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Synthesis of 2,2,6,6-tetrafluoro-4-phenylmethylmorpholin-3-ones: A simple approach from fluorinated triethylene glycol

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This contribution is dedicated to Professor Qing-Yun Chen on the occasion of his 80th birthday.

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ABSTRACT

2,2,6,6-Tetrafluoro-4-phenylmethylmorpholin-3-ones are obtained from a new single step, preparative route by reacting triethylene glycol di(trifluoromethanesulfonate), which contains poly $-CF_2O-$ groups, with benzylamine. Reaction of trifluoromethylsulfonate and trifluoromethoxy derivatives with benzylamine gave either the nucleophilically-substituted product or the product resulting from the basic hydrolysis of the difluoromethoxy group. Replacement of a fluoroether chain by a fluoroalkane gave rise to fluorinated phenylmethylpiperidine and phenylmethylazepine via the combination of trifluoromethanesulfonic fluoroalkyldiyl esters and benzylamine.

1. Introduction

It is well-known that the introduction of a fluorine atom or a fluoroalkyl group into heterocyclic compounds has a profound influence on their chemical, physical and biological properties [1]. Many biologically important compounds that possess a lactone or lactam structure are known, e.g., morpholin-3-one and its derivatives, which are essentially lactams with important biological and pharmacological activity, are used as building blocks for an HIV-1 protease inhibitor [2], tachykinin receptors [3], cornea permeable calpain inhibitors [4], and an A549 lung cancer cell inhibitor [5]. Synthetic routes to morpholin-3-ones are diverse, e.g., by direct oxidation of morpholine in the presence of a cobalt catalyst to give morpholin-3-ones in 24% yield [6], or by treating ethanolamine derivatives with chloroacetyl chloride in the present of base to form morpholin-3-ones in moderate yield [7]. N-substituted morpholin-3-one derivatives have been obtained under rigorous conditions [8]. However, few reports describing the synthesis of fluorinated morpholin-3-ones are available. For example, the direct fluorination of morpholin-3-ones with a strong fluorinating reagent results in ring opening, and the lack of stability of fluorinated ethanolamines which arises from the likelihood of elimination of hydrogen fluoride precludes their use. Previously, fluorinated morpholin-3-ones, N-aryl-2-methyl-2-trifluoromethylmorpholin-3-ones, were prepared by condensation of 2-hydroxy-2-(trifluoromethyl)propanoic acid and aniline, followed by further treatment with1-bromo-2-chloroethane under basic conditions for one week [9]. 4-(4-Aminophenyl)-6,6-difluoro-3-morpholinone has been reported as a pharmacological active molecule [10].

2. Results and discussion

Our efforts are directed toward the development of fluorinated heterocyclic compounds as potential bioactive molecules as well as nitrogen-rich energetic, functional materials. A large number of fluorinated imidazole-, pyrazole-, triazole-, and tetrazole-containing compounds with promise of ionic liquids are in the literature [11]. Polyfluoroalkyl-bridged diimidazolium ionic liquids were prepared by us earlier using the combination of trifluoromethanesulfonic acid polyfluoro alkyldiyl esters, **2a–2d** (Scheme 1) and alkylimidazoles. These diimidazolium ionic liquids with high fluorine content showed good thermal stability and consistently low friction up to 300 °C [12].

Previously, a two-step reaction of trifluoromethanesulfonic acid 3,3,4,4-tetrafluoro-1,4-butanediyl ester, and benzylamine

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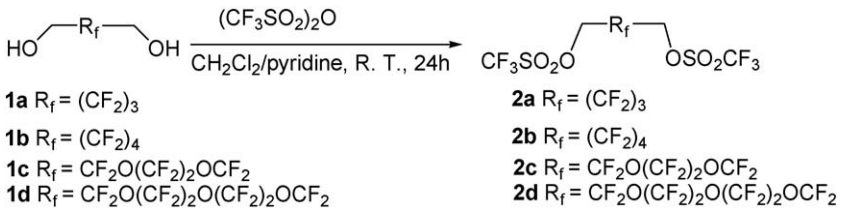
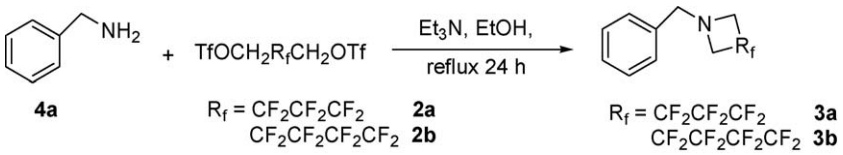


Scheme 1. Syntheses of trifluoromethanesulfonic acid polyfluoroalkyldiyl esters.



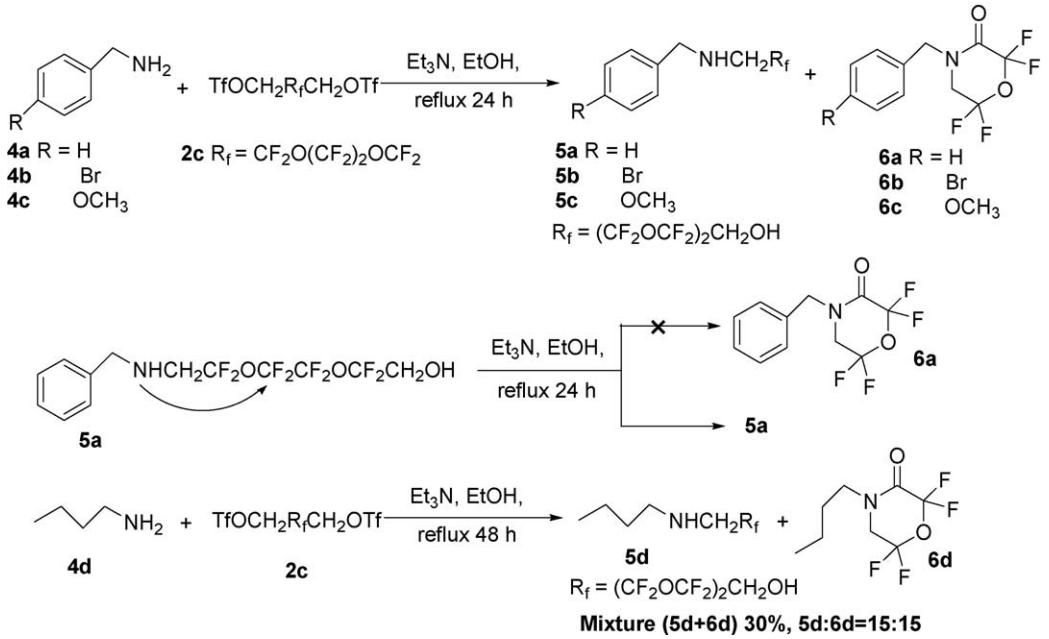
Scheme 2. Synthesis of fluorinated piperidine, and azepine.

gave the fluorinated five member heterocycle, 3,3,4,4-tetrafluoropyrrolidine (F content > 53%) [13]. We anticipated that utilization of this simple synthetic pathway, i.e., to react trifluoromethanesulfonic acid perfluoroalkyldiyl ester, **2a–2d**, having high C fluorocarbon alkyl groups, with amines would facilitate preparation of N-based heterocycles with higher fluorine content, e.g., six-membered piperidine (F content > 59%), seven-membered azepine (F content > 62%), and macro rings. Although diimidazolium ionic liquids with high fluorine content showed good tribological characteristics in our earlier report, the low stability of imidazolium ionic liquids in basic systems limited their scope of use as new lubricants [14]. These new heterocycles with high fluorine content would be expected to replace the imidazole ring in the synthesis of potential high temperature ionic liquid lubricants.

Following this strategy, we first explored the synthesis of fluorinated piperidine and azepine. Previously, 3,3,4,4,5,5-hexafluoro-2,2,6,6-tetradeutero-1-(phenylmethyl)piperidine was synthesized by a multistep, complex procedure by using lithium aluminum deuteride and polyfluorocyclic dione [15]. Cyclization of **4a** with trifluoromethanesulfonic fluoroalkyldiyl ester, **2a** or **2b** (mol ratio 1:1), in ethanol at reflux for 24 h, generated the fluorinated piperidine, 3,3,4,4,5,5-hexafluoro-1-(phenylmethyl)-piperidine, **3a**, and azepine, 3,3,4,4,5,5,6,6-octafluoro-1-(phenylmethyl)azepine, **3b**, in 50% yield (Scheme 2).

The formation of **3a** and **3b** encouraged us to extend this approach to employ longer chain trifluoromethanesulfonic acid fluoroalkyldiyl esters in order to synthesize fluorinated macro rings. An attempt to synthesize a fluorinated macro ring by using benzylamine and triethylene glycol di(trifluoromethane) disulfonate, **2c**, was unsuccessful as determined by ^{19}F NMR. However, increasing the reaction temperature to 110 °C for 48 h, resulted in a mixture of 2,2-difluoro-2-{2-[2-(phenylmethyl)amino-difluoroethoxy]-tetrafluoroethoxy} ethanol, **5a**, and the unexpected 2,2,6,6-tetrafluoro-4-phenylmethyl-morpholin-3-one, **6a** (Scheme 3).

The polarities of **5a** and **6a** are similar based on TLC. The mixture was carefully separated using chromatography to give **5a** (15%) and **6a** (25%) (Scheme 3) [16]. The structure of compound **6a** was confirmed by ^{19}F, and ^{1}H NMR, and mass spectral, and elemental analysis; there are two ^{19}F resonance bands at δ −75.38, and −72.03 ppm, and in the ^{1}H NMR spectrum, a triplet resonance at



Scheme 3. Synthesis of 2,2,6,6-tetrafluoro-4-phenylmethylmor-pholin-3-one.

Table 1
Synthesis of 2,2,6,6-tetrafluoro-4-phenylmethyl-morpholin-3-ones.

Entry	Amine	Condition[a]	**5**, %Yield[b]	**6**, %Yield[b]
1	**4a**	A	15	25
2	**4a**	B	20	35
3	**4a**	C	25	15
4	**4b**	B	20	35
5	**4c**	B	20	35
6	**4d**	B	15[c]	30[c]

[a] Condition A: amine (1 mmol), mole ratio of amine:**2c**:Et_3N = 1:1:3; Condition B: amine (1 mmol), mole ratio of amine:**2c**:Et_3N = 1:1:5; Condition C: amine (1 mmol), mole ratio of amine:**2c**:Et_3N = 1:1:10; reaction in Pyrex tube 110 °C, 2 ml EtOH as solvent, for 48 h.
[b] After chromatographic purification.
[c] By GC–MS analysis.

3.79 ppm was assigned to the proton at the 5 position for **6a**.This is the first example of the synthesis of a fluorinated morpholin-3-one by direct reaction of a fluorinated triethylene glycol di(trifluoromethanesulfonate) with an amine. When K_2CO_3 or the stronger base, KOH, was used in place of Et_3N, the cyclized product **6a** was not observed. However, when the reaction conditions were optimized by increasing the mole ratio of reactants **4a**:**2c**:Et_3N = 1:1:5 at 110 °C over 48 h (Table 1), the yield of **6a** was increased to 35%.

2,2-Difluoro-2-{2-[2-(phenylmethyl)amion-difluoroethoxy]tetrafluoro-ethoxy}ethanol, **5a** was thought to be the intermediate in the formation of 2,2,6,6-tetrafluo-4-phenylmethylmorpholin-3-one, **6a**, occurring by intramolecular cyclization (Scheme 3). However, no reaction occurred when 0.5 mmol **5a** was mixed with 1 mmol Et_3N in a Pyrex tube and all of the **5a** was recovered.

When changing the fluorinated alkyl chain from triethylene glycol to tetraethylene glycol, **2d**, and reacting with benzylamine, **4a**, under the same conditions, resulted in only the nucleophilically-substituted product **7** (Scheme 4).

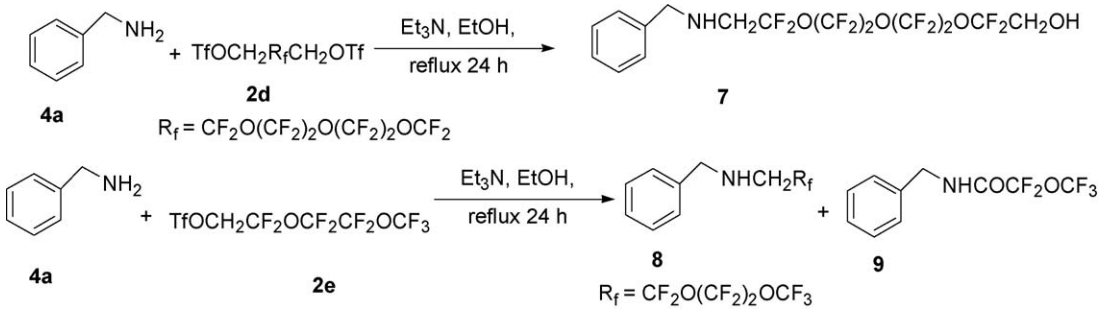
Replacing the trifluoromethane sulfonate substituent in **2c** by the diethylene glycol trifluoromethanesulfonatetrifluoromethoxy derivative **2e**, 2,2-difluoro-2-[1,1,2,2-tetrafluoro-2-(trifluoromethoxy)-ethoxy]ethyl-trifluoromethanesulfonate ester, which then was reacted under the same conditions with **4a** gave, after separation of the reaction mixture, N-(2-trifluoromethoxy-2-difluoroethyl)-benzenemethane-amine, **8** (20% yield), and 2-trifluoromethoxy-N-(phenylmethyl)difluoro-acetamide, **9** (15%) (Scheme 4).

Previously, hydrolysis of ethers by sulfuric acid which contain the $–CF_2O–$ group, a procedure for formation of hydrogen fluoride and fluorosulfonic acid, had been used for the synthesis of the esters of various fluorinated acids [17]. The acetamide product, **9**, or lactam product, **6**, obtained from the poly $–CF_2O–$ groups found in **2e** or **2c** in the presence of Et_3N, may involve the basic hydrolysis of the difluoromethyleneoxy group. It is suggested that the reaction may take place according to Scheme 5.

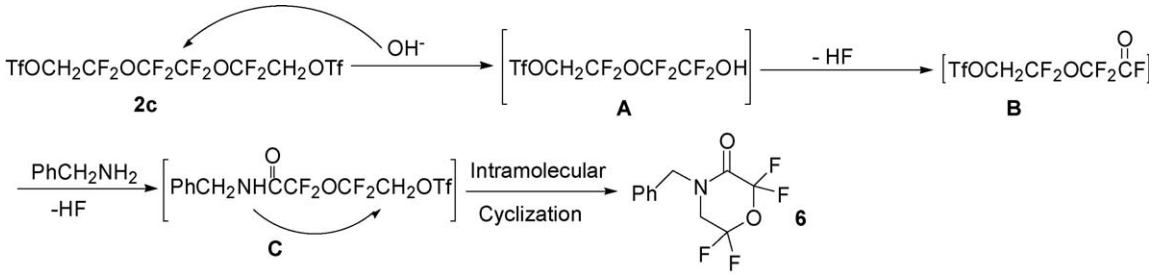
Basic hydrolysis of **2c** at 110 °C gives rise to fluorinated alcohol **A**. The formation of the intermediate acetyl fluoride, **B**, likely the key procedure, rapidly reacts with the amine to give acetamide **C** with concomitant loss of HF. Then C undergoes intramolecular cyclization to yield 2,2,6,6-tetrafluoro-4-phenylmethyl-morpholin-3-one, **6**.

N-fluoroalkylbenzenamine was isolated from reaction of aniline and fluoroalkyl alcohol methanesulfonate or benzenesulfonate in 50% yield [17]. When 4-iodo-benzenamine, **4d**, was heated with **2c** in ethanol at 110 °C, in an effort to obtain the cyclization product, 2,2,6,6-tetrafluoro-4-iodophenylmor-pholin-3-one, approximately five products were observed by TLC. These were subsequently isolated from the reaction mixture by column chromatography (Scheme 6). Two major products,2,2-difluoro2-{2-[2-(4-iodo-phenylmethyl-amino)difluoroethoxy]-tetra-fluoro-ethoxy}ethanol, **10** (20%) and N,N'-1,2-[2,2-difluoroethanediylbis(oxy-2,1-tetrafluoroethanediyl)]-bisbenzenamine, **11** (15%) were found.

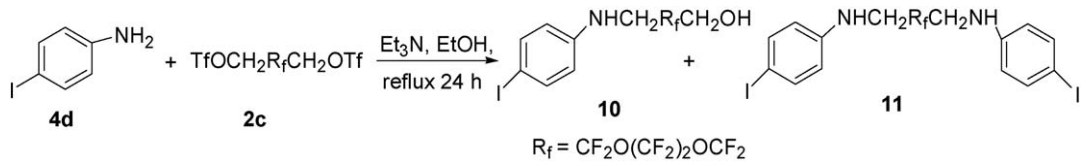
In conclusion, a new, straightforward approach was developed for the preparation of fluorinated morpholin-3-ones. Reaction of fluorinated triethylene glycol di(trifluoromethanedisulfonate), **2c**, and benzylamine resulted in 2,2,6,6-tetrafluoro-4-phenylmethyl-morpholin-3-one. Changing the fluorinated alkyl chain from triethylene glycol to tetraethylene glycol, **2d**, and reacting with benzylamine, **4a**, under the same conditions, resulted solely in the nucleophilically-substituted product. Replacing the trifluoromethane sulfonate substituent in **2c** by the trifluoromethoxy



Scheme 4. Reaction of trifluoromethylsulfonate and trifluoromethoxy derivatives with benzylamine.



Scheme 5. A plausible reaction mechanism for the formation of **6**.



Scheme 6. Reaction of **2c** with 4-iodobenzenamine.

moiety in **2e**, and reacting with **4a**, gave the nucleophilically-substituted compounds **8**, and **9** which result from the basic hydrolysis of the difluoromethoxy group. Combination of the trifluoromethanesulfonic fluoroalkyldiyl ester with benzylamine resulted in fluorinated phenylmethylpiperidine and phenylmethylazepine.

3. Experimental section

3.1. General considerations

All the reagents used were analytical reagents purchased from commercial sources and used as received. ^{1}H, ^{19}F NMR and ^{13}C NMR spectra were recorded on a 300 MHz nuclear magnetic resonance spectrometer operating at 300.13, 282 and 75.48 MHz, respectively. Chemical shifts were reported relative to Me_4Si for ^{1}H, and ^{13}C, CCl_3F for ^{19}F. The solvent was $CDCl_3$ unless otherwise specified. GC–MS was carried out using a SHIMADZU GCMS-QP5000 Gas Chromatography/Mass Spectrometer. Elemental analyses were performed on an EXETER CE-440 Elemental Analyzer.

3.2. General procedure for the preparation of trifluoromethanesulfonic acid polyfluoroalkyldiyl ester

2,2,3,3,4,4-Hexafluoro-1,5-pentanediol, **1a** (1 mmol), 2,2,3,3,4,4,5,5-octafluoro-1,6-hexanediol, **1b** (1 mmol), 1H,1H,8H,8H-octafluoro-3,6-dioxaoctane-1,8-diol, **1c** (1 mmol), or 1H,1H,11H,11H-perfluoro-3,6,9-trioxaundecane-1,8-diol, **1d**, pyridine (2.3 mmol) and dichloromethylene (20 mL) were stirred at room temperature under a nitrogen atmosphere. After 20 min, trifluoromethanesulfonic anhydride (2.5 mmol) in 10 mL dichloromethylene was slowly added over 1 h by using an addition funnel. The mixture was stirred for 24 h, then washed with water (3× 10 mL), 10% sodium bicarbonate (2× 10 mL), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give trifluoromethanesulfonic acid polyfluoroalkyldiyl ester, **2a–2d**.

2a. *Trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanediyl ester*: 80% yield, colorless solid: ^{1}H NMR δ ($CDCl_3$, ppm): 4.85 (t, J = 11.6 Hz, 4H); ^{19}F NMR δ ($CDCl_3$, ppm): −124.38 (s, 2F), −119.56 (t, J = 11.6 Hz, 4F), −73.88 (s, 6F).

2b. *Trifluoromethaneulfonic acid 2,2,3,3,4,4,5,5-octafluoro-1,6-hexanediyl ester:* 80% yield, colorless solid: ^{1}H NMR δ ($CDCl_3$, ppm): 4.83 (t, J = 11.9 Hz, 4H); ^{19}F NMR δ ($CDCl_3$, ppm): −122.91 (s, 4F), −119.61 (t, J = 11.6 Hz, 4F), −73.85 (s, 6F).

2c. *Fluorinated triethylene glycol di(trifluoromethanesulfonate)*: 80% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 4.68 (t, J = 7.9 Hz, 4H); ^{19}F NMR δ ($CDCl_3$, ppm): −88.63 (m, 4F), −77.68 (m, 4F), −74.13 (s, 6F). GC–MS (EI) *m/z:* 674 (M^+). Anal. Calcd (%) for $C_{10}H_4F_{18}O_9S_2$ (673.90): C, 17.81; H, 0.60. Found: C, 17.76; H, 0.47.

2d. *Fluorinated tetraethylene glycol di(trifluoromethanesulfonate)*: 80% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 4.68 (t, J = 7.9 Hz, 4H); ^{19}F NMR δ ($CDCl_3$, ppm): −88.63 (m, 8F), −77.68 (m, 4F), −74.13 (s, 6F). Anal. Calcd (%) for $C_{10}H_4F_{18}O_9S_2$ (674.23): C, 17.81; H, 0.60. Found: C, 17.76; H, 0.47.

3.3. Preparation 3,3,4,4,5,5-hexafluoro-1-(phenylmethyl)piperidine 3a, and 3,3,4,4,5,5,6,6-octafluoro-1-(phenylmethyl)azepine 3b

Trifluoromethanesulfonic acid 2,2,3,3,4,4-hexafluoro-1,5-pentanedily ester, **2a** (1 mmol), or trifluoromethaneulfonic acid 2,2,3,3,4,4,5,5-octafluoro-1,6-hexanedily ester, **2b** (1 mmol), **4a** (1 mmol), and Et_3N (3 mmol) in 2 mL ethanol are placed in a round-bottomed-flask fitted with a reflux condenser, and heated at reflux for 24 h. After cooling, the organic solvent was removed under reduced pressure and to the residue was added 30 mL dichloromethane then washed with water (3× 20 mL), and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by silica gel column chromatography (DCM:Hexane = 1:5) to give 3,3,4,4,5,5-hexafluoro-1-(phenylmethyl)piperidine **3a**, or 3,3,4,4,5,5,6,6-octafluoro-1-(phenylmethyl)azepine **3b**.

3a. *3,3,4,4,5,5-hexafluoro-1-(phenylmethyl)piperidine*: 50% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.34 (m, 5H), 3.79 (s, 2H), 3.02 (t, J = 8.8 Hz, 4H). ^{19}F NMR δ (ppm): −139.28 (m, 2F), −121.96 (s, 4F). GC–MS (EI) *m/z:* 283 (M^+). Anal. Calcd (%) for $C_{12}H_{11}F_6N$ (283.08): C, 50.89; H, 3.91; N, 4.95. Found: C, 50.78; H, 3.90; N, 4.89.

3b. *3,3,4,4,5,5,6,6-octafluoro-1-(phenylmethyl)azepine*: 45% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37 (m, 5H), 3.95 (s, 2H), 3.56 (t, J = 14.2 Hz, 4H). ^{19}F NMR δ (ppm): −128.04 (s, 4F), −112.73 (s, 4F). GC–MS (EI) *m/z:* 333 (M^+). Anal. Calcd (%) for $C_{13}H_{11}F_8N$ (333.08): C, 46.86; H, 3.33; N, 4.20. Found: C, 46.46; H, 3.37; N, 4.09.

3.4. General procedure for the preparation 2,2,6,6-tetrafluoro-4-phenyl-morpholin-3-one

Fluorinated triethylene glycol di(trifluoromethanesulfonate), **2c** (1 mmol), benzylamine, **4a** (1 mmol), and Et_3N (5 mmol) in 2 mL ethanol are placed in a Pyrex glass tube, sealed and heated at 110 °C for 48 h. After cooling, the organic solvent was removed under reduced pressure and the residue was added 30 mL dichloromethane then washed with water (3× 20 mL), and the organic layer was dried over anhydrous Na_2SO_4. After the solvent is removed, the crude product was purified by silica gel column chromatography (DCM:hexane = 1:3) to give 2,2-difluoro-2-{2-[2-(phenylmethyl)amino-difluoroethoxy]-tetrafluoroethoxy} ethanol, **5a**, and 2,2,6,6-tetrafluoro-4-phenyl-morpholin-3-one, **6a**.

5a. *2,2-Difluoro-2-{2-[2-(phenylmethyl)amino-difluoroethoxy]-tetrafluoroethoxy} ethanol:* 20% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.32 (m, 5H), 4.61 (m, 2H), 3.94 (s, 2H), 3.22 (t, J = 10.5 Hz, 2H). ^{19}F NMR δ (ppm): −88.67 (m, 4F), −80.51 (m, 2F), −74.89 (m, 2F). GC–MS (EI) *m/z:* 384 (M^++1). Anal. Calcd (%) for $C_{13}H_{13}F_8NO_3$ (383.08): C, 40.74; H, 3.42; N, 3.65. Found: C, 41.00; H, 3.22; N, 3.37.

6a. *2,2,6,6-Tetrafluoro-4-phenyl-morpholin-3-one*: 35% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.43 (m, 3H), 7.26 (m, 2H), 4.71 (s, 2H), 3.79 (t, J = 8.1 Hz, 2H). ^{19}F NMR δ (ppm): −75.38 (t, J = 8.1 Hz, 2F), −72.03 (m, 2F). GC–MS (EI) *m/z:* 263 (M^+). Anal. Calcd (%) for $C_{11}H_9F_4NO_2$ (263.06): C, 50.20; H, 3.45; N, 5.32. Found: C, 49.57; H, 3.40; N, 5.32.

5b. *2,2-Difluoro-2-{2-[2-(4-bromophenylmethyl-amino)difluoroethoxy]tetrafluoro-ethoxy}ethanol*: 20% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.49 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 10.4 Hz, 2H), 4.61 (m, 2H), 3.89 (s, 2H), 3.21 (t, J = 10.5 Hz, 2H). ^{19}F NMR δ (ppm): −88.71 (m, 4F), −80.48 (m, 2F), −74.92 (m, 2F). GC–MS (EI) *m/z:* 463 (M^+). Anal. Calcd (%) for $C_{13}H_{11}BrF_9NO_2$ (462.98): C, 33.79; H, 2.62; N, 3.03. Found: C, 34.01; H, 2.32; N, 3.17.

6b. *2,2,6,6-Tetrafluoro-4-(4-bromophenyl)-morpholin-3-one*: 35% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.57 (d, J = 4.2, 2H), 7.16 (d, J = 8.3, 2H), 4.66 (s, 2H), 3.80 (t, J = 8.1 Hz, 2H). ^{19}F NMR δ (ppm): −75.38 (t, J = 8.3 Hz, 2F), −72.05 (m, 2F). GC–MS (EI) *m/z:* 341 (M^+). Anal. Calcd (%) for $C_{11}H_8BrF_4NO_2$ (340.97): C, 38.62; H, 2.36; N, 4.09. Found: C, 38.61; H, 2.34; N, 4.19.

5c. *2,2-Difluoro -2-{2-[2-(4-Methoxyphenylmethy-amino)difluoroethoxy]-tetrafluoro-ethoxy}ethanol:* 20% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.57 (m, 2H), 3.84 (s, 2H), 3.79 (s, 3H), 3.17 (t, J = 10.6 Hz, 2H). ^{19}F NMR δ (ppm): −88.69 (m, 4F), −80.48 (m, 2F), −74.83 (m, 2F). GC–MS (EI) *m/z:* 415 (M^+). Anal. Calcd (%) for $C_{14}H_{14}F_9NO_3$ (415.08): C, 40.49; H, 3.40; N, 3.37. Found: C, 40.85; H, 3.57; N, 3.41.

6c. *2,2,6,6-Tetrafluoro-4-(4-methoxyphenyl)-morpholin-3-one:* 35% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.17 (d, J = 8.5, 2H), 6.90 (d, J = 8.3, 2H), 4.62 (s, 2H), 3.80 (s, 3H), 3.73 (t, J = 8.1 Hz, 2H). ^{19}F NMR δ (ppm): −75.44 (t, J = 8.3 Hz, 2F), −72.05 (m, 2F). GC–MS (EI) *m/z:* 293 (M^+). Anal. Calcd (%) for $C_{12}H_{11}F_4NO_3$ (293.07): C, 49.15; H, 3.78; N, 4.78. Found: C, 49.46; H, 3.88; N, 4.72.

3.5. Preparation 2,2-difluoro-2-{2-[2-(butylamino)difluoroethoxy]tetrafluoroethoxy}ethanol and 2,2,6,6-tetrafluoro-4-butyl-morpholin-3-one **6d**

The reaction was carried out as above with **2c** and **4d**.

Mixture of **5d** and **6d**: 45% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.92 (t, J = 8.1 Hz, 2H), 3.52 (d, J = 7.4 Hz, 4H), 1.63 (m, 4H), 1.37 (m, 4H), 0.96 (t, J = 8.2 Hz, 6H). ^{19}F NMR δ (ppm): −88.79 (m, 4F), −80.53 (m, 2F), −77.71 (m, 2F), −75.97 (t, J = 4.5, 2F), −72.31 (m, 2F). GC – two peaks at 8.2 min and 8.7 min. GC–MS (EI) *m/z:* 350 (M^++1, 8.2 min), 229 (M^+, 8.7 min).

3.6. Preparation 2,2-difluoro -2-{2-[2-(2-benzylamino-difluoroethoxy)-tetrafluoro-ethoxy]tetrafluoroethoxy}ethanol **7**

Fluorinated tetraethylene glycol di(trifluoromethanesulfonate), **2d** (1 mmol), benzylamine, **4a** (1 mmol), and Et_3N (3 mmol) in 2 mL ethanol are placed in a Pyrex glass tube, sealed and heated at 110 °C for 48 h. After cooling, the organic solvent was removed under reduced pressure and to the residue was added 30 mL dichloromethane then washed with water (3× 20 mL), and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by silica gel column chromatography (DCM:Hexane = 1:5) to give *2,2-difluoro -2-{2-[2-(2-benzylamino-difluoroethoxy)-tetrafluoro-ethoxy]tetrafluoroethoxy}ethanol,* **7**.

7. *2,2-Difluoro -2-{2-[2-(2-benzylamino-difluoroethoxy)-tetrafluoro-ethoxy]tetrafluoroethoxy}ethanol*: 15% yield, colorless liquid; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.31 (m, 5H), 4.53 (m, 2H), 3.94 (s, 2H), 3.19 (t, J = 10.5 Hz, 2H). ^{19}F NMR δ (ppm): −88.77 (m, 4F), −88.55 (m, 4F), −80.51 (m, 2F), −74.87 (m, 2F). GC–MS (EI) *m/z:* 499 (M^+). Anal. Calcd (%) for $C_{15}H_{13}F_{12}NO_4$ (499.07): C, 36.09; H, 2.62; N, 2.81. Found: C, 36.39; H, 2.48; N, 2.95.

3.7. Preparation N-(2-trifluoromethoxy-2-difluoroethyl)-benzenemethaneamine, **8** *and 2-trifluoromethoxy-N-(phenylmethyl)-difluoroacetamide,* **9**

1H,1H,8H,8H-Nonafluoro-3,6-dioxaheptan-1-ol, **1e** (1 mmol), pyridine (2.3 mmol) and dichloromethylene (20 mL) were stirred at room temperature under a nitrogen atmosphere. After 20 min, trifluoromethanesulfonic anhydride (2.5 mmol) in 10 mL dichloromethylene was slowly added (over 1 h) by using an addition funnel. The mixture was stirred for 24 h, then washed with water (3× 10 mL), 10% sodium bicarbonate (2× 10 mL), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to give trifluoromethanesulfonic acid 2,2-difluoro-2-[1,1,2,2-tetrafluoro-2-(trifluoromethyoxy)ethoxy]-ethyl esters, **2e**.

2e. *Trifluoromethanesulfonic acid 2,2-difluoro-2-[1,1,2,2-tetrafluoro-2-(trifluoro-methyoxy)-ethoxy]-ethyl esters*: 80% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 4.69 (t, J = 7.7 Hz, 2H); ^{19}F NMR δ ($CDCl_3$, ppm): −90.58 (t, J = 8.7 Hz, 2F), −88.54 (t, J = 12.7 Hz, 2F), −77.56 (m, 2F), −74.06 (s, 3F), −55.18 (t, J = 8.7 Hz, 3F). GC–MS (EI) *m/z:* 414 (M^+). Anal. Calcd (%) for $C_6H_2F_{12}O_5S{\cdot}H_2O$ (431.95): C, 16.68; H, 0.93. Found: C, 17.01; H, 0.47.

Then, **2e** (1 mmol), benzylamine, **4a** (1 mmol), and Et_3N (3 mmol) in 2 mL ethanol are placed in a Pyrex glass tube, sealed and heated at 110 °C for 48 h. After cooling, the organic solvent was removed under reduced pressure and to the residue was added 30 mL dichloromethane then washed with water (3× 20 mL), and the organic layer was dried over anhydrous Na_2SO_4. After the solvent is removed, the crude product was purified by silica gel column chromatography to give N-(2-trifluoromethoxy-2-difluoroethyl)-benzenemethaneamine, **8** (20% yield) and 2-trifluoromethoxy-N(phenylmethyl)-difluoroacetamide, **9** (15%).

8. *N-(2-Trifluoromethoxy-2-difluoroethyl)-benzenemethaneamine:* 20% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 7.36 (m, 5H), 3.93 (s, 2H), 3.21 (t, J = 10.5 Hz, 2H); ^{19}F NMR δ ($CDCl_3$, ppm): −90.89 (m, 2F), −88.58 (m, 2F), −74.97 (t, J = 13.2 Hz, 2F), −55.30 (t, J = 9.0 Hz, 3F); GC–MS (EI) *m/z*: 371 (M^+); Anal. Calcd (%) for $C_{12}H_{10}F_9NO_2$ (317.06): C, 38.83; H, 2.72; N, 3.77. Found: C, 38.53; H, 2.54; N, 3.77.

9. *2-Trifluoromethoxy-N-(phenylmethyl)-difluoroacetamide*: 15% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 7.35 (m, 5H), 6.48 (s, 1H), 4.53 (d, J = 5.7 Hz, 2H); ^{19}F NMR δ ($CDCl_3$, ppm): −80.06 (m, 2F), −54.93 (m, 3F); GC–MS (EI) *m/z*: 269 (M^+); HRMS Calcd for $C_{10}H_8F_5NO_2$: 269.0457. Found: 269.0450.

3.8. 2,2-Difluoro2-{2-[2-(4-iodo-phenylmethyl-amino)difluoroethoxy]-tetra-fluoro-ethoxy}ethanol, **10** *and N,N'-[1,2-[2,2-difluoro-ethanediylbis(oxy-2,1-tetrafluoroethanediyl)]-bisbenzenamine,* **11**

Fluorinated triethylene glycol di(trifluoromethanesulfonate), **2c** (1 mmol), 4-iodophenylamine, **4d** (1 mmol), and Et_3N (5 mmol) in 2 mL ethanol are placed in a Pyrex glass tube, sealed and heated at 110 °C for 48 h. After cooling, the organic solvent was removed under reduced pressure and the residue was added 30 mL dichloromethane then washed with water (3× 20 mL), and the organic layer was dried over anhydrous Na_2SO_4. After the solvent was removed, the crude product was purified by silica gel column chromatography (DCM:Hexane = 1:2) to give, 2,2-difluoro -2-[2-[2-[(4-iodophenylmethyl)amino]difluoroethoxy]tetrafluoroethoxy]ethanol, **10** (20% yield) and N,N'-[1,2-[2,2-difluoroethanediylbis(oxy-2,1-tetrafluoroethanediyl)]bisbenzenamine, **11** (15%).

10. *2,2-Difluoro2-{2-[2-(4-iodo-phenylmethyl-amino)difluoroethoxy]-tetra-fluoro-ethoxy}ethanol*: 20% yield, colorless liquid: ^{1}H NMR δ ($CDCl_3$, ppm): 7.45 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 8.8 Hz, 2H), 4.53 (m, 2H), 3.96 (s, 2H), 3.75 (m, 2H); ^{19}F NMR δ ($CDCl_3$, ppm): −89.19 (m, 4F), −80.95 (m, 2F), −76.31 (m, 2F); GC–MS (EI) *m/z*: 497 (M^++1); Anal. Calcd (%) for $C_{12}H_{10}F_8INO_3$ (495.1): C, 29.36; H, 1.74; N, 2.83. Found: C, 29.36; H, 1.76; N, 2.83.

11. *N,N'-[1,2-[2,2-Difluoroethanediylbis(oxy-2,1-tetrafluoroethanediyl)]bis-benzenamine:* 15% yield, colorless solid: ^{1}H NMR δ ($CDCl_3$, ppm): 7.45 (d, J = 8.9 Hz, 4H), 6.45 (d, J = 8.9 Hz, 4H), 3.92 (t, J = 6.9 Hz, 2H), 3.67 (m, 4H); ^{19}F NMR δ ($CDCl_3$, ppm): −89.30 (m,

4F), −76.31 (m, 4F); GC–MS (EI) *m*/*z*: 696 (M^+); Anal. Calcd (%) for $C_{18}H_{14}F_8I_2N_2O_2$ (695.90): C, 31.06; H, 2.03; N, 4.02. Found: C, 31.53; H, 2.13; N, 3.82.

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