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F-Amphiphilic 1,2,3-Triazoles by Unexpected Intramolecular Cyclisation of Vinyl Azides

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Keywords: 1,2,3-Triazoles / Vinyl azides / Intramolecular cycloadditions / Fluorinated compounds

A series of fluoroalkylated 1,2,3-triazoles have been synthetised in significant yields through unexpected intramolecular cyclisations of vinyl azides bearing electron-withdrawing groups. The mechanism proposed in this study implies the participation of a catalytic amount of azide ions in the cyclisations of the vinyl azides to triazoles. The study includes the alkylation of these compounds with various alkylating agents and the evaluation of the surface activities of the ionic derivatives.

Introduction

Triazole derivatives have received significant attention as biologically important heterocycles and have been reported to display pharmacological, insecticidal, fungicidal and herbicidal activities.[1,2] They are interesting for a wide range of applications covering a spectrum of therapeutic areas. Indeed, many 1,2,3-triazoles have been found to be potent antimicrobial,[3,4] analgesic,[5] anti-HIV and antiviral agents,[6,7] as well as anti-betalactamase[8] drugs, while some exhibit anticancer activity.[9] They also have numerous applications as agrochemicals, dyes, corrosion-retarding agents or photostabilisers.[10]

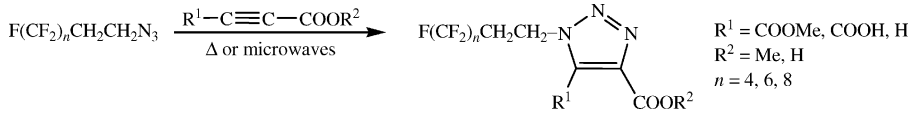
For these reasons, methodologies for the preparation of 1,2,3-triazoles have attracted much attention over the last few years.

One of the most attractive ways to prepare these compounds involves thermal 1,3-dipolar cycloadditions of azides with alkynes, as initially proposed by Huisgen.[11] The compounds are typically prepared by thermal cycloaddition of azides and alkynes to yield mixtures of regioisomers. Interest in this reaction was much enhanced after the discovery of the advantages of the copper(I) catalyst reported by Sharpless.[12] This concept has been developed in click chemistry reactions in numerous studies.[13]

Alternative methods to improve the regioselectivity, such as the use of push-pull alkenes containing leaving groups, have also been developed.[14] Only a few methods involve the synthesis of 1,2,3-triazoles through intramolecular cyclisation.

We have recently reported the synthesis of a series of highly fluoroalkylated amphiphilic 1,2,3-triazoles through efficient and regioselective 1,3-dipolar cycloadditions between 2-(perfluoroalkyl)ethyl azides and acetylenic esters or acids[15] (Scheme 1).

A large variety of well-defined pure perfluoroalkylated amphiphiles have been synthesised during the last few years. They display properties and performances that generally cannot be attained with standard surfactants, such as thermal and chemical stability, high surface activity and surface-modification ability, as well as low critical-micelle concentrations, and have been investigated as emulsion stabilisers, vesicle-forming components, components of fluorinated emulsions for template preparation of mesoporous silica and, above all, as components of drug preparation and drug-delivery systems.[16] Continuing the synthesis of original fluorocarbon amphiphilic compounds, we have therefore studied the reactivity of ramified fluorocarbon vinyl azides.



Scheme 1. Fluoroalkylated amphiphilic 1,2,3-triazoles from azido compounds.

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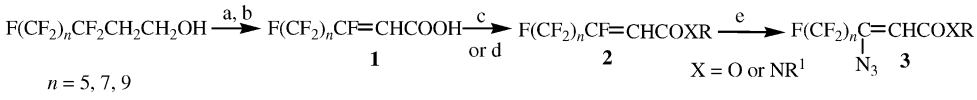


Scheme 2. New conditions for efficient syntheses of azido compounds. a: CrO_3, H_2SO_4, r.t., 2 h; b: 2 M NaOH, THF, H_2O, r.t., 2 h; c: EtOH, H_2SO4, toluene, 18 h, reflux; d: $SOCl_2$, reflux, 15 h, then $PhCH_2OH$ or solketal or HNR^1R, Et_3N, THF, 0 °C; e: 10 equiv. NaN_3, acetone, reflux, 24 h.

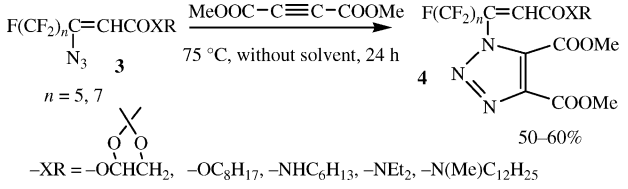
Results and Discussion

Synthesis of Triazoles

In our efforts to develop polyfunctional amphiphilic triazoles, we have studied the reactivities of amide and ester derivatives **3** (Scheme 2) of 3-azido-3-(perfluoroalkyl)propenoic acids, the synthesis of which was described in a previous paper.[17] We now propose a faster and more efficient method for the preparation of this raw material. Indeed, the replacement of the vinylic fluorine atom in **2** by azido groups through addition/elimination is now accomplished in acetone at reflux in the presence of a large excess of sodium azide in less than 3 h.

Under the new conditions the reactions lead to the products with yields higher than 90%. Only the (*Z*) isomers are formed. The identification of this configuration was achieved by detailed analyses and comparison of ^1H and ^{19}F NMR literature data for similar products as described previously.[17]

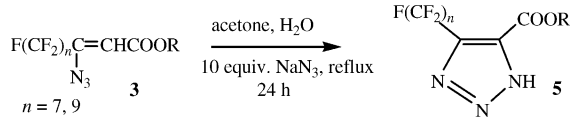
The reactivities of vinylic azides of this type were assessed. Treatment with alkynes produced triazole rings through 1,3-dipolar cycloadditions (Scheme 3).



Scheme 3. 1,3-Dipolar cycloadditions with alkynes.

Despite many attempts to improve the yields of these reactions by varying different parameters, they would not exceed 60%.

On the other hand, if the vinyl azides are heated in the presence of a mixture of acetone/polar solvent component (water, formamide) with excess sodium azide, intramolecular cyclisation takes place to produce 1,2,3-triazoles **5** (Scheme 4).



Scheme 4. Intramolecular triazoles.

These transformations have also been accomplished directly by starting from the unsaturated esters **2** (Scheme 5). The results depend on the experimental conditions (solvents and temperature; Table 1).

Table 1. Influence of the temperature and the nature of the solvent.

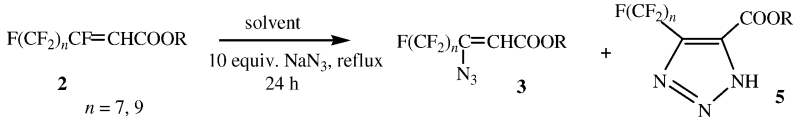
Solvent	Time	Temperature	Product	Yield
Acetone	24 h	70 °C	**3**	100%
Formamide	24 h	70 °C	**3**	100%
Acetone/formamide (1:1)	10 h	70 °C	**5**	60%
Acetone/formamide (9:1)	24 h	70 °C	**5**	90%
Acetone/water (9:1)	24 h	50 °C	**3** (12%), **5** (88%)	100%
Acetone/water (9:1)	24 h	70 °C	**5**	100%

The triazoles **5** were obtained quantitatively in acetone/water mixtures (9:1) (Table 1). The total conversion needs a temperature of 70 °C (reflux in acetone).

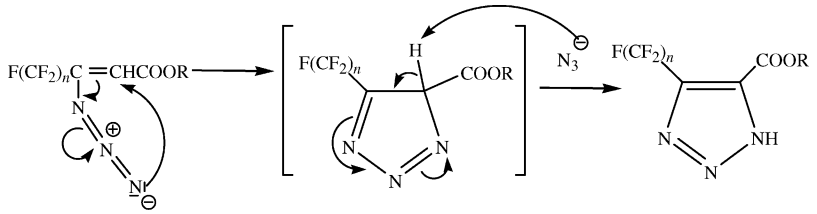
We also modified conditions to elucidate the mechanism of this reaction. According to the literature, cyclisations of vinyl azides to form triazoles are not characteristic.[18] However, consistently with the proposals made in this study and with other results, such cyclisations can be achieved when electron-acceptor substituents are present at the carbon atoms of the double bonds in the vinyl azides.[19]

A first hypothesis to explain this reaction is to consider the addition of the terminal nitrogen atom of the azide moiety on the double bond in the β-position relative to the electron-withdrawing fluorinated group, together with a second step relating to the weak basic character of sodium azide, leading to aromatic compounds by proton elimination (Scheme 6).

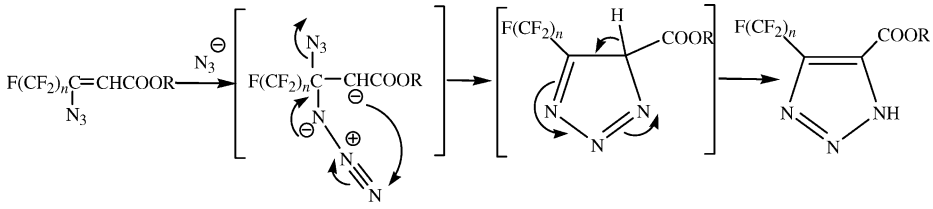
However, when the sodium azide is replaced by a tertiary amine or by sodium iodide as soft base, the reaction does not take place. The role of the sodium azide is thus not



Scheme 5. Formation of azides **3** and/or triazoles **5**.



Scheme 6. First hypothesis for the mechanism of formation of triazole.



Scheme 7. Hypothesis for the mechanism of the triazole formation.

limited to that of a base. Therefore, it is very probable that the mechanism corresponds to two successive additions of azide before the cyclisation, as proposed by Timoshenko. The second azide group acts as a leaving group (Scheme 7).

Reactivities of Triazole Compounds 5

Deprotonation of the triazole rings of compounds **5** is indicated by different colours of the two forms (yellow in acidic environments, red under basic conditions), confirmed by UV/Vis spectroscopy (Scheme 8 and Figure 1).

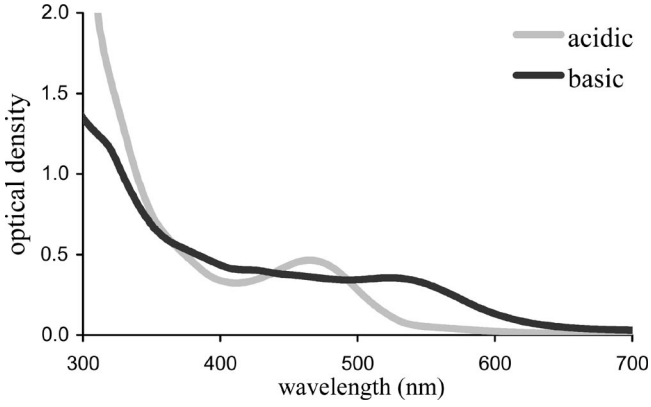
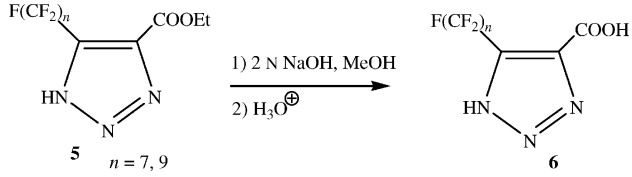


Figure 1. UV/Vis spectra of **5** at different pH values.

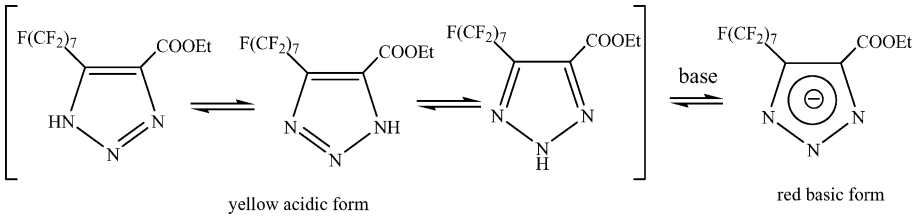
Ester Hydrolysis

To modify the hydrophilic–lipophilic balance, it is necessary to hydrolyse the ester moieties. The reactions are efficient under classical conditions and lead to the corresponding acids (Scheme 9).



Scheme 9. Ester saponification.

Determination of acidity constants by potentiometry and by fitting the curves with PSEQUAD[20] gave two values (4.5 ± 0.5 and 5.89 ± 0.05), attributed on the basis of IR spectroscopy to the NH/N^- and COOH/COO^- functions, respectively. Figure 2 shows IR spectra measured at different pH values. At pH = 7 an absorption corresponding to a carboxylate function appears at 1565 cm^{-1}, while at pH = 5 another band is observed at 1730 cm^{-1}, corresponding to a carboxylic acid function. The acidity of the triazole is comparable to that of other known triazoles with electron-acceptor substituents.[19,21]



Scheme 8. Triazole deprotonation.

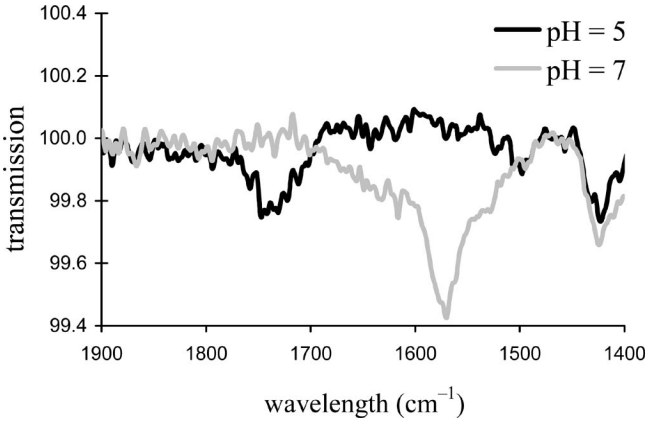


Figure 2. Changes in the IR spectrum of **6** (n = 7) with the pH in aqueous solution.

Alkylation

Alkylation of the triazoles was achieved by an economically and environmentally friendly microwave procedure (Scheme 10). In view of the pK_a value (ca. 5.89, depending on the nature of R^1), triethylamine is sufficient to deprotonate the triazole ring. Alkylation results in two regioisomeric five-membered heterocycles, alkylated on nitrogen atom N-2 or N-3 depending on the reaction conditions.[18,22]

The N-2 isomer is generally the major product, probably due to steric hindrance. Product yields and ratios are summarised in Table 2. In most cases, alkylation gave mixtures of inseparable regioisomers.

Table 2. Alkylation of the triazole ring.

Series	R^1	R^{2}X	Solvent[a]	Time	Yield	N-2/N-3
7a	CH_2CH_3	CH_3I	A	20 min	68%	50:50
7b	CH_2CH_3	$C_6H_5CH_2Br$	A	5 min	81%	65:35
7c	CH_2Ph	$C_6H_5CH_2Br$	B	30 min	87%	70:30
7d	CH_2CH_3	p-$O_2NC_6H_4CH_2Br$	A	5 min	80%	60:40
7e	CH_2CH_3	$Me(OCH_2CH_2)_3OTs$	A	180 min	70%	75:25
7f	CH_2CH_3	EtO_2CCH_2Br	A	10 min	89%	75:25

[a] A = 1,4-dioxane; B = 1,4-dioxane/formamide.

The isomers were identified by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. The regioselectivity obtained in the case of compound **7c** was unambiguously confirmed by X-ray diffraction of the acid form obtained after saponification, showing the benzyl group at the N-2 position (Figure 3).

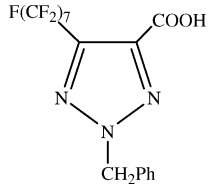


Figure 3. N-2 isomer of the acid derivative of **7c**.

Surface Activities of Salt Derivatives of Compounds 6

Self-association of surfactants is a well-known phenomenon. Hydrophobic interactions are the driving forces that induce the adsorption of the surfactant at the water/air interface. Once this surface is saturated, the surfactant molecules self-associate to minimise the free energy of the whole system. The surfactant properties of the aqueous solutions were evaluated by surface tension measurements (γ) carried out by the Wilhelmy method.[23] Measurements were made with basic solutions to limit the species to the dianionic form. The solubility in sodium hydroxide solution was sufficient to obtain a γ vs. log C (concentration) plot, allowing the determination of the Critical Aggregative Concentration (CAC) and of the minimal surface tension (γ_{CAC}). Typical curves of monodisperse surfactants were obtained for the synthesised products (Figure 4, Table 3). For concentrations superior to the CAC, γ remains practically constant and equal to the minimum value of γ attainable with a given amphiphilic compound. The good linearity of the points below the CAC, and the constant values of γ above it, as well as the sharp break in the curve, are a confirmation of the purities of the compounds. At room temperature, the two compounds lower the surface tension of water to about 20 mN m^{-1}, which corresponds to classical behaviour for fluorinated surfactants.

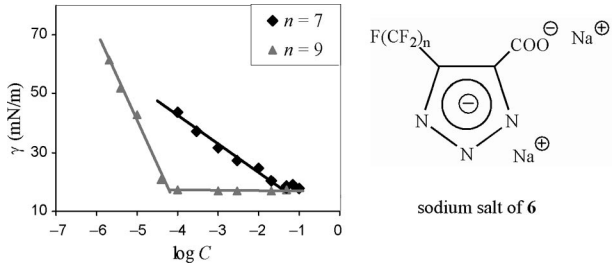
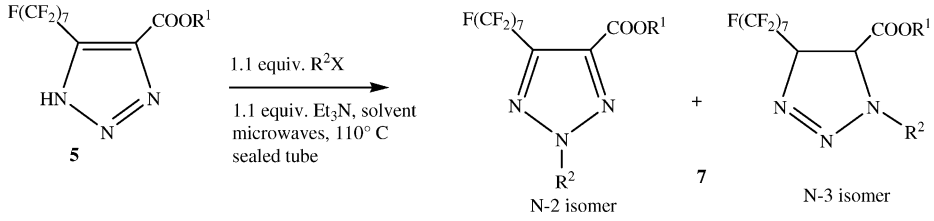


Figure 4. Surface activities of salt derivatives of **6**.



Scheme 10. Triazole alkylation.

Table 3. Physicochemical properties of amphiphiles **6**.

Product	n	γ_{CAC} [mN m^{-1}]	CAC [mol L^{-1}]	σ [Å^2/molecule]
a	7	18.4	3.8 10^{-2}	308
b	9	17.2	6.1 10^{-5}	93

The minimum area per surfactant head group at the micellar interface (σ, in Å^2) was calculated from the slope of the γ vs. log C curve below the CAC from the classical Gibbs equation. The surface saturation (Γ_{max}) can be used as a measure of the maximum extent of adsorption of surfactant at the air/water interface and can be calculated from the Gibbs adsorption equation for dilute systems:

$$\Gamma_{max} = -(1/2.303nRT)\cdot(d\gamma/d\log C)\ (R = 8.314\ J\,K^{-1}\,mol^{-1})$$

From the surface excess values, it is possible to calculate the minimum area per molecule in Å^2 at the air/water interface from the following relation, where R = 8.314 J K^{-1} mol^{-1}, T = 298.15 K, with γ expressed in N m^{-1}, N_A is Avogadro's number (6.022×10^{23}), and n is a constant that depends on the number of species constituting the surfactant and which are adsorbed at the interface:

$$A_{min} = 10^{20}/N_A\ \Gamma_{max}$$

For a univalent ionic surfactant the value n = 2 is generally used. In the case of the dianionic compounds, we have considered the value n = 3. The surface area per polar head group for these anionic surfactants is very important. The planarity of the system and the repulsion between the two negative charges could be a reasonable explanation for this high mean area per molecule.

Conclusion

We propose an efficient synthesis of single-chain perfluoroalkylated 1,2,3-triazoles from vinyl azides by intramolecular cyclisation, or directly from fluoroalkenes with electron-withdrawing substituents. The lowering of the surface tension of pure water by addition of small amounts of the amphiphile salt derivatives shows that they are surface-active agents. The alkylation of the triazole ring is carried out under simple conditions and could be extended to attach other functional groups.

Experimental Section

General: All solvents were of reagent grade and used without further purification. The progress of reactions was determined by IR spectroscopy. NMR spectra were recorded with a Bruker AM 400 or AC 200 instrument. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard for the ^{1}H NMR spectra and to $CFCl_3$ for the ^{19}F NMR spectra. Coupling constants (J) are given in Hz. IR spectra were recorded with a Perkin–Elmer FTIR instrument in ATR. Melting points were determined with a Tottoli apparatus and are not corrected. Elemental analyses were performed by CNRS Vernaison. Reactions were performed in a CEM 300 W chemistry microwave oven. Starting material **1** was prepared from the corresponding alcohol according a the published method.[24]

Synthesis of Ethyl 3-Fluoro-3-(perfluoroalkyl)prop-2-enoate (2): Ethanol (10 mL) and concentrated sulfuric acid (some drops) were added to a solution of acid **1** (10 mmol) in toluene (75 mL). The resulting mixture was heated under azeotropic reflux for 16 h. The solvent was evaporated under reduced pressure, and the residue was then taken up again with ethyl acetate. The organic phase was washed with a saturated aqueous solution of NaCl, a solution of $NaHCO_3$ until it was neutral and once more with a saturated aqueous solution of NaCl. After drying with magnesium sulfate, the solvent was evaporated under vacuum, and the ester **2** was obtained as a yellow liquid. Yield: 90% (3.47 g for n = 5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –C*H*$_3$), 4.28 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –C*H*$_2$–), 5.98 (d, $^3J_{H,F}$ = 29.4 Hz, 1 H, =C*H*–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (–*C*H$_3$), 62.0 (–*C*H$_2$–), 106.8 (=*C*H–), 110–120 (*C*–F), 155.5 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –79 (t, $^3J_{F,F}$ = 9 Hz, 3 F, C*F*$_3$–), –108 (m, 1 F, –C*F*=CH–), –120 (m, 2 F, –C*F*$_2$–CF=), –123 to –127 [m, (2n – 4) F, CF$_3$–(C*F*$_2$)$_{n-2}$–CF$_2$–CF=] ppm. IR: $\tilde{\nu}$ = 1740 (C=O), 1700 (C=C), 1100–1300 (C–F) cm^{-1}.

Synthesis of 3-Fluoro-3-(perfluoroalkyl)prop-2-enoyl Chloride: Acid **1** (15 mmol) was dissolved in freshly distilled thionyl chloride (8 mL), and the mixture was heated under reflux for 15 h. The total conversion of the acid into the acyl chloride was checked by IR.

Synthesis of Amide and Ester Derivatives 2 with R ≠ OEt: The corresponding alcohol or amine (10 mmol) was dissolved in anhydrous THF (20 mL), and triethylamine (15 mmol) was added. The mixture was then cooled to 0 °C. The acyl chloride was added dropwise, and the mixture was continuously stirred for 3 h. Afterwards, HCl (0.1 N, 20 mL) was added, and the product was extracted three times with diethyl ether, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and dried with magnesium sulfate. The solvent was evaporated under vacuum, and after purification by chromatography on silica (ether/hexane), the product was obtained as a colourless liquid.

R = OCH$_2$Ph: Yield 80% (3.58 g for n = 5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.17 (s, 2 H, –C*H*$_2$–), 5.95 (d, $^3J_{H,F}$ = 29.4 Hz, 1 H, =C*H*–), 7.2 (m, 5 H, *Ph*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 67.4 (–*C*H$_2$Ph), 106 (=*C*H–), 110 to 120 (*C*$_{fluor}$), 128.1, 128.5, 128.7, 134.9 (*Ph*), 161 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –79 (t, $^3J_{F,F}$ = 9 Hz, 3 F, C*F*$_3$–), –107.5 (m, 1 F, –C*F*=CH–), –120 (m, 2 F, –C*F*$_2$–CF=), –123 to –127 [m, (2n – 4) F, CF$_3$–(C*F*$_2$)$_{n-2}$–CF$_2$–CF=] ppm. IR: $\tilde{\nu}$ = 1738 (C=O), 1700 (C=C), 1100–1300 (C–F) cm^{-1}.

Representative Amide Derivative with R = NEt$_2$: Yield 3.32 g for n = 5. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.18 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –C*H*$_3$), 1.20 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –C*H*$_3$), 3.32 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –C*H*$_2$–), 3.47 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –C*H*$_2$–), 6.21 (d, $^3J_{H,F}$ = 32.0 Hz, 1 H, =C*H*–) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.1, 14.5 (–*C*H$_3$), 40.1, 43.1 (–*C*H$_2$–), 109 (=*C*H–), 110 to 120 (*C*–F), 160 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –79 (t, $^3J_{F,F}$ = 9 Hz, 3 F, C*F*$_3$–), –106.8 (m, 1 F, –C*F*=CH–), –120 (m, 2 F, –C*F*$_2$–CF=), –123 to –127 [m, (2n – 4) F, CF$_3$–(C*F*$_2$)$_{n-2}$–CF$_2$–CF=] ppm. IR: $\tilde{\nu}$ = 1701 (C=C), 1641 (C=O), 1100–1300 (C–F) cm^{-1}.

Synthesis of Alkyl 3-Azido-3-(perfluoroalkyl)prop-2-enoates or *N*-Alkyl-3-azido-3-(perfluoroalkyl)prop-2-enamides (3): The ester derivative **2** (15 mmol) or amide derivative **3** was dissolved in acetone (80 mL), and sodium azide (10 equiv.) was then added. The mixture was stirred at 50 °C for 3 h. Water (50 mL) was added, and the product was extracted with diethyl ether. The organic phase was washed with water and dried with sodium sulfate, and the solvent

was evaporated under vacuum. The product was obtained as a yellow liquid. Yield: 90%.

Representative Ester Derivative with R = OEt: Yield 5.78 g for n = 5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.28 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 6.14 (s, 1 H, =CH–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (–CH$_3$), 62.3 (–CH$_2$–), 113.3 (=CH–), 110–120 (C–F), 140.9 (C–N$_3$), 163.9 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.4 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –115 [m, 2 F, –CF_2–C(N$_3$)=], –122.4 to –126.7 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 2164 (N$_3$), 1720 (C=O), 1100–1300 (C–F) cm^{-1}.

Representative Amide Derivative with R = NEt$_2$: Yield 6.36g for n = 5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 1.21 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 3.33 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 3.47 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 6.35 (s, 1 H, =CH–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 14.6 (–CH$_3$), 40.5, 43.6 (–CH$_2$–), 115 (=CH–), 110–120 (C–F), 141 (C–N$_3$), 164 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.7 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –115 [m, 2 F, –CF_2–C(N$_3$)=], –122 to –127 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 2150 (N$_3$), 1647 (C=O), 1100–1300 (C–F) cm^{-1}.

Synthesis of Dimethyl 1-{1-[(Alkoxycarbonyl)methylene]perfluoroalkyl}-1*H*-1,2,3-triazole-4,5-dicarboxylates 4: The azide derivative **3** (5 mmol) and dimethyl acetylenedicarboxylate (1.3 equiv.) were placed in a round-bottomed flask. The mixture was heated in an oil bath at 75 °C for 24 h. The product was then purified by chromatography on silica (ether/hexane). Yield: 55–60%.

Representative Ester Derivative with R = OEt: Yield 1.56g for n = 5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 3.97 (s, 3 H, COOCH_3), 4.01 (s, 3 H, COOCH_3), 4.11 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 6.93 (s, 1 H, =CH–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (–CH$_3$), 53.6, 54.2 (–OCH$_3$), 63.4 (–CH$_2$–), 110–120 (C–F), 132.3, 133.5 ($C_{triazole}$), 134 [–$C_{triazole}$=], 140.4 (=CH–), 158.2, 160.6, 160.8 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –110 to –118 [m, 2 F, –CF_2–C$_{triazole}$=], –122 to –127 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1735 (C=O), 1100–1300 (C–F) cm^{-1}.

Representative Amide Derivative with R = NEt$_2$: Yield 1.65g for n = 5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 1.22 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 3.23 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 3.33 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 3.96 (s, 3 H, COOCH_3), 3.98 (s, 3 H, COOCH_3), 7.25 (s, 1 H, =CH–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7, 14.2 (–CH$_3$), 40.2, 43.1 (–CH$_2$–), 53.2, 53.9 (–OCH$_3$), 129.5 (–$C_{triazole}$=), 134, 139.8 ($C_{triazole}$), 135.5 (=CH–), 157.4, 160.2 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –110 to –115 [m, 2 F, –CF_2–C$_{triazole}$=], –122 to –127 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1739, 1638 (C=O), 1100–1300 (C–F) cm^{-1}.

Synthesis of Alkyl 5-(Perfluoroalkyl)-3*H*-1,2,3-triazole-4-carboxylates 5: The azide derivative **3** (2 mmol) was dissolved in acetone (9 mL) and water (1 mL), and sodium azide (10 equiv.) was then added. The mixture was heated under reflux for 24 h.

Treatment for R = OEt: On cooling to room temperature, ethyl acetate (60 mL) was added, and the organic phase was washed three times with a saturated aqueous solution of NaCl, and then with a solution of HCl (0.1 N). The organic phase was then dried with sodium sulfate, and the solvent was evaporated under vacuum to give the triazole as a yellow solid. Yield: quantitative (1.01 g for n = 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.45 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15 (–CH$_3$), 63 (–CH$_2$–), 110–120 (C_{fluor}), 138, 140 ($C_{triazole}$), 160 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –79 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –105.4 [m, 2 F, –CF_2–C$_{triazole}$=], –119 to –124 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1704 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{12}H_6F_{15}N_3O_2$ (509.17): calcd. C 28.31, H 1.19, F 55.97, N 6.28; found C 27.76, H 1.21, F 51.15, N 7.89.

Treatment for R = OCH$_2$Ph: On cooling to room temperature, the solvent was evaporated under vacuum, and diethyl ether was then added to precipitate the product, which was recovered by filtration. A white solid was obtained. Yield: 85% (0.97 g for n = 7). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 2.94 (s, 1 H, NH), 5.35 (s, 2 H, –CH_2–), 7.3 (m, 5 H, *Ph*) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 67.1 (–CH$_2$Ph), 110–120 (C_{fluor}), 129.1, 129.3, 129.5, 137.9 (*Ph*), 135.7, 136.9 ($C_{triazole}$), 164.5 (CO) ppm. ^{19}F NMR (188 MHz CD_3COCD_3): δ = –79 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –101.6 (m, 2 F, –CF_2–triazole), –119 to –124 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$– CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1707 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{17}H_8F_{15}N_3O_2$ (571.25): calcd. C 35.74, H 1.41, F 49.89, N 7.36; found C 34.68, H 1.20, F 47.14, N 7.11.

Ester Saponification. Preparation of 5-(Perfluoroalkyl)-1*H*-1,2,3-triazole-4-carboxylic Acids 6: NaOH (2 M, 5 mL) was added to a solution of triazole **5** (2 mmol) in acetone (30 mL). The mixture is stirred at room temperature for 8 h and then acidified with HCl (1 M) until pH = 1. The product was extracted with diethyl ether, and the combined organic phases were washed with water and dried with magnesium sulfate. The solvent was evaporated under vacuum, and the acid triazole was obtained as a yellow transparent solid. Yield: 95% (0.91 g for n = 7). ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 110–120 (C–F), 138.2 and 160.3 ($C_{triazole}$) ppm. ^{19}F NMR (188 MHz, CD_3COCD_3): δ = –80.6 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –106.3 (m, 2 F, –CF_2–triazole), –120 to –127 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1703 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{10}H_2F_{15}N_3O_2$ (481.12): calcd. C 24.96, H 1.41, F 59.23, 8.73; found C 24.92, H 0.58, F 56.66, N 8.73.

General Procedure for the Alkylation of Triazoles. Preparation of Ethyl 2- or 3-Alkyl-5-(perfluoroalkyl)-2*H*-1,2,3-triazole-4-carboxylates (7): The triazole **5** (0.2 mmol) was dissolved in 1,4-dioxane (1 mL, and 4 drops formamide in the case of **8c**), and triethylamine (1.1 equiv.) and R^{2}X [1.1 equiv., or 0.9 equiv. for Me(OCH$_2$CH$_2$)$_3$-OTs] were then added. The mixture was placed in a microwave tube, sealed and then microwave-irradiated at 110 °C under pressure for the time indicated in Table 3. After the system had cooled to room temperature, diethyl ether was added, and the organic phase was washed with a solution of HCl (1 N), and twice with a saturated aqueous solution of NaCl. The organic phase was dried with sodium sulfate, and the solvent was evaporated under vacuum to give the triazole, which was purified by chromatography on silica (Et$_2$O/hexane).

R^1 = Et, R^2 = CH$_3$: Colourless liquid. Yield: 68% (71.15 mg for n = 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.31 [s, 3 H, –NCH_3 (50%)], 4.33 [s, 3 H, –NCH_3 (50%)], 4.41 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 14 (–CH$_3$), 38.6, 43.3 (NCH$_3$), 62.6, 63.3 (–CH$_2$–), 110–120 (C–F), 129.5, 137.5, 137.9, 139.5 ($C_{triazole}$) 157.5, 159 (CO) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.4 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.5 [m, 2 F, –CF_2–triazole (50%)], –107.7 [m, 2 F, –CF_2–triazole (50%)], –119 to –124 [m, (2n – 4) F, CF$_3$–(CF_2)$_{n-2}$–CF$_2$–] ppm. IR: $\tilde{\nu}$ = 1741 (C=O), 1100–1300 (C–F) cm^{-1}.

R^1 = Et, R^2 = CH$_2$Ph: Colourless liquid. Yield: 81% (97.22 mg for n = 7). **N-2**: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.43 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 5.70

(s, 2 H, –CH_2Ph), 7.37 (m, 5 H, *Ph*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (–*C*H_3), 60.6 (–*C*H_2Ph), 62.6 (–*C*H_2–Me), 110–120 (*C*–F), 128.7, 129.4, 129.5, 133.5 (*Ph*), 138.2, 139.9 ($C_{triazole}$), 159.1 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.7 (m, 2 F, –CF_2–triazole), –121 to –127 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1743 (C=O), 1100–1300 (C–F) cm^{-1}. **N-3**: 35%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.36 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –CH_2–), 5.93 (s, 2 H, –CH_2Ph), 7.3 (m, 5 H, *Ph*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (–*C*H_3), 54.7 (–*C*H_2Ph), 63.4 (–*C*H_2–Me), 110–120 (*C*–F), 128.4, 129.2, 129.3, 134.4 (*Ph*), 129.4, 138.1 ($C_{triazole}$), 157.7 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.6 (m, 2 F, –CF_2–triazole), –121 to –127 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1733 (C=O), 1100–1300 (C–F) cm^{-1}.

R^1 = CH$_2$Ph, R^2 = CH$_2$Ph: Yield: 87% (115.25 mg for *n* = 5). **N-2**: 70%. White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39 (s, 2 H, O–CH_2–), 5.67 (s, 2 H, N–CH_2), 7.2 (m, 10 H, *Ph*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.6 (N–*C*H_2), 68.3 (O–*C*H_2–), 110–120 (C_{fluor}), 128.8, 129.0, 129.2, 129.4, 129.5, 133.4, 135.1 (*Ph*), 138.3, 139.6 ($C_{triazole}$), 159.0 (*C*O) ppm. IR: $\tilde{\nu}$ = 1743 (C=O), 1100–1300 (C–F) cm^{-1}. **N-3**: 30%. Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.30 (s, 2 H, O–CH_2–), 5.88 (s, 2 H, N–CH_2), 7.2 (m, 10 H, *Ph*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.8 (N–*C*H_2), 66.3 (O–*C*H_2–), 110–120 (*C*–F), 128.4, 129.1, 129.2, 129.3, 129.4, 134.0, 134.2 (*Ph*), 129, 138.3 ($C_{triazole}$), 157.6 (*C*O) ppm. IR: $\tilde{\nu}$ = 1732 (C=O), 1100–1300 (C-F) cm^{-1}.

R^1 = Et, R^2 = CH$_2$C$_6$H$_4$NO$_2$: Yield: 80% (103.20 mg for *n* = 5). White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (m, 3 H, –CH_3), 4.4 (m, 2 H, –CH_2–), 5.80 [s, 2 H, –CH_2Ph (60%)], 6.03 [s, 2 H, –CH_2Ph (40%)], 7.5 (m, 2 H, *Ph*), 8.2 (m, 2 H, *Ph*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.2 (–*C*H_3), 53.8, 59.4 (–*C*H_2Ph), 62.9, 63.8 (–*C*H_2–Me), 110–120 (*C*–F), 124.6, 124.7, 129.4, 129.7, 140.4, 141.0, 148.6, 148.8 (*Ph*), 130.3, 138.6, 140.0 ($C_{triazole}$), 157.5, 158.8 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.6 (m, 2 F, –CF_2–triazole), –121 to –127 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1736 (C=O), 1520 (NO_2), 1100–1300 (C–F) cm^{-1}. $C_{24}H_{14}F_{15}N_3O_2$ (661.37): calcd. C 43.59, H 2.13, F 43.09, N 6.35; found C 43.87, H 2.26, F 41.92, N 6.35.

R^1 = Et, R^2 = CH$_2$COOEt: Colourless liquid. Yield: 89% (106.10 mg for *n* = 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 4.26 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –OCH_2–), 4.41 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, –OCH_2–), 5.33 [s, 2 H, NCH_2– (75%)], 5.52 [s, 2 H, NCH_2– (25%)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.16, 14.19, 14.23 (–*C*H_3), 52.5, 57.0 (N*C*H_2–), 62.8, 63.0, 63.1, 63.6 (O*C*H_2–), 130.0 138.8, 140.4 ($C_{triazole}$), 157.6, 158.8, 165.3, 165.9 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.5 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.8 [m, 2 F, –CF_2–triazole (75%)], –108.1 [m, 2 F, –CF_2–triazole (25%)], –121 to –127 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1711 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{16}H_{12}F_{15}N_3O_2$ (595.27): calcd. C 32.28, H 2.03, N 7.06; found C 33.48, H 1.96, N 6.87.

R^1 = Et, R^2 = (CH$_2$CH$_2$O)$_3$Me: Yield: 70% (91.94 mg for *n* = 7). Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, –CH_3), 3.32 (s, 3 H, –OCH_3), 3.4 to 3.7 (m, 8 H, CH_2O), 3.86 [m, 2 H, NCH$_2$CH_2O (25%)], 4.02 [m, 2 H, NCH$_2$CH_2O (75%)], 4.41 (m, 2 H, –CH_2–), 4.68 [m, 2 H, NCH_2 (75%)], 4.88 [m, 2 H, NCH_2 (25%)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.2 (–*C*H_3), 50.8, 56.5 (N*C*H_2), 59.3 (–O*C*H_3), 62.6, 63.4 (–*C*H_2Me), 68.7, 69.6, 70.8, 70.9, 71, 72.2 (*C*H_2O), 110–120 (*C*–*F*), 130.7, 137.5, 139.6 ($C_{triazole}$) 157.9, 159.1 (*C*O) ppm. ^{19}F NMR (188 MHz, $CDCl_3$): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –107.5 [m, 2 F, –CF_2–triazole (75%)], –107.8 [m, 2 F, –CF_2–triazole (25%)], –121 to –127 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1742 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{19}H_{20}F_{15}N_3O_2$ (655.36): calcd. C 34.82, H 3.08, F 43.48, N 6.41; found C 34.15, H 2.96, F 46.07, N 6.33.

Synthesis of Tosyl Triethylene Glycol Monomethyl Ether: Triethylene glycol monomethyl ether (20 mmol) and pyridine (12 mL) were placed in a round-bottomed flask fitted with an addition funnel. The mixture was cooled to 0 °C, and tosyl chloride (30 mmol), dissolved in pyridine (12 mL), was added dropwise. The ice bath was removed, and the mixture was stirred at room temperature for 3 h. Diethyl ether (60 mL) was then added, and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ followed by a saturated aqueous solution of NaCl until neutralisation. The organic phase was then dried with sodium sulfate, and the solvent was evaporated under vacuum to give the tosyl triethylene glycol monomethyl ether as a colourless liquid. Yield: 78% (4.98 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3Ph), 3.32 (s, 3 H, –OCH_3), 3.4–3.7 (m, 8 H, CH_2O), 4.11 (m, 2 H, SO_3CH_2–), 7.30 (d, 2 H, H_{aromat}), 7.74 (d, 2 H, H_{aromat}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (*C*H$_3$Ph), 59.3 (–O*C*H$_3$), 69 (SO_3*C*H$_2$), 68.9, 69.6, 70.8, 70.9, 71.0, 71.6, 72.2 (*C*H$_2$O), 128.3, 130.2, 133.4, 145.2 (*Ph*) ppm. IR: $\tilde{\nu}$ = 1353 (SO_2) cm^{-1}.

Saponification of the Ester Function of 7c: The procedure was the same as that used for the saponification of the triazole **6**.

N-2: Yield: 95% (1.08 g for *n* = 7). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 5.86 (s, 2 H, N–CH_2), 7.4–7.5 (m, 5 H, *Ph*) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 61 (N–*C*H$_2$), 110–120 (*C*–*F*), 129.6, 130.0, 130.2, 135.3 (*Ph*), 138.3 and 141 ($C_{triazole}$), 160.2 (*C*O) ppm. ^{19}F NMR (188 MHz, CD_3COCD_3): δ = –80.7 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –106.2 (m, 2 F, –CF_2–triazole), –120 to –126 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1711 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{17}H_8F_{15}N_3O_2$ (571.25): calcd. C 35.74, H 1.41, F 49.89, N 7.36; found C 36.00, H 1.45, F 47.69, N 7.34.

N-3: Yield: 95% (1.08 g for *n* = 7). ^{1}H NMR (400 MHz, CD_3COCD_3): δ = 6.03 (s, 2 H, N–CH_2), 7.4–7.45 (m, 5 H, *Ph*) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 55 (N–*C*H$_2$), 110–120 (*C*–*F*), 129.2, 129.8, 136.3 (*Ph*), 131.3 and 138.3 ($C_{triazole}$), 158 (*C*O) ppm. ^{19}F NMR (188 MHz, CD_3COCD_3): δ = –81.3 (t, $^3J_{F,F}$ = 9 Hz, 3 F, CF_3–), –106.3 (m, 2 F, –CF_2–triazole), –120 to –126 [m, (2*n* – 4) F, CF_3–(CF_2)$_{n-2}$–CF_2–] ppm. IR: $\tilde{\nu}$ = 1715 (C=O), 1100–1300 (C–F) cm^{-1}. $C_{17}H_8F_{15}N_3O_2$ (571.25): calcd. C 35.74, H 1.41, F 49.89, N 7.36; found C 36.29, H 1.44, F 47.96, N 7.29.

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