectroscopy. The obtained solution of **2a** was used further without purification for the visible light-promoted thiocyanation. Ammonium thiocyanate was used as a source of thiocyanate anion under irradiation with blue light emitting diodes (450 nm). Copper thiocyanate was needed for the reaction to occur, and its stoichiometric amount was found optimal (see Table 1, entries 1–3). Other sources of thiocyanate anion, as well as other copper salts, were less efficient. Lowering the temperature provided some increase in yield and gave cleaner reaction (entries 3 *vs.* 4). Also, the variation of the irradiation conditions (wavelength and light intensity) led to unsatisfying results (see entry 5 and Online Supplementary Materials for details). The reaction proceeded without photocatalyst (PC), but addition of $Ir(ppy)_3$ (0.25 mol%), a typical catalyst used for the activation of phosphonium salts,[34,36] increased the yield of the product (entries 6 *vs.* 7). It is worth noting that poor results obtained with catalytic amounts of copper cannot be improved by the addition of phenanthroline ligand (entry 9). Though compound **3a** was formed in 70% yield determined by NMR spectroscopy, the reaction mixture contained small amounts of phosphine sulfide ($Ph_3PS$), which complicates purification of the desired product. Finally, performing the reaction on 2 mmol scale of nitrone **1a** allowed us to obtain pure product **3a** *via* a sequence of column chromatography and vacuum short-path distillation, albeit in only 56% yield (entry 8).

Under the optimized conditions, a series of nitrones **1a–f** were transformed into *N*-methoxyamines **3a–f** bearing the $CF_2SCN$ motif (Scheme 3). Products **3** were generally obtained in moderate yields, which mostly reflected the step of thiocyanation reaction. Only in case of thienyl-containing product **3f**, the decreased yield is in part associated with the reduced yield of generation of the corresponding phosphonium salt. Unfortunately, we have failed to obtain phosphonium salts derived from alkyl nitrones due to almost complete enolization,



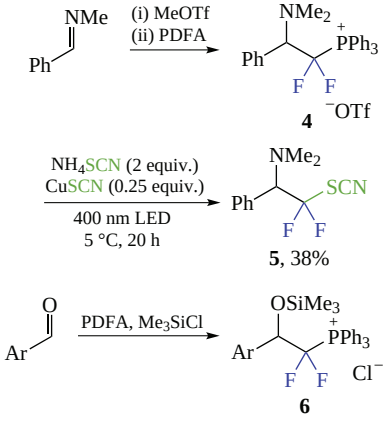

**1a–f** **3a–f**

**a** Ar = 4-$FC_6H_4$, 56% **d** Ar = 3-$MeOC_6H_4$, 51%
**b** Ar = 2-$FC_6H_4$, 52% **e** Ar = Ph, 46%
**c** Ar = 4-$MeOC_6H_4$, 48% **f** Ar = 2-thienyl, 35%

**Scheme 3** *Reagents and conditions*: i, MeOTf; ii, PDFA; iii, $NH_4SCN$, CuSCN, $Ir(ppy)_3$ (0.25%), Blue LED.

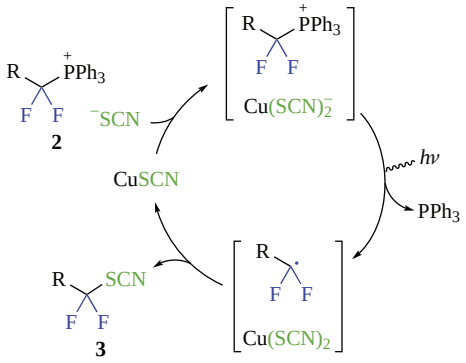
which impedes the formation of difluorinated phosphonium salts.

We also briefly evaluated other difluorinated phosphonium salts obtained using PDFA (Scheme 4). Thus, salt **4** derived from *N*-methylimine gave the expected product **5** under standard conditions, although in low yield. After a series of experiments, we could improve this yield to 38% by performing the reaction with the reduced amount of the copper salt under irradiation with purple LED. Unfortunately, our attempts to similarly transform oxygen-containing phosphonium salts **6** derived from aromatic aldehydes failed.




**Scheme 4**

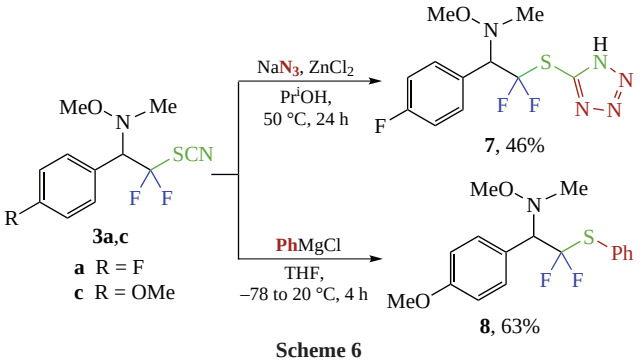
The proposed mechanism for the light-induced displacement of phosphonium group by thiocyanate anion is shown in Scheme 5. In the presence of thiocyanate, copper(II) ate complex is generated, which forms the ion pair with the difluorinated phosphonium salt. Then, under irradiation, the electron is transferred from the negatively charged ate complex to the positively charged phosphonium ion leading to the cleavage of the C–P bond and the formation of difluorinated radical and a copper(II) species. At the final step, the thiocyano group is transferred from copper(II) to the alkyl radical affording product **3** and regenerating the copper(I) catalyst.




**Scheme 5**

To demonstrate the synthetic potential of compounds **3**, we subjected them to transformations involving thiocyano group (Scheme 6). For example, thiocyanate **3a** was converted into tetrazol-5-yl sulfide **7** in reaction with sodium azide and zinc chloride. The reaction of thiocyanate **3c** with phenyl magnesium chloride gave product **8** resulting from nucleophilic substitution of the cyano group. The structure of product **8** was supported by the X-ray diffraction analysis (Figure 1).†

† *Crystal data for* **8**. Crystals were obtained by recrystallization from light petroleum. $C_{17}H_{19}F_2NO_2S$ (*M* = 339.39), monoclinic, space group *C*2/*c* at 100.0 K, *a* = 21.3569(6), *b* = 7.3979(2) and *c* = 21.7330(6) Å,




**Scheme 6**

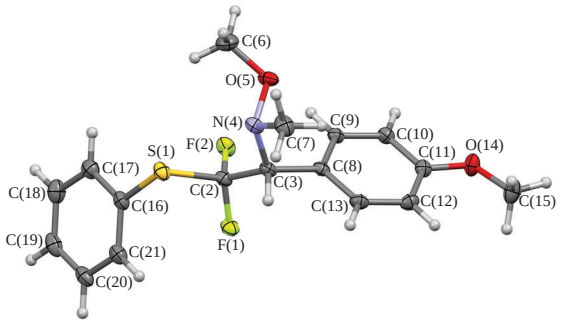



**Figure 1** X-ray structure of compound **8**. The anisotropic displacement ellipsoids are shown at 50% probability level.

In summary, a series of *N*-methoxyamines bearing the $CF_2SCN$ fragment were synthesized from nitrones *via gem*-difluorinated phosphonium salts according to a one-pot three-step protocol. The key step of the reaction proceeds *via* copper-mediated phosphonium/thiocyanate exchange under visible-light irradiation.

This work was supported by the Russian Science Foundation (grant no. 23-43-00026).

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.06.016.

## References

1 M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633.
2 Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467.
3 E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832.
4 C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765.
5 X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731.
6 R. Jia, X. Wang and J. Hu, *Tetrahedron Lett.*, 2021, **75**, 153182.
7 D. Soorukram, C. Kuhakarn, V. Reutrakul and M. Pohmakotr, *Synlett*, 2014, **25**, 2558.
8 F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415.
9 X. Shao, C. Xu, L. Lu and Q. Shen, *Acc. Chem. Res.*, 2015, **48**, 1227.
10 S. Barata-Vallejo, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 7150.
11 H.-Y. Xiong, X. Pannecoucke and T. Besset, *Chem. – Eur. J.*, 2016, **22**, 16734.
12 X. Xiao, Z.-T. Zheng, T. Li, J.-L. Zheng, T. Tao, L.-M. Chen, J.-Y. Gu, X. Yao, J.-H. Lin and J.-C. Xiao, *Synthesis*, 2020, **52**, 197.
13 C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao and Y.-C. Gu, *Coord. Chem. Rev.*, 2014, **261**, 28.
14 Q. Xie and J. Hu, *Chin. J. Chem.*, 2020, **38**, 202.
15 A. W. Erian and S. M. Sherif, *Tetrahedron*, 1999, **55**, 7957.
16 R. G. Guy, in *Cyanates and Their Thio Derivatives*, ed. S. Patai, Wiley, New York, 1977, vol. 2, pp. 819–886.
17 Y. Yasman, R. A. Edrada, V. Wray and P. Proksch, *J. Nat. Prod.*, 2003, **66**, 1512.
18 S. Dutta, H. Abe, S. Aoyagi, C. Kibayashi and K. S. Gates, *J. Am. Chem. Soc.*, 2005, **127**, 15004.
19 I. C. Piña, J. T. Gautschi, G.-Y.-S. Wang, M. L. Sanders, F. J. Schmitz, D. France, S. Cornell-Kennon, L. C. Sambucetti, S. W. Remiszewski, L. B. Perez, K. W. Bair and P. Crews, *J. Org. Chem.*, 2003, **68**, 3866.
20 T. Castanheiro, J. Suffert, M. Donnard and M. Gulea, *Chem. Soc. Rev.*, 2016, **45**, 494.
21 Q. Xu, L. Zhang, G. Feng and C. Jin, *Chin. J. Org. Chem.*, 2019, **39**, 287.
22 M. Gao, M. Vuagnat, M.-Y. Chen, X. Pannecoucke, P. Jubault and T. Besset, *Chem. – Eur. J.*, 2021, **27**, 6145.
23 S. Rezayati and A. Ramazani, *Tetrahedron*, 2020, **76**, 131382.
24 P. G. Karmaker, M. A. Alam and F. Huo, *RSC Adv.*, 2022, **12**, 6214.
25 H. Chen, X. Shi, X. Liu and L. Zhao, *Org. Biomol. Chem.*, 2022, **20**, 6508.
26 A. Haas, M. Spitzer and M. Lieb, *Chem. Ber.*, 1988, **121**, 1329.
27 D. Mandal, R. Gupta, A. K. Jaiswal and R. D. Young, *J. Am. Chem. Soc.*, 2020, **142**, 2572.
28 R. Idogawa, Y. Kim, K. Shimomori, T. Hosoya and S. Yoshida, *Org. Lett.*, 2020, **22**, 9292.
29 V. V. Levin, A. L. Trifonov, A. A. Zemtsov, M. I. Struchkova, D. E. Arkhipov and A. D. Dilman, *Org. Lett.*, 2014, **16**, 6256.
30 A. L. Trifonov, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2017, **19**, 5304.
31 A. L. Trifonov, A. A. Zemtsov, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2016, **18**, 3458.
32 A. L. Trifonov, L. I. Panferova, V. V. Levin, A. D. Volodin, A. A. Korlyukov and A. D. Dilman, *J. Fluorine Chem.*, 2019, **220**, 78.
33 A. L. Trifonov and A. D. Dilman, *Org. Lett.*, 2021, **23**, 6977.
34 L. I. Panferova, A. V. Tsymbal, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2016, **18**, 996.
35 A. L. Trifonov, L. I. Panferova, V. V. Levin, V. A. Kokorekin and A. D. Dilman, *Org. Lett.*, 2020, **22**, 2409.
36 Q.-Y. Lin, X.-H. Xu, K. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2016, **55**, 1479.
37 Y. Ran, Q.-Y. Lin, X.-H. Xu and F.-L. Qing, *J. Org. Chem.*, 2016, **81**, 7001.
38 C. Zhang, *Adv. Synth. Catal.*, 2017, **359**, 372.
39 L. I. Panferova, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Chem. Commun.*, 2019, **55**, 1314.
40 J. Zheng, J. Cai, J.-H. Lin, Y. Guo and J.-C. Xiao, *Chem. Commun.*, 2013, **49**, 7513.
41 *Bruker APEX-III*, Bruker AXS Inc., Madison, WI, 2019.
42 L. Krause, R. Herbst-Irmer, G. M. Sheldrick and D. Stalke, *J. Appl. Crystallogr.*, 2015, **48**, 3.
43 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
44 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.
45 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.
46 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Crystallogr.*, 2020, **53**, 226.

---

$V$ = 3270.69(16) Å$^3$, $Z$ = 8, $d_{calc}$ = 1.378 g cm$^{-3}$, $\mu$(MoK$_\alpha$) = 0.227 mm$^{-1}$, $F$(000) = 1424. Total of 56357 reflections were collected [6245 independent reflections with $I > 2\sigma(I)$, $R_{int}$ = 0.0698] and used in the refinement, which converged to $wR_2$ = 0.0897, GOOF = 1.024 for all independent reflections [$R_1$ = 0.0455 was calculated for 6245 reflections with $I > 2\sigma(I)$].

X-ray diffraction data were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (shutterless ϕ- and ω-scan technique), using graphite-monochromatized MoK$_\alpha$-radiation. The intensity data were integrated by the SAINT program[41] and were corrected for absorption and decay using SADABS.[42] The structure was solved by direct methods using SHELXT[43] and refined on $F^2$ using SHELXL-2018[44] in the OLEX2 program.[45] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The Mercury program suite[46] was used for molecular graphics.

CCDC 2250778 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

*Received: 23rd March 2023; Com. 23/7127*