

Regioselective 1,3-Dipolar Cycloaddition and 1,2-Addition between Benzaldoxime NH-nitrone and Perfluoro-2-methyl-2-pentene

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Regioselective perfluorinated [3+2] cycloadducts and 1,2-adducts have been prepared by 1,3-dipolar cycloaddition between benzaldoxime NH-nitrone and perfluorinated alkene, perfluoro-2-methyl-2-pentene. Although the cycloaddition reaction is carried out at room temperature, the corresponding perfluorinated compounds are effectively produced in a high yield. In particular, the methoxy-substituted adducts (**4** and **7a**) show the self-assembled structure by intermolecular interactions. These derivatives were characterized by IR, ¹H and ¹⁹F NMR, and the absolute structure of perfluorinated adducts was confirmed by X-ray crystallography.

Key Words: NH-nitrone, Perfluorinated olefin, Cycloaddition, Regioselectivity

Introduction

Perfluorinated organic compounds have attracted many attentions owing to their unique properties such as excellent thermal and chemical stability as well as their super hydrophobic nature. The synthesis of fluoro-substituted heterocycles has received a great deal of attention in recent years, because the peculiar biological activity of these compounds makes them effective as antifungal, antiviral, antitumor agents.¹ However, although a great number of achiral fluorinated heterocycles have been described, only a few selectively fluorinated derivatives have been prepared by asymmetric synthesis. In addition, although many perfluorinated linear and cyclic organic compounds are either commercially available or have been reported in the literatures, perfluorinated heterocyclic compounds are relatively rare. For example, perfluorinated porphyrins and oligofluorenes are reported.^{2,3} Considering the significance of the perfluorinated organic compounds and the relative rareness, it should be important to develop methodologies for the preparation of the perfluorinated heterocycles.

Recently, Noguchi, Donas and coworkers reported synthesis of isoxazolidine derivatives derived from cycloaddition reactions between NH-nitrone and maleimide or electron deficient acetylene system.^{4,5} The electron deficient olefin-promoted cycloaddition reactions reported by the authors, however, were carried out at high temperature (e.g. refluxing MeOH). An evaluation of these properties led us to predict that a perfluorinated olefin (highly electron deficient) might display improved reactivity with NH nitrone in a mild room temperature condition. Herein, we report a facile approach for the synthesis and self-assembled structure formation of the perfluorinated heterocyclic compounds based on a 1,3-dipolar cycloaddition reaction between various benzaldoxime NH-nitrones and perfluorinated alkene, perfluoro-2-methyl-2-pentene.

Experimental Section

General procedure. 4-Methoxy benzaldehyde is quantita-

tively converted to the corresponding anisaloxime *via* reaction with hydroxylamine. The solution of anisaloxime (0.2 g, 1.32 mmol) and perfluoro-2-methyl-2-pentene (3.9 g, 13.2 mmol) in ethanol (50 mL) was reacted under room temperature for 10 h. After reaction, the solvent and perfluoro-2-methyl-2-pentene were evaporated to dryness. The crude products were purified by silica gel column chromatography to give **4** (73%) and **7** (19%). Similarly, the reaction product **5** (57%) and **8** (7%) were obtained from benzaldoxime and perfluoro-2-methyl-2-pentene in ethanol, and the product **6** (36%) and **9** (5%) were obtained from 4-fluoro-benzaldoxime and perfluoro-2-methyl-2-pentene.

Spectral data for compound 4b: White crystals, mp 47 ~ 48 °C; X-ray data (CCDC-673145): C₁₄H₉NO₂F₁₂, *M* = 451.22, Orthorhombic, *Pbca* (No. 61), *a* = 6.642(1) Å, *b* = 16.163(3) Å, *c* = 29.547(6) Å, *V* = 3172.0(11) Å³, *Z* = 8, *T* = 90 K, μ (λ = 0.75000 Å) = 0.248 mm⁻¹, *d*_{calc} = 1.890 g/cm³, 13121 reflections measured, 3906 unique (*R*_{int} = 0.0428), *R*₁ = 0.0618, *wR*₂ = 0.1760 (*I* > 2σ(*I*)), *R*₂ = 0.0668, *wR*₂ = 0.1798 (all data), GOF = 1.063. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; ¹H-NMR (300 MHz, CDCl₃) δ 7.24 (d, 2H, aromatic), 6.92 (d, 2H, aromatic), 6.93 (d, 1H, NH), 5.06 (d, 1H, CH, *J* = 12.0 Hz), 3.81 (s, 3H, methoxy); ¹⁹F-NMR δ -59.20 and -64.22 (CF₃), -79.97 (CF₂CF₃), -116.0 (br, CF), -118.72, -119.80, -121.72, 122.69 (CF₂); FAB-MS (*m/z*) 452.04 (*M*⁺ + 1), 307.1, 154.2; IR (cm⁻¹) 3300, 3010, 2990, 2970, 1620, 1510, 1210, 1150, 1050 (C-F bending).

Spectral data for compound 4a: White crystals, mp 47 ~ 48 °C; ¹H-NMR (300 MHz, CDCl₃) δ 7.24 (d, 2H, aromatic), 6.92 (d, 2H, aromatic), 6.93 (d, 1H, NH), 5.39 (d, 1H, CH, *J* = 12.0 Hz), 3.81 (s, 3H, methoxy); IR and MASS data of compound **4a** are identical compared with that of compound **4b**.

Spectral data for compound 7a: White crystals, mp 47 °C; ¹H-NMR (300 MHz, CDCl₃) δ 8.21 (s, 1H, ArCH), 7.57 (d, 2H, aromatic), 6.94 (d, 2H, aromatic), 4.52 (qqd, 1H, *trans*-CH), 3.84 (s, 3H, methoxy); ¹⁹F-NMR δ -59.83 and -60.42 (CF₃),

-79.41 (CF₂CF₃), -112.45 (CF), -119.90, -120.91, 121.30, and -122.32 (CF₂); FAB-MS (*m/z*) 452.04 (M⁺+1), 135.2; IR (cm⁻¹) 3600, 2990, 2920, 1610, 1505, 1210, 1150, 1050 (C-F bending).

Spectral data for compound 7b: White crystals, mp 46 °C; X-ray data (CCDC-673144): C₁₄H₉NO₂F₁₂, *M* = 451.22, Monoclinic, *P*2₁/*c* (No. 14), *a* = 16.744(3) Å, *b* = 6.931(1) Å, *c* = 15.626(3) Å, β = 116.09(3)°, *V* = 1628.7(6) Å³, *Z* = 4, *T* = 90 K, μ (*λ* = 0.85000 Å) = 0.338 mm⁻¹, *d*_{calc} = 1.840 g/cm³, 3978 reflections measured, 2350 unique (*R*_{int} = 0.0422), *R*₁ = 0.0421, *wR*₂ = 0.1179 (*I* > 2σ(*I*)), *R*₁ = 0.0441, *wR*₂ = 0.1202 (all data), GOF = 1.022; ¹H-NMR (300 MHz, CDCl₃) δ 7.74 (d, 2H, aromatic), 7.55 (s, 1H, ArCH), 6.94 (d, 2H, aromatic), 4.75 (qqd, 1H, *cis*-CH), 3.85 (s, 3H, methoxy); ¹⁹F-NMR δ -59.51 and -60.74 (CF₃), -79.58 (CF₂CF₃), -114.66 (CF), -121.14 (CF₂); FAB-MS (*m/z*) 452.04 (M⁺+1), 307.1, 154.2; IR (cm⁻¹) 3010, 2990, 2920, 1610, 1505, 1210, 1150, 1050 (C-F bending).

Spectral data for compound 5b: White crystals, mp 40 °C; X-ray data; C₁₃H₇F₁₂NO, *M* = 421.20, Tetragonal, *I*-4 (No. 82), *a* = 15.226(2) Å, *b* = 15.226(2) Å, *c* = 12.709(3) Å, *V* = 2946.3(8) Å³, *Z* = 8, *T* = 90 K, μ (*λ* = 0.70000 Å) = 0.212 mm⁻¹, *d*_{calc} = 1.899 g/cm³, 7996 reflections measured, 4507 unique (*R*_{int} = 0.0479), *R*₁ = 0.0785, *wR*₂ = 0.2199 (*I* > 2σ(*I*)), *R*₁ = 0.0805, *wR*₂ = 0.2223 (all data), GOF = 1.074; ¹H-NMR (300 MHz, CDCl₃) δ 7.44 (bs, 5H of aromatic (4H) and NH), 5.10 (d, 1H, *J* = 12.0 Hz); ¹⁹F-NMR δ -59.01 and -64.12 (CF₃), -79.96 and -80.02 (CF₂CF₃), 116.5 (broad, CF), -118.65, -119.63, -121.50, and -122.5 (CF₂); IR (cm⁻¹) 3600, 2990, 2970, 1600, 1210, 1150, 1050 (C-F bending).

Spectral data for compound 5a: White crystals, mp 40 °C; ¹H-NMR (300 MHz, CDCl₃) δ 7.44 (bs, 5H of aromatic (4H) and NH), 5.50 (d, 1H, *J* = 12.0 Hz); IR and MASS data of compound 5a are identical compared with that of compound 5b.

Spectral data for compound 8a: ¹H-NMR (300 MHz, CDCl₃) δ 4.51 (qqd, 1H, *trans*-CH), 7.40-7.52 (m, 3H, aromatic), 7.61-7.64 (m, 2H, aromatic), 8.28 (s, 1H, ArCH); ¹⁹F-NMR δ -59.84 and -60.43 (CF₃), -79.38 and -79.42 (CF₂CF₃), -112.88 (CF), -119.85, -120.87, -121.22, and -122.25 (CF₂); IR (cm⁻¹) 3300, 2990, 2820, 1730 (imine), 1480, 1300, 1250, 1150, 980; Mass (*m/z*) C₁₃H₇N₁O₁F₁₂, calcd. 421.181; found 421, 121 (base), 104 (styrene).

Spectral data for compound 8b: ¹H-NMR (300 MHz, CDCl₃) δ 4.71 (qqd, 1H, *cis*-CH), 7.42-7.53 (m, 3H, aromatic), 7.74-7.75 (m, 2H, aromatic), 7.72 (s, 1H, ArCH); ¹⁹F-NMR δ -59.57 and -60.73 (CF₃), -79.59 and -79.63 (CF₂CF₃), -114.61 (CF), -121.10 (CF₂); IR (cm⁻¹) 3300, 3105, 2990, 2820, 1720 (imine), 1480, 1300, 1250, 1150, 980; Mass (*m/z*) C₁₃H₇N₁O₁F₁₂, calcd. 421.181; found 421, 121 (base), 104 (styrene).

Spectral data for compound 6a: ¹H-NMR (300 MHz, CDCl₃) δ 7.40-7.50 (m, 2H, aromatic), 6.95-7.10 (m, 2H, aromatic), 6.93 (d, 1H, NH, *J* = 11.0 Hz), 5.50 (d, 1H, CH, *J* = 11.0 Hz) of 6a and 5.06 (d, 1H, CH, *J* = 11.0 Hz) of 6b (6a : 6b = 7 : 3); ¹⁹F-NMR δ -58.20 and -63.25 (CF₃), -80.09 (CF₂CF₃), -110.5 and 116.5 (br, CF), -119.72, -119.80, -121.72, 122.69, 124.4, 125.7 (CF₂); IR (cm⁻¹) 3250, 3030, 2990, 2970, 1615, 1530, 1230, 1150, 1050 (C-F bending).

Spectral data for compound 9a: White crystals, mp 67 °C; X-ray data; C₁₃H₆F₁₃NO, *M* = 439.19, Tetragonal, *I*-4 (No. 82), *a* = 15.226(2) Å, *b* = 15.226(2) Å, *c* = 12.709(3) Å, *V* =

2946.3(8) Å³, *Z* = 8, *T* = 90 K, μ (*λ* = 0.75000 Å) = 0.225 mm⁻¹, *d*_{calc} = 1.980 g/cm³, 6577 reflections measured, 3477 unique (*R*_{int} = 0.0535), *R*₁ = 0.0643, *wR*₂ = 0.1780 (*I* > 2σ(*I*)), *R*₁ = 0.0667, *wR*₂ = 0.1806 (all data), GOF = 1.031; ¹H-NMR (300 MHz, CDCl₃) δ 7.81 (d, 2H, aromatic), 7.75 (s, 1H, ArCH), 7.21 (d, 2H, aromatic), 4.68 (qqd, 1H, *trans*-CH) 9a and 4.72 (qqd, 1H, *cis*-CH) of 9b (9a : 9b = 7 : 3); ¹⁹F-NMR δ -59.23 and -61.50 (CF₃), -79.80 (CF₂CF₃), -107.6 (CF), -117.90, -123.3 (CF₂); IR (cm⁻¹) 3400 (NH), 2985, 2950, 1615, 152, 1215, 1130, 1050 (C-F bending).

Results and Discussion

Our exploratory efforts began with a study of the reaction between anisaloxime (1) (1 equiv.) and perfluoro-2-methyl-2-pentene (10 equiv.) as shown in Figure 1. Stirring of the mixture in EtOH at room temperature for 24 h afforded the isoxazolidine 4 (73%) and the addition product 7 (19%). The neutral anisaloxime is expected to change into the NH-nitrone form *via* proton transfer from the OH to nitrogen atom (Figure 3), and then the resulting NH-nitrone species can smoothly be reacted with the perfluorinated olefin to provide the isoxazolidine products 4 and 1,2-addition product 7. Interestingly, the cycloaddition reaction was found to proceed in a regioselective fashion. Thus, the negative charged N-oxide species derived from tautomerization of the oxime was preferentially bonded with the positive charged olefin carbon atom. The unsubstituted benzaldoxime 2 and the fluoride substituted benzaldoxime 3 also gave the mixture of isoxazolidines and the 1,2-addition products.

The structural assignments of 4 were also confirmed by ¹⁹F-NMR, IR, and MASS analysis (see the experimental section). The molar ratio of two diastereomer 4a and 4b (6 : 4) was characterized by ¹H NMR analysis in an intensity ratio. The determination of stereochemistry of C₁H (1*R* form) of 4a (dia-

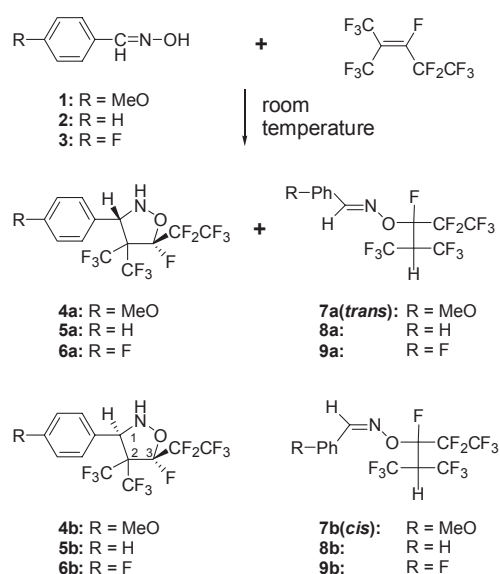


Figure 1. Synthesis of perfluorinated compounds by the 1,3-dipolar cycloaddition reaction between benzaldoximes (1-3) and perfluoro-2-methyl-2-pentene.

stereomer of **4b**) was deduced on the basis of analytical spectroscopic data. Thus, stereochemistry of **4b** (*1S* form) was fully characterized by NMR and X-ray crystallography (see the experimental part); for example, the structure and the absolute stereochemistry of the methine proton (5.39 ppm) in **4a** can easily be deduced to be “*R*” form on the basis of the chemical shift of **4b** (*1S* form, 5.06 ppm) and the other characteristic ^1H NMR data of **4a** were very similar with the **4b**.

On the other hand, reaction between anisaloxime (**1**) and olefin gave not only cycloaddition products but also a mixture of geometric isomers **7a** (*trans*) and **7b** (*cis*) in a ratio of 6 : 4. These would place the bulky phenyl group to stable *trans* position of NH nitron. As a result, adduct of **7a** (higher R_f value than **4a** in TLC) is mainly produced at the early stage and then isomerized into the adduct **7b** by acidic media as a chloroform solvent. Owing to the isomerization process, it is difficult to obtain absolutely pure crystal samples of the **7**. Nevertheless we obtained the “*S*” configuration at the one chiral center in a pure single crystal sample of **7b** (Figure 2b). Unfortunately, the absolute configuration at the one chiral center in adduct **7a** can not be simply determined. To characterize the absolute configuration of **7a**, we examine the isomerization of **7b** under toluene solvent at 80 °C. The resulting adducts are found to be *cis-trans* mixture in TLC. Accordingly, we think that the absolute configuration of **7a** has “*S*” configuration. In addition, geometric isomer **7a** can be characterized into the *trans* form by ^1H and ^{19}F NMR analysis of **7a** compared with that of **7b** (see the experimental section).

To investigate the generality and synthetic utility of this unique cycloaddition process, we performed in various solvent systems to verify cycloaddition products. A similar reaction in toluene or chloroform also gave **4** and **7**. The yields of cycloaddition products in nonpolar aprotic solvent were decreased drastically, while addition products were increased (Table 1,

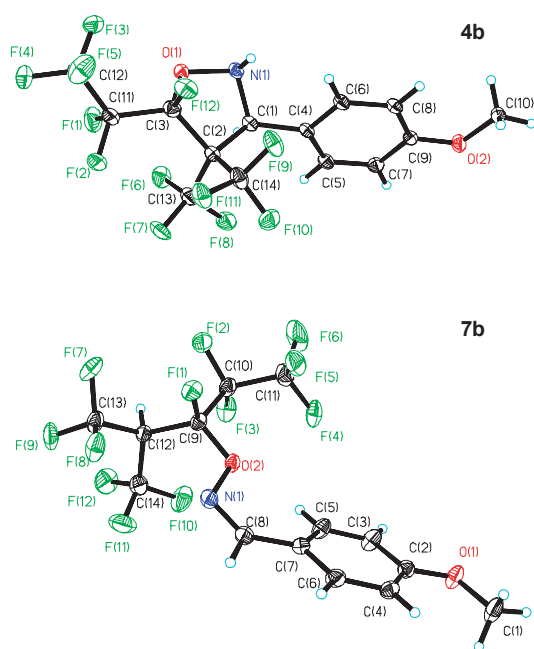


Figure 2. Crystal structures of compound **4b** and **7b**.

entry 1-3). The results indicate that NH-nitron intermediates are more stabilized by polar protic solvent than nonpolar solvent.

In order to elucidate the scope and features of oxime-NH-nitron isomerization system, additional two oximes **2** and **3** were prepared and examined the reaction behavior in the presence of perfluorinated olefin. A similar reaction at room temperature condition in ethanol also gave **5** and **6** in 57, and 36% yields, respectively (entry 4 and 6). A different trend is observed in the chloroform solvent compared with the ethanol; the yields of cycloaddition products (**5** and **6**) were drastically decreased (entry 5 and 7).

Furthermore, the unsubstituted benzaldoxime **2** and the fluoride substituted benzaldoxime **3** show lower reactivity than electron rich case as an anisaloxime **1**. These results demonstrate that NH-nitron does indeed lead to clean generation of the nitronium oxide form and that this intermediate is more stabilized by electron rich substituent as a methoxy group. We believe that the positively charged carbon atom due to inductive effect derived from the substituent of trifluoromethyl or pentafluoroethyl group in perfluorinated olefin prefers the formation of 3-substituted regioisomers uniting the larger coefficients in the transition state with negative oxygen atom. Consequently, cycloaddition efficiencies of anisaloxime **1** containing an electron donating group such as methoxy are higher than the case of unsubstituted benzaldoxime **2** or the fluoride substituted benzaldoxime **3** to give the corresponding products.

As shown in Figure 1, the cycloaddition between the benzaldoxime **2** (1 equiv.) and perfluoro-2-methyl-2-pentene (10 equiv.) gave also diastereomeric mixtures **5** (**5a** : **5b** = 6 : 4) and geometric isomers **8** (**8a** : **8b** = 7 : 3) in ethanol solvent. Similarly, the cycloaddition between the 4-fluoro-benzaldoxime **3** (1 equiv.) and perfluoro-2-methyl-2-pentene (10 equiv.) afforded a non-separable diastereomeric mixtures **6** (**6a** : **6b** = 5 : 5) and geometric isomers **9** (**9a** : **9b** = 7 : 3) in ethanol solvent. The structure of the corresponding products (**5-9**) was characterized by NMR, IR and X-ray analysis as described in experimental section. The configuration of C_3 (5-membered heterocycle) of diastereomeric mixtures **5** and **6** can easily be assigned to the *S* configuration. These results of the *S* configuration indicate that the approach of pentafluoroethyl group of olefin apart from the aromatic group of *trans* NH-nitron is more favored thereby leading to the preferential attack on this coordination to give the *S*-configuration of cycloaddition product **4b**. As a result, a similar trend in the cycloaddition products is observed

Table 1. Reaction results for the synthesis of isoxazolidines and addition products^a

entry	Oxime	Product (%)	Solvent	Time (hr)
1	1	4 (73) + 7 (19)	EtOH	24
2	1	4 (52) + 7 (37)	Toluene	36
3	1	4 (45) + 7 (43)	CHCl ₃	36
4	2	5 (57) + 8 (7)	EtOH	48
5	2	5 (25) + 8 (38)	CHCl ₃	48
6	3	6 (36) + 9 (5)	EtOH	48
7	3	6 (25) + 9 (55)	CHCl ₃	48

^aRefers to isolated yield.

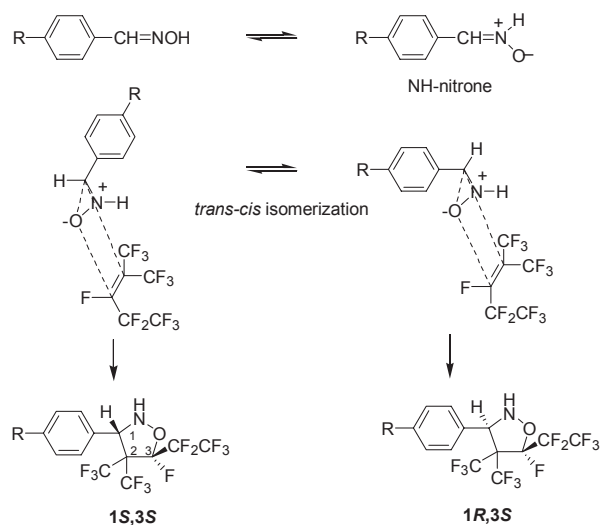


Figure 3. The regioselective cycloaddition between benzaldoxime NH-nitrone and perfluoro-2-methyl-2-pentene.

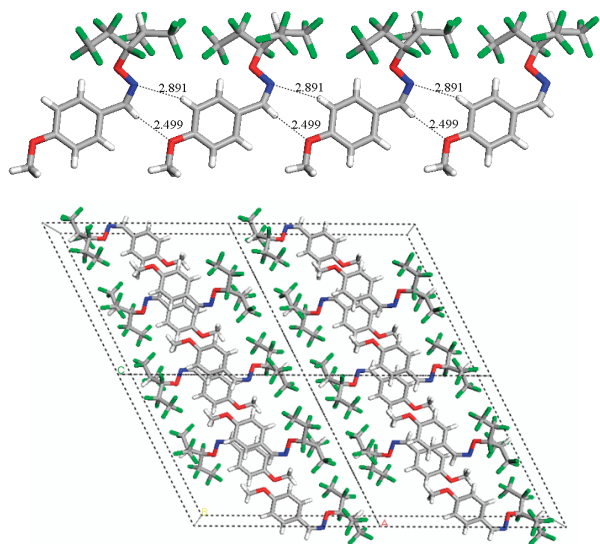


Figure 4. The hydrogen bond of the **7b** (up) and 3D networks of self assembly structure (down).

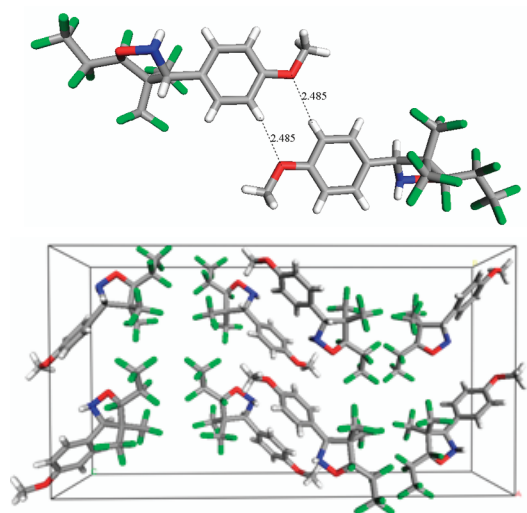


Figure 5. The hydrogen bond of the **4** and herringbone 3D networks.

to give the *S* configuration for the compounds **5** and **6** as shown in Figure 3. In addition, we investigated the possibility of ring-opening process of the cycloaddition compounds (**4-6**) to give the corresponding 1,2-addition adducts (**7-9**). The compounds (**4-6**) were reacted with the acidic media (acetic acid in chloroform solvent) or base media (triethylamine in chloroform solvent), respectively. However, we did not find 1,2-addition adducts derived from the cycloaddition compounds. Therefore, this means that the 1,2-addition adducts were directly derived from the inter-molecular 1,2-addition process between NH-nitrone and perfluoro-2-methyl-2-pentene.

In self-assembly chemistry, the hydrogen bonding interactions are strong and directional, and it can be applied to the construction of various supramolecular architectures, co-crystals, as well as to the diastereomeric resolution of racemic acids/amines.⁶⁻⁸ From a study of crystal packing diagram of addition product **7b**, we identify a discrete dimeric unit involving intermolecular aromatic C-H \cdots O hydrogen bond (2.59 Å) and aromatic C-H \cdots N hydrogen bond (2.90 Å) in an alternated fashion (Figure 4). This intermolecular hydrogen bonding interactions, with additional aromatic π - π and F \cdots F interactions, eventually lead to the formation of a 3D network of self assembly structure. As a result, the formation of self-assembled structure from three points interactions (hydrogen bond, π - π and F \cdots F), leading to a chiral porous 3D network, can be observed.

The 3D crystal structure of the diastereomeric mixture **4b** is different to that of **7b**, even though the intermolecular aromatic C-H \cdots OMe hydrogen bond, π - π and F \cdots F interactions are still persisted with respect to each other. The hydrogen bonds are robust (2.48 Å), but not too rigid, and can therefore “flex” to accommodate π - π and F \cdots F interactions within network while maintaining an efficient packing. These chains are propagated into 3D sheets *via* C-H \cdots O hydrogen bonds. Accordingly, the twist forms of benzene-isoxazolidine rings are not planar, and there are notable changes in the way in which herringbone structure (Figure 5) are packed by F \cdots F contact. This means that the perfluorinated alkyl group controls important interaction as an F \cdots F contact for 3D crystal structure.

Conclusions

In conclusion, the observations described and discussed above demonstrate that our studies between NH-nitrone dipole and perfluorinated olefin have uncovered new and synthetically useful chemistry in mild reaction condition. In the reaction, electron rich oxime as an anisaloxime was preferable to the expecting NH-nitrone. The regioselectivity and self assembly structure observed in our study reflect the scope and limitation inherent in these important cycloadditions.

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