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Aryl Fluorosulfate Trapped Staudinger Reduction

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Abstract

A chemoselective Staudinger reduction/sulfur-(VI) fluoride exchange cascade has been developed to join two chemical segments through an aryl sulfamate ester (RNH–SO₂–OAr) linkage. Aryl fluorosulfate is exploited in this work as the first tetrahedral electrophilic trap for the in situ generated iminophosphorane. Ten examples using azide-containing compounds are presented.

Graphical abstract

The Staudinger reaction, a reductive process of an azido group using a phosphine or a phosphite,¹ has been recognized as a well-established method to introduce an amine substituent through the sequence $R-X \rightarrow R-N_3 \rightarrow R-NH_2$ ($X = Br, Cl, OTs$, etc.). Derived from the original Staudinger reduction, Bertozzi² and Raines,³ in parallel, developed the

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Supporting Information

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Detailed experimental procedures; characterizations of new compounds (PDF)

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Notes

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interrupted variations using intramolecular electrophilic traps. This advance has so far found several applications in chemical biology⁴ and materials science.⁵ In the current repertoire of the Staudinger ligation, most methods end up with the formation of a planar, trigonal amide linkage.⁶ However, the original concept of “ligation” stems from the enzymatic process of joining two nucleic acid segments together via a tetrahedral phosphodiester bond between the 3'-hydroxyl of one DNA/RNA terminus and the 5'-phosphoryl of another.⁷ To date, a chemical ligation process that forges a three-dimensional, sulfur(VI)-based linker is unknown.

In mimicking the naturally occurring tetrahedral phosphodiester linkage of DNA/RNA, we sought to utilize the sulfur atom, a third-row neighbor of the phosphorus atom on the periodic table, to build a novel class of artificial tetrahedral linkages. Although the sulfur-containing compounds have long been used in synthetic chemistry for a variety of transformations, their connective characteristic has been overlooked. In 2014, Sharpless reviewed the chemistry of S^{VI} -F substances and coined the concept of sulfur(VI) fluoride exchange (SuFEx).⁸ Lying at the heart of SuFEx chemistry is the connective feature of high-valent sulfur. Inspired by Bertozzi's work and based on our knowledge of the SuFEx chemistry, we designed an aryl fluorosulfate trapped Staudinger reduction by introducing a fluorosulfate group onto a triarylphosphine (Scheme 1). When iminophosphorane is formed (steps I and II), the intramolecular reaction occurs to transfer the imino group from phosphorus(V) to sulfur(VI) as the fluoride leaves with the assistance of hydrogen bonding (step III). Eventually, the P-N bond is hydrolyzed to give an aryl sulfamate ester (step IV), and a connection between the azide moiety and fluorosulfate moiety is formed. Herein, we report the development of this novel tetrahedral linkage formation enabled by a combination of the Staudinger reaction and the SuFEx chemistry.

As outlined in Scheme 2, this study began with the synthesis of 2-(diphenyl)phosphanyl phenyl fluorosulfate (**1**). Palladium-(II) acetate catalyzed the carbon-phosphorus coupling reaction of 2-iodophenol and the diphenylphosphine, giving 2-(diphenyl)phosphanylphenol (**2**) in 76% yield.⁹ Phenol **2** was then treated with sulfuryl fluoride (SO_2F_2) in the presence of *N,N*-diisopropylethylamine (DIPEA) to provide 2-(diphenylphosphanyl)phenyl fluorosulfate (**1**) as a white crystalline compound in 97% yield. Compound **1** was found to be stable in air (at least 1 year) and phosphate buffer (at least 1 week).¹⁰

With fluorosulfate **1** in hand, we attempted to validate our proposed Staudinger ligation process. Compound **1** (0.031 M) was allowed to react with benzyl azide (**3a**, 0.62 M, 20 equiv) in $DMSO-d_6$ with 5% H_2O (v/v) at 37 °C in an NMR tube (Figure 1A). Using triphenylphosphine oxide ($\delta_P = 26.4$ ppm) as the internal standard, the progress of reaction was monitored by ^{31}P NMR. As the reaction proceeded, the starting material **1** ($\delta_P = -19.5$ ppm, doublet) was consumed, while a new peak in the region of phosphorus(V) accumulated ($\delta_P = 25.4$ ppm) (Figure 1B). Further analyses of the reaction mixture after 4 h using LC-MS, 1H NMR, and ^{13}C NMR gave solid evidence for the formation of the desired “ligation” product **4a**. Based on the ^{31}P NMR results, we observed pseudo-first-order kinetics for the consumption of compound **1**. The rate constant (k_{obs}) was determined to be $1.7 \times 10^{-4} s^{-1}$ (Figure 1C).¹¹

We then optimized the conditions of the Staudinger “ligation” between nearly equimolar amounts of compound **1** and **3a** (Table 1). When we applied a 1:5 (**1/3a**) molar ratio, the reaction in the solvent system used for the NMR study only gave 52% product after 3 h (entry 1). Surprisingly, when we performed the reaction neat in a heterogeneous manner with the starting materials suspended on pure water or aqueous phosphate buffer, the reaction was somehow facilitated to finish within 30 min (entries 2 and 3). However, this condition was found to be inapplicable to a wider range of substrates that are crystalline at room temperature or 37 °C. Since we observed that in the heterogeneous conditions **1** was actually dissolved in **3a**, it was likely that the “acceleration” was resulted from the high concentration of the neat reaction (1.6 M versus 0.05 M). Later, we found that when only 0.5 equiv of excess of **3a** in a homogeneous solution of DMSO and phosphate buffer (pH 7.4) was used, the product **4a** was obtained in 95% isolated yield in 3 h (entry 4). The same procedure was also effective on a millimolar scale (entry 5). We then used this homogeneous condition to study the substrate scope.

The scope of this ligation process is partly revealed in Table 2. The lack of interference of functional groups is noteworthy. When the homogeneous condition [i.e., 5/1 (v/v) DMSO/pH 7.4 phosphate buffer] was applied, eight new aryl sulfamate esters (**4b–i**) were obtained in excellent yields (88–96%) with virtually no side products observed. We found that the ester-containing molecules **3b** and **3c** were compatible with this reaction. The treatment of the compounds **3b** and **3c** with fluorosulfate **1** (1.5 equiv) under the homogeneous conditions described above provided the ligation products **4b** and **4c** in 95% and 91% yield, respectively (entries 2 and 3). Fmoc-Lys(N₃)-OH (**3d**), a building block for solid-phase peptide synthesis bearing a free carboxylic acid moiety, also reacted with fluorosulfate **1**, yielding the desired aryl sulfamate ester **4d** in 88% yield (entry 4). Moreover, Leelamine (dehydroabietylamine), a promising compound for cancer treatment,¹² was also successfully attached to compound **1** via a sulfur-containing tetrahedral linkage (entry 5). The ligation process was found to be effective for the azide-containing monosaccharide, and nucleotide-derived azides (**3f–h**) afforded the desired ligation products in 85–91% yields (entries 6–8). These results suggested that the hydroxyl group, purine, and the pyrimidine base were compatible with the ligation reaction, revealing the possibility of using this new reaction to build up an aryl sulfamate ester connection between two motifs acting as a mimic of the phosphodiester linkage. Importantly, we showed that the intramolecular ligation reaction was highly selective versus intermolecular reaction (entry 9). Even though a fluorosulfate group was embedded in the azide substrate, only the substitution of the *o*-fluorosulfate on the phosphine moiety was enabled by proximity.¹³

In the recent report on the reengineering of vancomycin, Sharpless has shown the capability to install an azide handle onto the complex antibiotic molecule selectively at its “head” carboxylic acid group.¹⁴ To demonstrate the fidelity of the present ligating process, we treated the azide derivative of vancomycin (**5**) with 5 equiv of compound **1**. Within 1 h, the reaction was complete, and the ligated product **6** was isolated by preparative HPLC in 94% yield as a white solid (Scheme 3).

Inapplicable examples include 3° alkyl azide, aryl azide, sulfonyl azide, and oxysulfonyl azide (Figure 2). *tert*-Butyl azide (**7**) was untouched under the ligation conditions. Others

(**8–10**) were, in fact, very reactive regarding the iminophosphorane formation (steps I and II). Compounds **8**, **9**, and **10**, respectively, reacted with **1** instantly at autogenous temperature (releasing both heat and gas) to give the corresponding azaylides. However, only in the case of phenyl azide (**8**) could the imino group transfer (step III), although very slow, be observed by LC–MS (~30% yield after 24 h). For the sulfonyl azide (**9**) or oxysulfonyl azide (**10**), the competing hydrolytic process of iminophosphorane is predominant.

Three other phosphines were examined to study the electronic effect. It can be concluded from Scheme 3 that, generally, electron-rich phosphines were oxidized by azides faster than electron-poor ones.¹¹ However, although phosphine **11** is oxidized more quickly by the azide ($k_{\text{rel},11/1} \sim 2.5$), the formation of desired **12** was not complete until 2.5 h. The post-Staudinger processes (steps III and IV) limited the overall reaction rate, with several intermediates being observed on LC–MS (see the Supporting Information for details). When an electron-withdrawing group (e.g., $-\text{CO}_2\text{H}$ in **13**) was present on the benzene ring that bears the fluorosulfate group, the phenoxide departure was preferred over the leaving of a fluoride anion probably because of its enhanced acidity. Electron-withdrawing groups on both of the other two benzene rings (phosphine **15**), although also slowing the reaction, did not change the selectivity in the sulfuryl group transfer event.

In summary, we have developed an aryl fluorosulfate trapped Staudinger reaction. The concept of Staudinger “ligation” was extended to the tetrahedral, heteroatom-based electrophile. This novel method showed great reliability for a variety of azides in aqueous solution under physiological conditions. Further study on developing a more effective phosphine reagent and using this chemistry as a tool for bioconjugation in a complex system is underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(A) Reaction of **1** and benzyl azide (**3a**). (B) Time-course of the reaction between **1** and **3a** monitored by ^{31}P NMR. (C) Plot of $\ln [1]$ versus time when $[3a]$ is considered constant at 0.62 M. The slope suggested a pseudo-first-order rate constant $1.7 \times 10^{-4} \text{ s}^{-1}$.

Figure 2.
Unsuccessful azide substrates for the new ligation reaction.

Scheme 1.

Design of the Aryl Fluorosulfate Trapped Staudinger Reduction

Scheme 2.

Synthesis of 2-(Diphenylphosphanyl)phenyl Fluorosulfate (1)

Scheme 3.
Evaluation of Other 2-Phosphanylaryl Fluorosulfates

Table 1

Optimization of the Reaction Conditions

entry	solvent ^a	time (h)	yield ^b (%)
1	DMSO/H ₂ O (95/5)	3	52
2	H ₂ O	0.5	75
3	pH 7.4 buffer ^d	0.5	100 (95)
4 ^c	DMSO/pH 7.4 buffer ^d (5/1)	3	95
5 ^e	DMSO/pH 7.4 buffer ^d (5/1)	3	(92)

^aRatios of volume are stated in the parentheses.

^bYields were determined by ¹H NMR using methylene bromide as the internal standard. Isolated yields are stated in the parentheses.

^c0.15 mmol (1.5 equiv) of **3a** and 1.0 mL of mixed solvent were used.

^dPhosphate buffer, 0.05 M.

^e1.0 mmol of **1**, 1.5 mmol of **3a**, and 10 mL of mixed solvent were used.

Table 2

Aryl Fluorosulfate Trapped Staudinger Reaction

entry	azide	time (h)	yield (%)	mp (°C)	entry	azide	time (h)	yield (%)	mp (°C)
1 ^a		0.5	95 (4a)	195–196	7 ^b		4	85 (4g)	182 (dec.)
2 ^b		2	96 (4b)	oil	8 ^b		1	91 (4h)	186 (dec.)
3 ^b		4	91 (4c)	86 (dec.)	9 ^b		5	90 (4i)	111–113
4 ^b		4	88 (4d)	125–127	10 ^c		1	94 (6)	N.D.
5 ^b		4	90 (4e)	115–116					
6 ^b		5	86 (4f)	syrup					

^aMethod A: as described in Table 1, entry 3. ^bMethod B: **1** (0.1 mmol) and azide **3** (0.15 mmol) were dissolved in 1.0 mL of 5/1 (v/v) DMSO/pH 7.4 buffer. The mixture was stirred at 37 °C under air atmosphere. ^cMethod C: **1** (0.25 mmol) and azide **5** (0.05 mmol) were dissolved in 0.6 mL of 5/5/2 (v/v/v) DMSO/DMF/pH 7.4 buffer. The mixture was stirred at under air atmosphere for 1 h. N.D. = not determined.