The first fluoroalkylation of amino acids and peptides in water utilizing the novel iodonium salt $(CF_3SO_2)_2NI(Ph)CH_2CF_3$

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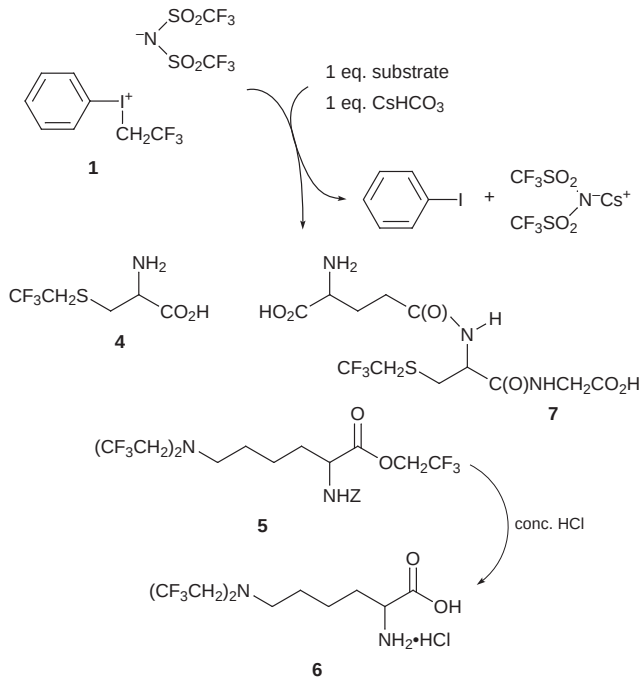
The novel iodonium salt $(CF_3SO_2)_2NI(Ph)CH_2CF_3$ is a powerful alkylating reagent which can be utilized in water to trifluoroethylate amino acids and peptides.

Fluorine-containing amino acids have been actively investigated in view of their high potential for biological studies and medical applications.[1] In particular, the use of ^{19}F NMR as a sensitive mechanistic probe has been intensively studied.[2] Synthetic routes to fluorinated amino acids normally involve several steps using fluorinated building blocks, mostly obtained by the conversion of carbon–heteroatom bonds to C–F bonds. A more direct approach to the introduction of fluorine into biochemically significant substrates might involve fluoroalkylations.[3] Cysteine and related amino acids and peptides can be alkylated by alkyl halides or esters if both the substrate and alkylating reagent can be solubilized in mixed water–organic solvents or in liquid ammonia.[4] However, simple fluorine containing alkyl halides and esters are of low reactivity in analogous alkylations. Increasing the reactivity by incorporation of fluoroalkyl groups into iodonium salts such as $CF_3CH_2I(Ph)O_3SCF_3$ is successful[3] but until now such compounds could not be employed in aqueous media or basic solvents since they are instantly destroyed under these conditions.

In contrast the novel iodonium salt $(CF_3SO_2)_2NI(Ph)CH_2CF_3$ (**1**) is unexpectedly stable to water. Herein we report the first fluoroalkylations in aqueous media and the application of **1** to the alkylation of representative biochemically significant substrates (Scheme 1).



Scheme 1 Reaction of **1** with cysteine N^{α}-Z-lysine and glutathione and the trifluoroethylated products obtained

Bis(trifluoromethylsulfonyl)imide, $(CF_3SO_2)_2NH$ (**2**), originally devised for establishing the existence of Xe–N bonds,[5] is one of the strongest acids known in the gas phase.[6] Derivatives of the acid typically have unusual properties as exemplified by the *N*-fluoro compound which is a powerful fluorinating reagent.[7,8] Perfluoroionomers and ionene polymers made in this laboratory, containing the repeating $(R_fSO_2NXSO_2R'_f)$ unit (X = H or other cation) have high potential in solid polymer electrolyte fuel cells and polymer lithium batteries, and are promising superacid catalysts.[9] In connection with this research, it is useful to synthesize novel salts of **2** as model compounds for structure and reactivity studies. The first iodine(III) compound we prepared, $[Ph_2I]^+[N(SO_2CF_3)_2]^-$ (**3**), is a stable, low-melting compound (67 °C) and a strong arylating agent.[10] Encouraged by this result, a high-yield synthesis of **1** was developed.‡ We found that **1** immediately transfers the trifluoroethyl group to nucleophiles, such as aniline, in organic solvents. Surprisingly **1**, which is very slightly soluble in water, is hydrolyzed only slowly. This fact led us to investigate fluoroalkylation reactions in water as a solvent. Using simple amines as model compounds, we observed high yields of trifluoroethylamines from 1 equiv. each of **1**, substrate, and $NaHCO_3$.

Based on this novel result, our goal became the alkylation of amino acids. The reactive side-chain of cysteine and lysine were considered, anticipating that the products would be of interest for biochemical studies. *S*-Trifluoroethyl-L-cysteine (**4**) was readily obtained in 60–90% isolated yields.§ Fig. 1 shows the X-ray crystal structure of **4**.¶

Under the same conditions the commercially available N^{α}-Z-protected L-lysine unexpectedly reacted with 3 equiv. of **1** to give the ester $(CF_3CH_2)_2N(CH_2)_4CH(NH\text{-}Z)COOCH_2CF_3$ (**5**). Hydrolysis of **5** in 37% HCl gave N^{ε}-bis(trifluoroethyl)-L-lysine hydrochloride (**6**) in 60% overall yield.

Compounds **4** and **6** are modified in the side-chains but are otherwise normal amino acids: they can be converted into the Fmoc-protected acyl fluorides in good overall yield. This form of protection–activation is very useful in the assembly of peptides of any size according to many literature examples.[11] By means of these acyl fluorides the unlikely event of extensive racemization under our alkylation conditions could be easily ruled out: reaction with (*R*)- or (*S*)-phenethylamine gave

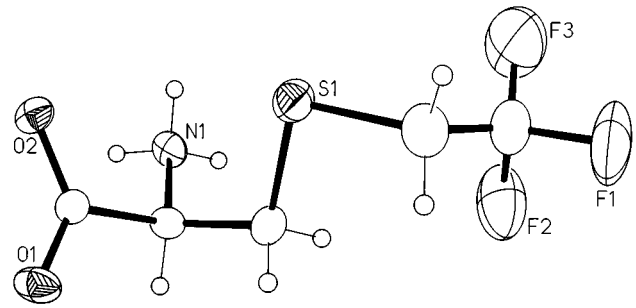


Fig. 1 Crystal structure of *S*-trifluoroethylcysteine **4** showing one of the two unique molecules in the unit cell

diastereoisomeric amides that are clearly distinguishable by ^{1}H and ^{19}F NMR.[12]

A different approach to the use of **1** is the direct reaction with a peptide having unprotected side-chains. We tested the reaction on glutathione (GSH, γ-Glu-Cys-Gly) because of its biochemical relevance and commercial availability in preparative amounts. Under the same conditions used for the preparation of **4**, we obtained complete conversion to a mixture of the desired *S*-trifluoroethylglutathione (**7**) and oxidized glutathione (**8**) in an 8:2 ratio. Compound **7** was separated from **8** by precipitation from water–ethanol.

In summary, we have reported that **1** reacts rapidly in water, under mildly alkaline conditions, with unprotected cysteine and glutathione, and with N^{α}-protected lysine, to give the novel amino acids **4** and **6**, and tripeptide **7**.

The covalent polar residue CF_3CH_2 can now be readily introduced into a variety of peptide building blocks or into suitable preassembled peptides. These results provide interesting potential for modifying the bioactivity of peptides and as probes for biochemical reactions.

The promise of **1** for the synthesis of other useful compounds, such as fluorine-tagged ligands for metal complexes,[13] is obvious, considering that the successful reactions described above were those with the greatest potential for failure, in our view. In fact, recent results show that the bis-fluoroalkylation observed with lysine is a general and facile reaction.[14]

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Notes and References

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‡ Bis(trifluoromethylsulfonyl)imide was obtained from its lithium salt (HQ-115™, 3M Co., St. Paul, MN) by vacuum sublimation from H_2SO_4 (see ref. 7). The other starting material $CF_3CH_2I(OCOCF_3)_2$, a hygroscopic solid that melts at 39–40 °C without decomposition, was prepared by oxidation of CF_3CH_2I with 50% H_2O_2 (available from Aldrich, Inc.) in TFAA under N_2 (3–5 d, RT). The preparation of **1** is simple, but anhydrous conditions must be maintained throughout the reaction. In a typical small-scale reaction, **2** (1.40 g, 5 mmol) was added under N_2, in one portion, into a solution of $CF_3CH_2(OCOCF_3)_2$ (2.16 g, 5 mmol) in CFC 113 (20 mL). This addition is endothermic. After 10 min, benzene (0.43 ml, 5 mmol) was rapidly added with ice–water cooling. The reaction mixture was allowed to return to 25 °C during 30 min and then stirred at 25 °C for 6 h. The volatiles were removed under vacuum and the residue was stirred with ice–water (50 ml) for 15 min. The precipitate was collected on a glass frit and freeze-dried to yield **1**, 1.28 g (46%) as a white powder, mp 77–79 °C. On a larger scale (up to 30 g of **1**) we have routinely obtained yields greater than 70%.

All other materials are commercially available and were used as received. The novel products **4–7** were fully characterized by ^{1}H, ^{19}F and ^{13}C NMR and elemental analysis.

§ Typical procedure. Cysteine (606 mg, 5 mmol), $CsHCO_3$ (968 mg, 5 mmol), and **1** (3.2 g, 5.6 mmol) were added into a degassed mixture of pH 10 buffer (Hydrion, Na_2CO_3–$NaHCO_3$, 20 mL) and CH_2Cl_2 (10 mL) at 5 °C under nitrogen with rapid stirring. The reaction mixture was allowed to return to 23 °C during 30 min. The aqueous phase was separated, neutralized and evaporated to a crystalline solid. This solid was refluxed twice in 30 mL CH_3CN to extract the Cs salt of **2**. The resulting powder was suspended in 10 mL water at pH 7, filtered through a syringe filter to remove insoluble cysteine and slowly evaporated to yield crystalline **4** (874 mg, 82%), $[\alpha]_D^{25}$ −15 (*c* 0.37, 4 M HCl).

¶ Crystal data of **4**: formula, $C_5H_8F_3NO_2S$; M = 203.2; monoclinic; $P2_1$(#4); T = 25 °C; a = 9.503(3), b = 5.166(3), c = 16.957(3) Å, β = 91.45(2)°; V = 832.2(6) Å^3; D_{calc} = 1.622 g cm^{-3}; Z = 4 (2 unique); μ = 0.40 mm^{-1}; empirical absorption correction (0.94–1.00); Mo-Kα radiation with graphite monochromator, λ = 0.71073 Å; Rigaku AFC7R diffractometer; 2119 measured reflections (R_{int} = 1.61%); 1676 reflections used with $F > 2\sigma(F)$; $2\theta_{max}$ = 55°; 217 parameters; non-H atoms refined anisotropically; H atoms fixed in calculated positions (C–H = 0.96 Å); full-matrix least-squares refinement; R = 4.68%/R_w = 5.93%. CCDC 182/1019.

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