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Palladium-Catalyzed Fluorosulfonylvinylation of Organic Iodides

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Abstract

A palladium-catalyzed fluorosulfonylvinylation reaction of organic iodides is described. Catalytic $\text{Pd}(\text{OAc})_2$ with stoichiometric silver(I) trifluoroacetate enables the coupling process between an (hetero)aryl or alkenyl iodide and ethenesulfonyl fluoride (ESF, **1**). The method is demonstrated in the successful syntheses of eighty-eight otherwise difficult to access compounds in up to 99% yields, including the unprecedented 2-heteroarylethenesulfonyl fluorides, and 1,3-dienylsulfonyl fluorides.

Fluorosulfonylvinylation

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Supporting information for this article is given via a link at the end of the document.

- R = (hetero)aryl, alkenyl (88 examples)
- 24–99% yield, E-selective
- base, phosphine ligand free
- no dry solvent or inert atmosphere needed
- entry to med chem & materials

Keywords

fluorosulfonylvinylation; palladium catalysis; click chemistry; sulfur fluoride exchange (SuFEx); ethenesulfonyl fluoride (ESF)

Sulfur(VI) fluoride exchange (SuFEx) represents the latest and one of the most powerful reactions in click chemistry. SuFEx features the unusual stability of $\text{S}^{\text{VI}}\text{-F}$ and the extreme fidelity of its activation in a nucleophilic substitution event under appropriate conditions.^[1] By employing three highly connective molecules, sulfuryl fluoride (SO_2F_2),^[1] thionyl tetrafluoride ($\text{O}=\text{SF}_4$),^[2] and ethenesulfonyl fluoride ($\text{CH}_2=\text{CHSO}_2\text{F}$, ESF, **1**),^{[1],[3],[4]} we are able to readily gain SuFEx-abilities for the compounds from nature's nucleophile pool or from the petrochemicals, and finally achieve functions in service of multiple disciplines^{[5],[6]} via catalytic SuFEx protocols (Figure 1a). Searching for new $\text{S}^{\text{VI}}\text{-F}$ functional groups and developing reliable methods for their installations are considered the major challenge for evolving the current SuFEx chemistry.

ESF, among the three irreplaceable scaffolds of SuFEx chemistry, is unique for its versatile reactivity. We have demonstrated ESF as an essential building block to prepare the otherwise difficult to access compounds, 2-arylethenesulfonyl fluorides, through a Heck-Matsuda process [Figure 1b(1)].^[7] 2-Arylethenesulfonyl fluorides represent a rare family of selectively addressable bifunctional electrophiles. Sulfonyl fluorides and vinyl sulfonates (or sulfone) can be readily prepared from 2-arylethenesulfonyl fluorides, via Michael addition and SuFEx, respectively, which are both important classes of electrophiles and potential covalent pharmacophores (Figure 1c).^{[8]–[10]} The latter provide permanent inhibition of target proteins, which is of special interest for us.^[11] Among the 152 approved S^{VI} -containing drugs,^[12] 96 (63%) of them are (hetero)aryl sulfonyl molecules [(Het)Ar- SO_2 -Q, including aryl sulfones, sulfonamides, sulfonic acids and sulfonate esters]. The vinylogous analogs [(Het)Ar- $\text{CH}=\text{CHSO}_2\text{-Q}$] are much less explored, but could be interesting. Rigosertib (Figure 1d), a Phase III drug candidate treating myelodysplastic syndrome, is first of this kind to show promising bioactivity.^[13]

It is reasonable to conclude from the above that general methods for the synthesis of 2-substituted ethenesulfonyl fluorides would open up access to a new and likely valuable scaffold for medicinal chemists. To date, our recent Heck-Matsuda process represents the best route to 2-arylethenesulfonyl fluorides, but the scope is limited. Besides, the use of diazonium salts raises safety issues, especially for potential scale-up purposes. Very recently, Arvidsson and coworkers reported an oxidative Heck coupling of aryl boronic acids and ESF

[Figure 1b(2)].^[14] In pursuit of a more general Heck-type coupling process with ESF,^{[15],[16]} we turned to organic iodides. Although the preliminary attempts using phosphine ligand or base failed (see SI), the combination of aryl halide/silver(I) salt^[17] was found the fix for this palladium catalyzed coupling process between iodobenzene (**2a**) and ESF (**1**) (equation 1).^[18] With the silver(I) salt boost, we have now extended the fluorosulfonylvinylation reaction to aryl, heteroaryl and alkenyl iodides [Figure 1b(3)].

(1)

Examination of the examples in Table 1 reveals that our Heck-type reaction has a broad scope for aryl iodides comprising various types of functional groups. Under mild reaction conditions and simple operation, catalytic Pd(OAc)₂ and stoichiometric AgTFA effected the transformations of aryl iodides (**2a–2ap**) to corresponding vinyl sulfonyl fluorides (**3a–2ap**) in good to excellent yields. For simple aryl iodides, the corresponding 2-arylethenesulfonyl fluorides were obtained in similar or better yields with those obtained via a previously described Heck-Matsuda protocol.^[7] It is notable that a phenolic hydroxyl group (**3p**, **3x**, **3ac**, and **3ag**) is well tolerated in this process, which was incompatible in the Heck-Matsuda process. Not surprisingly, the catalytic system distinguished between iodide and other potential reactive halides (**3h**, **3t** for Br and **3g** for Cl). Moreover, this new protocol succeeded with the multivalent substrate, 1,3-diiodobenzene (**2aj**), for the first time. 1,3-Phenylene bisethenesulfonyl fluoride (**3aj**) was obtained in excellent yield, and was readily scaled up to 10 mmol with the same outcome. The resulting divalent compound was found applicable in a SuFEx poly(aryl vinylsulfonate) synthesis.^[18] Three S^{VI}-F functional groups resident in the aryl iodides were tested and found to be untouched in the fluorosulfonylvinylation conditions, including sulfonyl fluoride (–SO₂F, **3ak**), sulfur pentafluoride (–SF₅, **3al**), and oxysulfonyl fluoride (a.k.a., aryl fluorosulfate, –OSO₂F, **3am**). Furthermore, to show the superiority of sulfur(VI) as a connective scaffold, compounds **3an** and **3ao** were synthesized, taking advantage of O=SF₄ and SO₂F₂, respectively, as the S^{VI}-hub displaying variable ligands in tetrahedral arrays out from the sulfur center.

We then examined heteroaryl iodides in this process. Iodine-substituted heterocycles, including indoles (**5a**, **5b**), carbazole (**5c**), pyrazoles (**5d**, **5e**), (benzo)furans (**5f–5i**), (benzo)thiophenes (**5j–5m**) and pyridines (**5n**, **5o**), underwent fluorosulfonylvinylation reactions efficiently giving corresponding unprecedented heteroarylethenesulfonyl fluorides. However, under the current conditions we were not able to utilize aza-heterocycles, wherein the ring nitrogen is exposed. Either steric hindrance (**5n**) or electron-withdrawing substituents (**5a–5e**, **5n**, **5o**) are essential for the reactions.

Encouraged by these facile syntheses of 2-(hetero)arylethenesulfonyl fluorides, we next turned to alkenyl iodide substrates. For the first time, the 1,3-dienylsulfonyl fluorides (**7a–ae**) were obtained (Table 2). (*E*)-styryl iodides containing a variety of functional groups were found applicable in this process, yielding (1*E*,3*E*)-dienylsulfonyl fluorides (**7a–r**) in moderate to good yields with exclusive *E*-selectivity of the ¹-olefin and full retention of configuration of the ³-olefin. X-ray crystallography studies proved the structure of **7a**, including the (*E*)-configuration of the two double bonds. [19]

Further evaluation of the substrate scope showed that a wide range of alkenyl iodides could be transformed into the corresponding dienyl sulfonyl fluorides. It was found possible to manipulate an aryl iodide and a styryl iodide in the same substrate molecule, realizing a two-fold fluorosulfonylvinylation (**7t**). Non-styryl type alkenyl iodides also yielded desired products (**7u–7w**). When the (*Z*)-alkenyl iodides (**6x**, **6y**) were examined, the (*E*)-configuration of the ¹-double bond in the resulting vinyl sulfonyl fluoride is unambiguous. However, in the case of (*Z*)-styryl iodide (**7x**), the ³-double bond ended up with a 10:1 (*Z*:*E*) ratio. We suggest that the hydridopalladium(II) species from β -elimination might reinsert into the ³-olefin to isomerize it into the thermodynamically more stable (*E*)-configuration.

Other than the simple alkenyl iodides, olefins with more substituents are also applicable. Readily derived from ketones by employing Barton's hydrazone iodination protocol,^[20] these alkenyl iodides were coupled with ESF to give unique new conjugated dienes (**7z–7ae**), which have trisubstituted or fully substituted olefinic moiety adjacent to vinyl sulfonyl fluoride group. The 1,3-dienylsulfonyl fluoride derivatives of (*R*)-camphor, cyclic ketones, 1,3-diketones and estrone were synthesized in moderate to excellent yields.

To evaluate ESF's reactivity as a Heck coupling partner, the relative rates of other Heck ene reactants (**8**) versus ESF were determined by competition experiments (Table 3). It was found that all the carbonyl substituted olefins are more reactive than ESF in the Heck-type coupling reaction. When ESF was allowed to compete *N,N*-dimethylacrylamide (**8d**), no **3a** was observed by ¹H NMR, the sole product being **9d**. Phenyl vinyl sulfone (**8e**), another commonly used vinyl sulfone, showed lower reactivity than ESF.

In summary, we have developed a general method for the preparations of 2-(hetero)arylethenesulfonyl fluorides and 1,3-dienylsulfonyl fluorides. Eighty-eight structurally diverse vinyl sulfonyl fluorides, including seventy-one unprecedented cases, were made on decent scales with full characterization. Studies on the potential bioactivities of these compounds are currently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Dong J, Krasnova L, Finn MG, Sharpless KB. *Angew Chem Int Ed*. 2014; 53:9430.
2. Li S, Wu P, Moses JE, Sharpless KB. *Angew Chem Int Ed*.
3. Krutak JJ, Burpitt RD, Moore WH, Hyatt JA. *J Org Chem*. 1979; 44:3847.
4. Zheng Q, Dong J, Sharpless KB. *J Org Chem*. 2016; 81:11360. [PubMed: 27764941]
5. For an example that SuFEx library compounds selectively captured proteins, see: Chen W, Dong J, Plate L, Mortenson DE, Brighty GJ, Li S, Liu Y, Galmozzi A, Lee PS, Hulce JJ, Cravatt BF, Saez E, Powers ET, Wilson IA, Sharpless KB, Kelly JW. *J Am Chem Soc*. 2016; 138:7353. [PubMed: 27191344]
6. For examples that catalytic SuFEx was used to fabricate polymers, see: Dong J, Sharpless KB, Kwisnek L, Oakdale JS, Fokin VV. *Angew Chem Int Ed*. 2014; 53:9466. Gao B, Zhang L, Zheng Q, Zhou F, Klivansky L, Lu J, Liu Y, Dong J, Wu P, Sharpless KB. submitted.
7. Qin HL, Zheng Q, Bare GAL, Wu P, Sharpless KB. *Angew Chem Int Ed*. 2016; 55:14155.
8. Adams DJ, Dai M, Pellegrino G, Wagner BK, Stern AM, Shamji AF, Schreiber SL. *Proc Natl Acad Sci*. 2012; 109:15115. [PubMed: 22949699]
9. Gushwa NN, Kang S, Chen J, Taunton J. *J Am Chem Soc*. 2012; 134:20214. [PubMed: 23190395]
10. Brouwer AJ, Álvarez NH, Ciaffoni A, van de Langemheen H, Liskamp RMJ. *Bioorg Med Chem*. 2016; 24:3429. [PubMed: 27316540]
11. Singh J, Petter RC, Baillie TA, Whitty A. *Nat Rev Drug Discov*. 2011; 10:307. [PubMed: 21455239]
12. According to the DrugBank (<https://www.drugbank.ca/>, accessed on January 24, 2017), there are totally 2022 approved drugs. 152 (8%) of the them contain a S^{VI} moiety, among which only 85 hits have a connective S^{VI} (i.e., no sulfates, sulfamates, sulfonic acids etc.). We suggest S^{VI} as good connective groups for drug discovery. SuFEx chemistry is developed to speed the assembly of different modules onto the S^{VI}-hub, and thus to open up a wider chemical space for drug discovery.^{[1],[2]}
13. Gumireddy K, Reddy MVR, Cosenza SC, Nathan RB, Baker SJ, Papathi N, Jiang J, Holland J, Reddy EP. *Cancer Cell*. 2005; 7:275. [PubMed: 15766665]
14. Chinthakindi PK, Govender KB, Kumar AS, Kruger HG, Govender T, Naicker T, Arvidsson PI. *Org Lett*. 2017; 19:480. [PubMed: 28075600]
15. Mizoroki T, Mori K, Ozaki A. *Bull Chem Soc Jpn*. 1971; 44:581.
16. Heck RF, Nolley JP. *J Org Chem*. 1972; 37:2320.
17. Ag⁺ as halide scavenger is known to increase the reaction rate of the Heck vinylation process. For an early example, see: Karabelas K, Westerlund C, Hallberg A. *J Org Chem*. 1985; 50:3896.
18. Zheng Q, Sharpless KB. unpublished results.
19. CCDC 1521671 (7s) contains the supplementary crystallographic data.
20. Barton DHR, O'Brien RE, Sternhell S. *J Chem Soc*. 1962:470.

Figure 1.

(a) Strategic diagram for harnessing the SuFEx click chemistry. (b) (i) Our recent Heck-Matsuda process and (ii) this work. (c) Bioactive compounds with sulfonyl fluoride or vinylsulfonyl group. (d) Drugs (candidates) share the $\text{ArC}-\text{C}-\text{SO}_2-$ structural moiety.

Table 1

Synthesis of 2-(hetero)arylethanesulfonyl fluorides.^[a]

<div>0.009 g (2 mol %) Pd(OAc)₂ 0.528 g (1.2 equiv) AgTFA</div> <div><div><div><div>R-I</div><div>+</div><div> </div></div><div><div>R = aryl, 2a–2ap R = heteroaryl, 4a–4o 2.00 mmol</div><div><div>1</div><div>4.00 mmol</div></div></div><div><div>5 mL (0.4 M) acetone, air reflux in 60 °C oil bath 6–24 h</div><div> </div></div></div><tr><th>R¹</th><th>product</th><th>R¹</th><th>product</th><th>R²</th><th>product</th><th>R³</th><th>product</th></tr><tr><td>H</td><td>3a, 95% (99–100 °C)</td><td>OCF₃</td><td>3i, 78% (118–119 °C)</td><td>OMe</td><td>3q, 94% (71–72 °C)</td><td>OMe</td><td>3y, 59% (oil)</td></tr><tr><td>Et</td><td>3b, 99% (94–95 °C)</td><td>CF₃</td><td>3j, 67% (133–134 °C)</td><td>Me</td><td>3r, 97% (29–30 °C)</td><td>Me</td><td>3z, 60% (27–28 °C)</td></tr><tr><td>OPh</td><td>3c, 98% (109–110 °C)</td><td>C(O)Me</td><td>3k, 87% (123–124 °C)</td><td>F</td><td>3s, 88% (69–70 °C)</td><td>C(O)Me</td><td>3aa, 90% (80–81 °C)</td></tr><tr><td>OMe</td><td>3d, 91% (70–71 °C)</td><td>NO₂</td><td>3l, 79% (159–160 °C)</td><td>Br</td><td>3t, 89% (81–82 °C)</td><td>CHO</td><td>3ab, 56% (73–74 °C)</td></tr><tr><td>Ph</td><td>3e, 88% (145–146 °C)</td><td>CN</td><td>3m, 91% (129–130 °C)</td><td>CF₃</td><td>3u, 91% (67–68 °C)</td><td>OH</td><td>3ac^b, 94% (73–75 °C)</td></tr><tr><td>F</td><td>3f, 88% (87–88 °C)</td><td>CO₂Et</td><td>3n, 97% (122–123 °C)</td><td>C(O)Me</td><td>3v, 92% (114–115 °C)</td><td></td><td></td></tr><tr><td>Cl</td><td>3g, 92% (129–130 °C)</td><td>CHO</td><td>3o, 81% (135–136 °C)</td><td>NO₂</td><td>3w, 61% (118–119 °C)</td><td></td><td></td></tr><tr><td>Br</td><td>3h, 86% (144–145 °C)</td><td>OH</td><td>3p, 98% (114–115 °C)</td><td>OH</td><td>3x^b, 98% (127–128 °C)</td><td></td><td></td></tr></div>								R ¹	product	R ¹	product	R ²	product	R ³	product	H	3a , 95% (99–100 °C)	OCF ₃	3i , 78% (118–119 °C)	OMe	3q , 94% (71–72 °C)	OMe	3y , 59% (oil)	Et	3b , 99% (94–95 °C)	CF ₃	3j , 67% (133–134 °C)	Me	3r , 97% (29–30 °C)	Me	3z , 60% (27–28 °C)	OPh	3c , 98% (109–110 °C)	C(O)Me	3k , 87% (123–124 °C)	F	3s , 88% (69–70 °C)	C(O)Me	3aa , 90% (80–81 °C)	OMe	3d , 91% (70–71 °C)	NO ₂	3l , 79% (159–160 °C)	Br	3t , 89% (81–82 °C)	CHO	3ab , 56% (73–74 °C)	Ph	3e , 88% (145–146 °C)	CN	3m , 91% (129–130 °C)	CF ₃	3u , 91% (67–68 °C)	OH	3ac^b , 94% (73–75 °C)	F	3f , 88% (87–88 °C)	CO ₂ Et	3n , 97% (122–123 °C)	C(O)Me	3v , 92% (114–115 °C)			Cl	3g , 92% (129–130 °C)	CHO	3o , 81% (135–136 °C)	NO ₂	3w , 61% (118–119 °C)			Br	3h , 86% (144–145 °C)	OH	3p , 98% (114–115 °C)	OH	3x^b , 98% (127–128 °C)		
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R ¹	R ¹	R ²	R ³

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Isolated % yields and melting points (in parentheses) are reported.

b 5 mol% Pd(OAc)₂ was used.

c 7 mol% Pd(OAc)₂, and 3.0 equiv AgTFA were used.

d 0.2 mmol scale.

e A second portion of 2.5 mol% Pd(OAc)₂, and 0.6 equiv AgTFA was added after the general procedure, and refluxed for another 12 h.

Table 2

Synthesis of dienylsulfonyl fluorides.^[a]

6a-ae 1 mmol	1 8 mmol		7a-ae (31 examples)
R	product	R	product
H	7a , 66% (74–76 °C)	3-Me	7h , 68% (50–51 °C)
		3-F	7i , 58% (49–50 °C)
		3-Br	7j , 42% (oil)
		3-CN	7k , 69% (140–141 °C)
		2-Me	7l , 67% (oil)
	7a		
4-Me	7b , 63% (95–96 °C)	2-F	7m , 76% (61–62 °C)
4- <i>t</i> Bu	7c , 59% (65–66 °C)	2-Cl	7n , 72% (oil)
4-Cl	7d , 60% (110–111 °C)	2-CF ₃	7o , 58% (104–105 °C)
4-Br	7e , 83% (102–103 °C)	2-NO ₂	7p , 35% (102–103 °C)
4-OCF ₃	7f , 42% (53–54 °C)	3,5-diOMe	7q , 64% (88–91 °C)
4-CF ₃	7g , 75% (72–73 °C)	3,4-diF	7r , 56% (85–86 °C)
7s 67% (153–154 °C)			
	7t 65% (223–224 °C)		7u 60% (oil)
7v 78% (69–70 °C)			
	7w 24% (oil)		7x 30% (1 <i>E</i> ,3 <i>Z</i>):(1 <i>E</i> ,3 <i>E</i>) = 10:1
7y 95% (29–31 °C)			
	7zb 81% (74–75 °C)		7aa 42% (64–66 °C)
			7ab 32% (66–67 °C)
7ac 83% (105–106 °C)			
	7ad 79% (84–85 °C)		7ae 91% (168–170 °C)

^[a] Isolated % yields and melting points (in parentheses) are reported.

[b] 0.2 mmol scale, 0.4 mmol (2 equiv) ESF was used.

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Table 3Competition experiments.^[a]

Entry	Olefin 8 (EWG)	Products	Relative rates ^[b]
1	ESF (SO ₂ F)	3a	1.0
2	8a (CO ₂ Me)	9a, 3a	27.1
3	8b (CN)	9b, 3a	3.5
4	8c [C(O)Et]	9c, 3a	90.4
5	8d [C(O)NMe ₂]	9d	>100
6	8e (SO ₂ Ph)	9e, 3a	0.38

^[a] Each of the competition experiments was carried at 1 mmol scale to about 2.5% conversion of “total olefin” (i.e., based upon the number of moles of double bonds) by limiting the amount of iodobenzene added.

^[b] The ratios refer to relative rates of olefin (**8**) versus ESF, and were determined by ¹H NMR based on the integrations of the α-olefinic hydrogen of the products.