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Anilide Formation from Thioacids and Perfluoroaryl Azides

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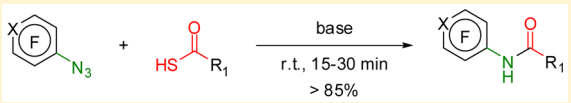
Supporting Information

ABSTRACT: A metal-free method for fast and clean anilide formation from perfluoroaryl azide and thioacid is presented. The reaction proved highly efficient, displaying fast kinetics, high yield, and good chemoselectivity. The transformation was compatible with various solvents and tolerant to a wide variety of functional groups, and it showed high performance in polar protic/aprotic media, including aqueous buffer systems.

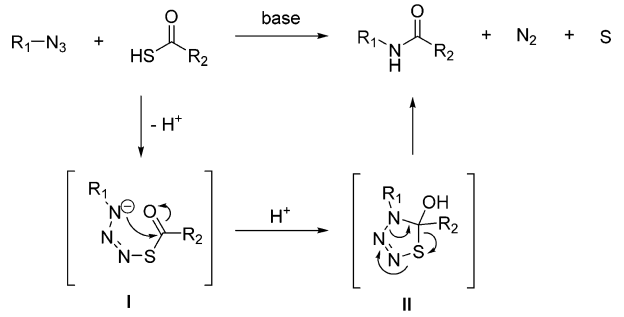


INTRODUCTION

Azide-mediated coupling reactions have a long history, dating back to Curtius' acyl azide-based amide coupling in the early 20th century,[1] and have regained intense interest after the introduction of Staudinger ligation[2] and metal-catalyzed azide−alkyne cycloaddition (CuAAC/RuAAC).[3] These "click-type" coupling reactions exhibit excellent chemoselectivity and have been employed in many applications, including surface functionalization and bioconjugation.[4] The use of metal catalysts, however, limits the utility of the corresponding coupling reactions for biological applications due to the concerns of cytotoxicity. A strategy to eliminate the catalyst involves preactivation of the reagents, by using, for example, strained alkynes in the reaction.[5] Coupling reactions that involve activated azides are less studied.[6] One example involves the thioacid/azide amidation reaction, first discovered in the 1980s,[7] and reinvestigated in the past decade.[8] Various azides can react with thiocarboxylic acids (−CSOH or −COSH) to form amide bonds while releasing nitrogen gas and elemental sulfur. Azides having electron-withdrawing groups generally display kinetics considerably faster than those of their electron-rich counterparts. This is in contrast to Staudinger ligation and azide−alkyne cycloaddition, where electron-rich azides show higher reactivity.[8b] The mechanism of the thioacid-azide reaction has been proposed to proceed by stepwise nucleophilic addition to give intermediate **I**, followed by cyclization to thiotriazoline intermediate (**II**), and final extrusion of N_2S to give the amide product (Scheme 1).[8b]

A key issue with the thioacid/azide amidation reaction is the slow kinetics. Sulfonyl azides showed the highest rate constants (k_{obs} = 5.7 × 10^{-3} M^{-1} s^{-1} for the reaction of benzenesulfonyl azide with thiobenzoic acid at 21 °C).[8b] Liskamp and co-workers called this a "sulfo-click" reaction to emphasize its potential as a general type of coupling reaction.[9] Subsequently, this sulfonyl azide/thioacid amidation reaction has been applied for the site-specific functionalization of peptides/proteins,[10] fluorophores, and metal chelators;[9] the detection of thioacids in the bacterial proteome;[11] and the kinetic target-guided synthesis.[12] However, sulfonyl azide/thioacid amidation has not led to widespread applications in surface and nanomaterials science, likely due to the lack of straightforward protocols to incorporate the sulfonyl azide functionality onto nanomaterials or surfaces. In comparison, acyl azides showed reactivities much lower than those of sulfonyl azides.[8a] Moreover, acyl azides are unstable, which limits their applications in materials functionalization.[13]

Scheme 1. Proposed Amidation Mechanism[8b]



In this context, perfluoroaryl azides (PFAAs) constitute a class of compounds that have been widely used as heterobifunctional photocoupling agents in photoaffinity labeling,[14] and functionalization of surfaces[15] and nanomaterials.[16] These azides have recently been applied in catalyst-free reactions with enamines and aldehydes to form amidines[17] and amides,[18] respectively. The enhanced reactivity was due to the electron-deficient perfluoroaryl group that renders the azide highly electrophilic. In this study, we report that electrophilic PFAAs react efficiently with thioacids at room temperature to yield amides. We explored the reaction kinetics, the effect of solvent and substrate scope, as well as the functional group tolerance of the reaction.

RESULTS AND DISCUSSION

Methyl 4-azido-2,3,5,6-tetrafluorobenzoate (**1**) was selected as a model azide for the optimization of the reaction conditions.

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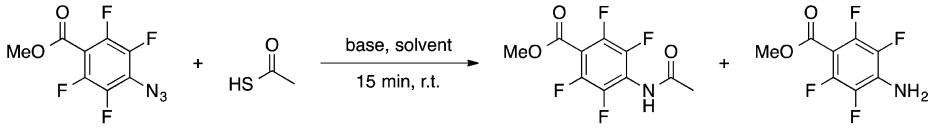
Table 1. Optimization of the Reaction Conditions[a]



1 2 3 4

			yield[b] (%)	
entry	base (equiv)	solvent	compd **3**	compd **4**
1	2,6-lutidine (1.3)	MeOH	74	7
2		MeOH	12	67
3	2,6-lutidine (1.3)	acetone	41	27
4	2,6-lutidine (1.3)	DCM	57	41
5	2,6-lutidine (1.3)	DMF	31	7
6	2,6-lutidine (1.3)	THF	48	2
7	2,6-lutidine (1.3)	DMSO	31	2
8	2,6-lutidine (1.3)	MeOH:H_2O (6:4)	95 (92[c])	<1
9	2,6-lutidine (1.3)	acetone:H_2O (7:3)	78	3
10	pyridine (1.3)	MeOH	43	5
11	NEt_3 (1.0)	MeOH	95	<1
12	NEt_3 (0.5)	MeOH	90	<1
13	NEt_3 (0.2)	MeOH	53	5
14	TBAOH (1.0)	acetone	96	4

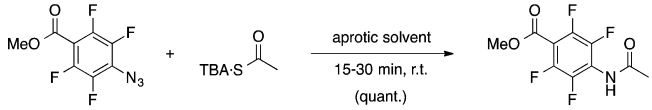
[a]Conditions: PFAA **1** (0.22 mmol), thioacid **2** (0.28 mmol), base, solvent (0.5 mL). [b]Determined by ^{19}F NMR. [c]Isolated yield.

When this PFAA was mixed with thioacetic acid in methanol at 25 °C in the presence of 1.3 equiv of 2,6-lutidine for 15 min, amide **3** (74%) together with a small amount of aniline **4** (7%) was observed by ^{19}F NMR (entry 1, Table 1). Thioacetic acid is weakly acidic (pK_a = 3.3), and 2,6-lutidine (pK_a = 6.6) was needed for the formation of the amide. When 2,6-lutidine was absent, aniline **4** was formed as the major product (entry 2), likely the result of reduction of the PFAA by thioacetic acid.

The base-promoted PFAA/thioacid amidation was strongly influenced by the solvent used, where amide formation was slower in nonpolar or polar aprotic solvents (Table 1, entries 3−7). Large amounts of aniline were formed when acetone (entry 3) or DCM (entry 4) was used as the solvent. When water was added to either methanol or acetone, the amide formation increased while the aniline byproduct decreased (entries 1 and 3 vs 8 and 9, respectively). The best condition, 2,6-lutidine in 60:40 water−methanol, provided 95% yield (92% isolated yield) of amide with only a trace amount of aniline (entry 8). The increased yield is likely due to the facilitated formation/stabilization of thioacetate anion in the protic solvent. The effect of base was further investigated using methanol as the solvent (entries 1, 10−14). Pyridine (pK_a = 5.23) resulted in slower transformation (entry 10), whereas triethylamine (pK_a = 10.78) yielded clean product formation with only 0.5 equiv needed. Lowering the amount of base to 0.2 equiv slowed the reaction (entry 13).

To improve the yield of the reaction in organic aprotic solvents, tetrabutylammonium hydroxide (TBAOH) was used as base. Toward this end, addition of TBAOH (1 equiv) to an acetone solution of PFAA **1** and thioacetic acid **2** gave the amide product in 96% yield together with trace amount of aniline (entry 14). If thioacetic acid was first treated with TBAOH and the isolated TBA-thioacetate salt (**5**) was added to PFAA **1**, amide product **3** was obtained in quantitative yield without any aniline byproduct (Scheme 2). These reaction conditions worked very well in aprotic solvents, including acetone, DMSO, THF, and DCM.

Scheme 2. Efficient Amide Formation in Aprotic Solvents



1 5 3

The reaction follows second-order kinetics. The rate constants (k_{obs}'s) were estimated using ^{19}F NMR spectroscopy with triethylamine as the base in CD_3OD at 25 °C. Various azides were tested, from which the amide products were isolated in high yields and no aniline was formed (Table 2). The reaction rates fell into the fast kinetic range (>10^{-3} M^{-1} s^{-1}). In a comparison with less electron-withdrawing substituents (entries 1−2), a more strongly electron-withdrawing substituent (CN) at the para position increased the rate (entry 3). A Hammett analysis showed good linear correlation with the σ_p constants (Supporting Information Figure S1), where the relatively large and positive reaction constant ($\rho \sim 1.3$) supports the proposed reaction mechanism (Scheme 1).

We next evaluated the performance of the reaction in aqueous solutions. Sodium 4-azido-tetrafluorophenylbenzoate (**6**) has good solubility in both water and phosphate-buffered saline (PBS) and was thus chosen as the model compound. As shown in Table 3, the reactions in water (entry 1) or in pH 7.4 buffer (entry 3) were completed within 2 h to give amide **7** in >90% yield. The reaction proceeded faster in the presence of a base (entry 2) or in more basic buffer solutions (entries 4, 5), giving the amide product in 95% and 99% yield, respectively. Furthermore, unlike the reactions in organic solvents, no aniline side product was observed in aqueous media.

The chemoselectivity of the reaction was studied with the concept introduced by Glorius and co-workers.[19] The reaction was carried out with addition of 1 equiv of an interfering compound to the reaction mixture, after which the products were analyzed. The results clearly demonstrated that the

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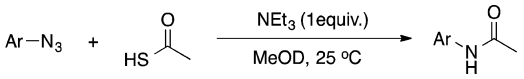
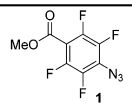
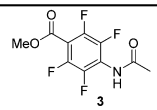
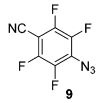
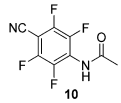
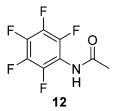
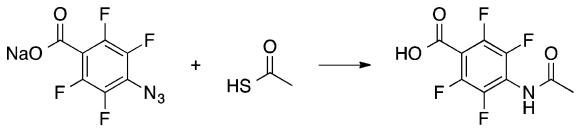
Table 2. PFAA Reactivities and Reaction Kinetics[d]



Entry	Azide	Product	Yield (%)[a]	k_{obs} (10^{-3} M^{-1} s^{-1})[b]	k_{rel}
1	 1	 3	95 (92[c])	16.6 ± 0.4	2.4
2	 9	 10	99 (88[c])	44 ± 2	6.5
3	 11	 12	87 (86[c])	6.8 ± 0.1	1
4	 13	 14	99 (91[c])	-	-

[a]Determined by ^{19}F NMR. [b]In CD_3OD, 25 °C, see Experimental Section for details. [c]Isolated yield. [d]Conditions: azide (0.66−0.85 mmol), thioacid **2** (1.3 equiv), rt.

Table 3. Reaction in Aqueous Solution[a]



6 **2** **7**

entry	solvent	base (equiv)	time (min)	yield[c] (%)
1	H_2O		100	90
2	H_2O	NaOH (1.0)	20	95 (88[d])
3	PBS pH 7.4[b]		120	95
4	PBS pH 8[b]		40	99
5	PBS pH 9[b]		20	99

[a]Conditions: PFAA **6** (0.44 mmol), thioacid **2** (0.6 mmol), solvent (1 mL), rt. [b]0.2 M. [c]Determined by ^{19}F NMR in $CDCl_3$. [d]Isolated yield.

reaction displayed excellent chemoselectivity (Table 4). Aliphatic/aromatic aldehydes, amides, nitriles, alkynes, alkenes, aliphatic azides, and aliphatic/aromatic halogens did not influence the amide formation, and these reagents were recovered almost quantitatively. Similar to sulfonyl azides,[9] aliphatic amines and thiols interfered with the reaction to some extent, which is expected since aliphatic sulfhydryl moieties are known to reduce azides.[20] However, the impact decreased significantly when water was added. Thiophenol and anilines showed very little interference, and other sulfur-containing groups such as thiolesters and disulfides did not interfere with the reaction either.

We hypothesize that the formation of aniline in the presence of aliphatic amines is a result of competing addition of amine to intermediate **I-1** (Scheme 3). Aniline **4** is subsequently formed via intermediate **IV**. This mechanism is supported by the observation of compound **V** in the product. The hypothesis is further supported by the results obtained at pH 9.0, where a higher amount of aniline was observed in comparison with that observed for the reaction in neutral buffer (entries 20, 21, Table 4).

CONCLUSIONS

In summary, we have demonstrated that PFAAs undergo efficient and rapid amidation reaction with thioacids at room temperature. Unlike other azide reactions, PFAAs show better reactivity in aqueous media. The reaction is metal-free, and shows a high degree of chemoselectivity. In addition, a variety of PFAAs can be readily prepared from commercially available starting materials and are stable as long as they are protected from UV light. These features make PFAA-thioacid amidation an attractive coupling reaction for bioconjugation and nanomaterials functionalization. Moreover, this method provides access to perfluoroaryl amides under mild conditions, which have recently been developed as very powerful and unique auxiliaries in Pd-catalyzed C−H activations.[21]

EXPERIMENTAL SECTION

General Methods. All reagents and solvents were used as commercially received. Chromatography was conducted using silica gel, visualized with ultraviolet light. Chemical shifts are reported as δ values (ppm) in $CDCl_3$ (^1H δ = 7.26, ^{13}C δ = 77.16) or DMSO-d_6 (^1H δ = 2.50, ^{13}C δ = 39.52). ^{19}F NMR signals were recorded in reference to hexafluorobenzene (δ = −161.75 in $CDCl_3$ or −162.65 in DMSO-d_6). High resolution mass spectrometry (HRMS) data were obtained with TOF analyzer in the electrospray ionization (+) model.

*Methyl 4-Azido-2,3,5,6-tetrafluorobenzoate (**1**).*[22] Colorless crystals. ^1H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 145.5 (dm, J_{C-F} = 260 Hz), 140.6 (dm, J_{C-F} = 250 Hz), 123.5, 107.8, 53.4. ^{19}F NMR (376 MHz, $CDCl_3$): δ −138.62 (m, 2F), −150.91 (m, 2F).

*Methyl 4-Acetamido-2,3,5,6-tetrafluorobenzoate (**3**).* Thioacetic acid (65 mg, 0.85 mmol) and triethylamine (119 μL, 0.85 mmol) were mixed with methanol (1.5 mL) in a round-bottomed flask, and PFAA **1** (165 mg, 0.66 mmol) was added. The reaction mixture was stirred at room temperature for 15 min, after which the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (2:1 hexane/EtOAc, R_f = 0.19) to provide the title compound as white crystals (151 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.98 (s, 3H), 7.01 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 53.5, 110.1 (m), 119.5 (m), 142.1 (dm, 2C, J_{CF} = 251 Hz), 145.0 (dm, 2C, J_{CF} = 259 Hz), 160.2, 168.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −139.20 (m, 2F), −144.09 (d, 2F). ESI-HRMS

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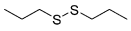
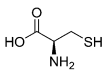
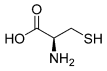
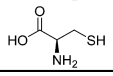
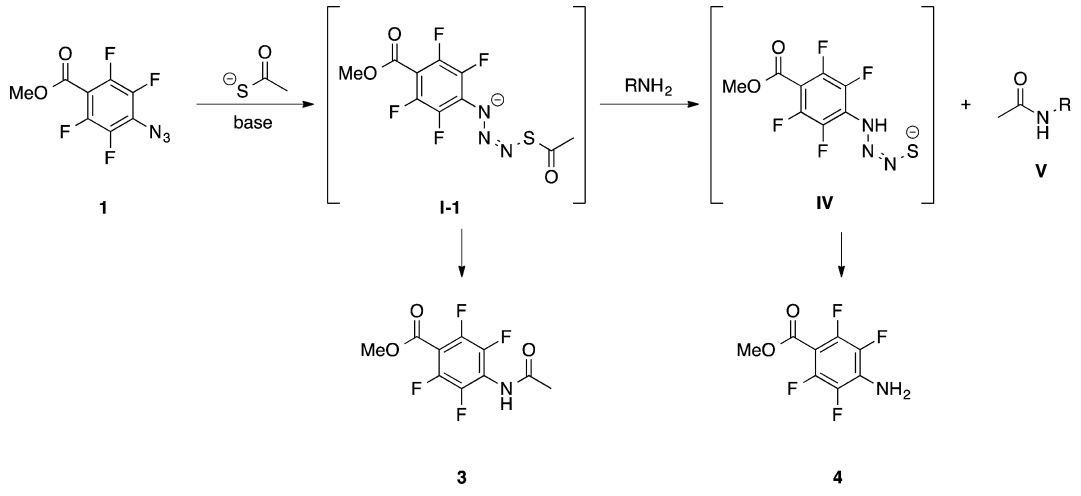
Table 4. Chemoselectivity Tests[d]

Entry	Azide	Additive	Solvent	Amide (%)[a]	Aniline (%)[a]	Remaining additive (%)[a]
1	**1**		MeOH	>99	n.d.	>99
2	**1**		MeOH	>99	n.d.	>99
3	**1**		MeOH	>99	n.d.	>99
4	**1**		MeOH	>99	n.d.	>99
5	**1**		MeOH	>99	n.d.	>99
6	**1**		MeOH	>99	n.d.	>99
7	**1**		MeOH	>99	n.d.	>99
8	**1**		MeOH	>99	n.d.	96
9	**1**		MeOH	>99	n.d.	86
10	**1**		MeOH	>99	n.d.	>99
11	**1**		MeOH	>99	n.d.	-
12	**1**		MeOH	>99	n.d.	>99
13	**1**		MeOH	96	4	95
14	**1**		MeOH	80	20	41
15	**1**		MeOH	75	25	70
16	**1**		H_2O/MeOH[b]	91	9	85
17	**1**		MeOH	60	40	54
18	**1**		H_2O/MeOH[b]	74	26	70
19	**1**		DMF	85	15	-
20	**6**		PBS (pH 7.4)[c]	70	30	-
21	**6**		PBS (pH 9.0)[c]	26	74	-

[a]Determined by ^{19}F and ^{1}H NMR ($CDCl_3$) upon complete conversion of azide using an internal standard. [b]12% H_2O (v/v). [c]0.2 M. [d]Conditions: azides (0.22 mmol), thioacid **2** (0.28 mmol), NEt_3 (0.28 mmol, except in PBS buffers), additive (0.28 mmol), rt, solvent (0.5 mL).

Scheme 3. Proposed Reaction of PFAA 1 with Thioacetic Acid in the Presence of Aliphatic Amines



Calcd for $C_{10}H_8F_4NO_3$ $[M + H]^+$: 266.0440. Found: 266.0441. IR (ATR): 3246.8, 1735.5, 1690.9, 1502.0, 1469.6, 1437.6, 1325.5, 1233.9, 1021.9, 935.8, 895.1, 691.1 cm^{-1}.

*Methyl 4-Amino-2,3,5,6-tetrafluorobenzoate (**4**).*[22] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H, CH_3), 4.35 (br, 2H, NH_2). ^{13}C NMR (125 MHz, d_6-DMSO): δ 161.7, 146.2 (dm, 2C, J_{C-F} = 251.1 Hz), 136.0 (dm, 2C, J_{C-F} = 239.61 Hz), 129.9 (m, 1C), 99.1, 52.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −140.60 (m, 2F), −162.14 (m, 2F).

*4-Azido-2,3,5,6-tetrafluorobenzoic Acid (**8**).*[23] Pale yellow solid. ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 144.2 (dm, J_{C-F} = 252 Hz), 140.1 (dm, J_{C-F} = 250 Hz), 122.5, 108.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −136.93 (m, 2F), −150.64 (m, 2F). 4-Azido-2,3,5,6-tetrafluorobenzoic soldium salts (**6**) were prepared by addition of an aqueous solution of NaOH to **8** until pH neutral.

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4-Acetamido-2,3,5,6-tetrafluorobenzoic Acid (7). To a solution of 4-azido-2,3,5,6-tetrafluorobenzoic acid (103 mg, 0.44 mmol) in water (1 mL) was added NaOH (35 mg, 0.88 mmol). When the azide was completely dissolved after sonication, thioacetic acid (46 mg, 0.6 mmol) was added, and the mixture was stirred for 20 min. After this, the reaction was quenched with 1 M HCl (10 mL), and the solvent was evaporated. The residue was purified by flash column chromatography (3:1 DCM/MeOH, R_f = 0.25) to yield the product as white crystals (98 mg, 88%). ^{1}H NMR (400 MHz, D_2O): δ 2.21 (s, 3H). ^{13}C NMR (100 MHz, DMSO): δ 22.5, 116.4 (m), 117.0 (m), 142.0 (dm, 2C, J_{CF} = 248 Hz), 142.7 (dm, 2C, J_{CF} = 245 Hz), 160.5, 168.6. ^{19}F NMR (376 MHz, D_2O): δ −144.12 (m, 2F), −145.56 (m, 2F). ESI-HRMS Calcd for $C_9H_6F_4NO_3$ $[M + H]^+$: 252.0284. Found: 252.0282. IR (ATR): 3189.8, 2499.5, 1686.2, 1624.7, 1473.7, 1400.1, 1362.9, 1247.3, 1013.5, 983.8, 950.6, 848.7, 827.7, 741.8 cm^{-1}.

4-Azido-2,3,5,6-tetrafluorobenzonitrile (9).[22] Light yellow liquid. ^{13}C NMR (100 MHz, $CDCl_3$): δ 89.1 (t, 1C, CN, J = 18 Hz), 107.2 (t, 1C, J = 4 Hz), 126.7 (m, 1C), 140.3 (dm, 2C, J_{C-F} = 252 Hz), 147.5 (dm, 2C, J_{C-F} = 262 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −132.05 (m, 2F), −148.68 (m, 2F).

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)acetamide (10). The compound was synthesized following the protocol of compound **3** from 4-azido-2,3,5,6-tetrafluorobenzonitrile (184 mg, 0.85 mmol) and thioacetic acid (84 mg, 1.1 mmol). The reaction mixture was evaporated under reduced pressure, and the residue was purified by flash column chromatography (2:1 hexane/EtOAc, R_f = 0.14) to give the product as a pale yellow solid (165 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 7.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 91.5, 107.4 (m), 122.6 (m), 141.8 (dm, 2C, J_{CF} = 246 Hz), 147.5 (dm, 2C, J_{CF} = 262 Hz), 167.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −132.27 (m, 2F), −141.50 (m, 2F). ESI-HRMS Calcd for $C_9H_5F_4N_2O$ $[M + H]^+$: 233.0338. Found: 233.0339. IR (ATR): 3296.6, 2243.2, 1686.1, 1647.5, 1542.2, 1504.9, 1482.5, 1371.4, 1320.6, 1282.3, 1259.1, 1141.2, 999.8, 963.2, 924.2, 706.9 cm^{-1}.

1-Azido-2,3,4,5,6-pentafluorobenzene (11).[24] Amber liquid. ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.9 (dt, J = 4.63, 12.5 Hz), 138.1 (dm, J = 261 Hz), 141.0 (dm, J = 250 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −151.48 (m, 2F), −159.62 (m, 1F), −161.11 (m, 2F).

N-(Perfluorophenyl)acetamide (12). The compound was synthesized following the protocol of compound **3** from pentafluorophenyl azide (167 mg, 0.8 mmol) and thioacetic acid (76 mg, 1.0 mmol). Purification was done by flash column chromatography (2:1 hexane/EtOAc, R_f = 0.29) to give the product as white crystals (121 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (br, 1H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 111.9 (m), 137.9 (dm, 2C, J_{CF} = 253 Hz), 140.4 (dm, 1C, J_{CF} = 235 Hz), 143.1 (dm, 2C, J_{CF} = 253 Hz), 168.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −144.81 (m, 1F), −156.24 (m, 2F), −162.18 (m, 2F). ESI-HRMS Calcd for $C_8H_5F_5NO$ $[M + H]^+$: 226.0291. Found: 226.0293. IR (ATR): 3215.3, 1689.1, 1523.4, 1493.0, 1461.9, 1378.4, 1274.8, 1160.7, 1033.8, 1007.4, 980.6, 942.0, 735.0, 666.8 cm^{-1}.

4-Azido-2,3,5,6-tetrafluoropyridine (13).[25] Colorless liquid. ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.2 (m), 135.4 (dm, 2C, J_{C-F} = 262 Hz), 143.6 (dm, 2C, J_{C-F} = 244 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ −89.59 (m, 2F), −152.91 (m, 2F).

N-(Perfluoropyridine-4-yl)acetamide (14). The compound was synthesized following the protocol of compound **3** from 4-azido-2,3,5,6-tetrafluoropyridine (163 mg, 0.85 mmol) and thioacetic acid (84 mg, 1.0 mmol). Purification was done by flash column chromatography (2:1 hexane/EtOAc, R_f = 0.23) to give the product as a white solid (151 mg, 91%). ^{1}H NMR (400 MHz, DMSO): δ 2.17 (s, 3H), 10.77 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 128.2 (m), 136.6 (dm, 2C, J_{CF} = 261 Hz), 143.7 (dm, 2C, J_{CF} = 245 Hz), 167.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −145.67 (m, 2F), −89.44 (m, 2F). ESI-HRMS Calcd for $C_7H_5F_4N_2O$ $[M + H]^+$: 209.0338. Found: 209.0338. IR (ATR): 3220.4, 2979.4, 1694.6, 1643.7, 1524.4, 1461.8, 1420.7, 1372.9, 1279.8, 1248.1, 1088.7, 1012.3, 985.9, 924.6, 723.6, 689.6, 613.8 cm^{-1}.

Kinetic Studies. Rate constants were measured with the following protocol. To a mixture of azide (2 equiv) and NEt_3 (1 equiv) in CD_3OD (0.4 mL) in an NMR tube at 25 °C was added thioacetic acid (1 equiv in 0.4 mL of CD_3OD). The reaction was monitored by ^{19}F NMR, and the rate constants were estimated by nonlinear curve fitting following a second-order kinetic model.[8b]

Chemoselectivity Studies. The functional group tolerance was evaluated with the strategy suggested by Glorius and co-workers.[19] The azide (0.22 mmol) was dissolved in the solvent (0.5 mL) to which NEt_3 (39 μL) was added (except for buffer systems). The additive (0.28 mmol) and the thioacid (0.28 mmol) were premixed in the solvent; the solution was added to the azide solution, and the resulting mixture was stirred at room temperature until complete conversion of the azide was recorded. The products were analyzed by ^{19}F and ^{1}H NMR before and after reaction to determine the percentage of each component in the reaction mixture.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data including ^{1}H, ^{13}C, and ^{19}F NMR spectra; IR spectra; and kinetic study data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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