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Assessment of the intramolecular C—H···X (X=F, Cl, Br) hydrogen bonding of 1,4-diphenyl-1,2,3-triazoles

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ABSTRACT

The intramolecular six-membered C—H···X (X=F, Cl, Br) hydrogen bonding motif of halogen-substituted 1,4-diphenyl-1,2,3-triazole compounds has been assessed. Twelve triazole derivatives have been designed and prepared, which bear fluorine, chlorine or bromine atoms on the *ortho*- and/or *para*-positions of the benzene rings. ^{1}H NMR, X-ray crystallography, and DFT calculation investigations revealed that the *ortho*-fluorine, chlorine, and bromine atoms of the benzene ring on the C-4 of the triazole unit all can form six-membered C—H···X hydrogen bonding. In contrast, only fluorine forms similar, relatively stable intramolecular hydrogen bonding on the N-1 side of the triazole unit.

1. Introduction

Hydrogen bonding is one of the most important noncovalent forces that plays a pivotal role in the study of the conformational and binding properties of organic and biological molecules.[1–5] Strong hydrogen bonds, such as the N—H···O and N—H···N motifs, have been well-established in as early as 1940s.[6,7] In the past decades, the assessment of relatively weak hydrogen bonding motifs has attracted considerable attention because of their increasing importance in crystal engineering, supramolecular chemistry, and life science.[8,9] In this context, the survey of the Cambridge Structural Database by Taylor et al. on the crystallographic evidence has stimulated increasing interest in the evaluation of the CH groups as proton donors of hydrogen bonding.[10] Currently, the C—H···O, C—H···N, and C—H···π hydrogen bonding patterns have been well established and widely utilized in crystal engineering.[9,11–13]

We have a longstanding interest in the construction of foldamers,[14] that is, the linear molecules that are driven by intramolecular non-covalent forces to adopt compact conformations.[3–5,15] Although it was previously proposed that organic halogen atoms are very weak acceptors to hardly form hydrogen bonds,[16] we and other groups demonstrated that intramolecular N—H···F hydrogen bonding is quite stable and able to induce arylamide oligomers to form folded conformations.[17–20] We further established that, if strong intermolecular N—H···O=C hydrogen bonding is inhibited, even weaker intramolecular N—H···X (X=Cl, Br, I) hydrogen bonding may also form.[21] This N—H···Cl hydrogen bonding motif has been successfully utilized by Jiang et al. to assemble double helices from quinoline-based oligoamides.[22] Recently, we and Hecht et al. found that 1,4-diaryl-1,2,3-triazole compounds can also form intramolecular C^5—H···O and C^5—H···N hydrogen bonding,[23–25] which has been utilized to induce linear backbones to generate folded conformations.[26] In this paper, we report a systematic assessment of the intramolecular six-membered C^5—H···X (X=F, Cl, Br) hydrogen bonding motifs in 1,4-diaryl-1,2,3-triazoles by using ^{1}H NMR, X-ray crystallography, and DFT calculations.

2. Results and discussion

Compounds **1a**–**4a**, **1b**–**4b**, and **1c**–**4c** were designed and synthesized from Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions of the corresponding phenylacetylene and phenyl azide precursors.[27] All these compounds are soluble in chloroform.

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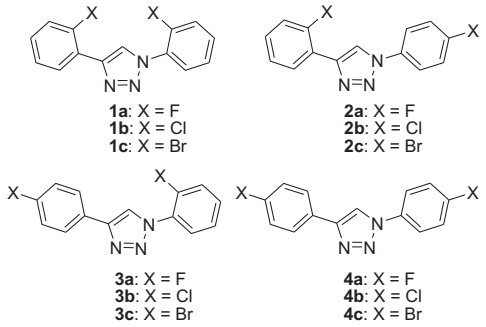


Hecht and co-workers performed DFT calculation for compound **1a**, which indicated that both of its two fluorine atoms could form intramolecular six-membered C–H···F hydrogen bonding with the C^5–H proton of the triazole unit.[24] However, no experimental evidences have been reported for this compound, although ^1H and ^{19}F NMR experiments supported the formation of the C–H···F hydrogen bonding in simple 1-(2-fluorophenyl)-1,2,3-triazoles.[24] For all other eleven 2-substituted compounds, neither theoretical nor experimental investigations have been reported concerning the possibility of forming the corresponding intra- or intermolecular C–H···X hydrogen bonding.[28]

The ^1H NMR spectra of compounds **1a**–**4a**, **1b**–**4b**, and **1c**–**4c** of identical concentrations were first recorded in chloroform-*d*. The C^5–H signal of **1a**, **2a**, and **3a** was split due to the coupling between the C^5–H and neighboring fluorine atoms. Comparing with that of the related control compounds (**4a**, **4b**, and **4c**), the triazole C^5–*H* signal of compounds **1a**, **1b**, and **1c** all shifted downfield remarkably (Fig. 1, Table 1), which provided the first evidence for the formation of the intramolecular C^5–H···X (X=F, Cl, Br) hydrogen bonding. Compared with that of the controls, the C^5–H signals of compounds **2a**, **2b**, **2c**, and **3a** also appeared in the downfield area, while the signals of compounds **3b** and **3c** just exhibited a very slight downfield shifting ($\Delta\delta \leq 0.04$ ppm). These observations suggested that the *ortho*-halogen atoms on the benzene ring on C-4 of the triazole unit and the *ortho*-F on the benzene ring on N-1 of the

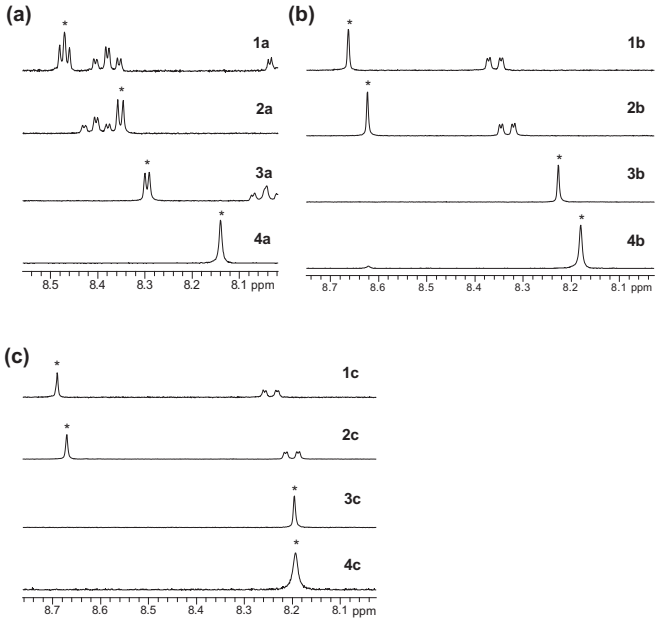


Fig. 1. Partial ^1H NMR spectra (300 MHz) of (a) **1a**–**4a**, (b) **1b**–**4b**, and (c) **1c**–**4c** in $CDCl_3$ at 25 °C (5.0 mM). The C^5–H signal of the triazole unit is highlighted with a star.

Table 1
Chemical shifting of the C^5–H signal of the triazole unit of compounds **1a**–**4a**, **1b**–**4b**, and **1c**–**4c** in the ^1H NMR spectrum in chloroform-*d* at 5 mM[a]

1a 8.47 (0.33)	**1b** 8.65 (0.48)	**1c** 8.68 (0.50)
2a 8.35 (0.21)	**2b** 8.61 (0.44)	**2c** 8.65 (0.47)
3a 8.29 (0.15)	**3b** 8.21 (0.04)	**3c** 8.19 (0.01)
4a 8.14	**4b** 8.17	**4c** 8.18

[a] The values in parentheses represent the changes related to that of the corresponding control compounds (**4a**–**c**).

triazole unit could all form relatively stable intramolecular six-membered C^5–H···X (X=F, Cl, Br) hydrogen bonding, whereas the *ortho*-Cl and Br atoms on the N-1 side could only form, if any, very weak hydrogen bonding with the C^5–H hydrogen in chloroform, which itself is also a weak hydrogen bonding acceptor and donor.

The intramolecular C^5–H···X hydrogen bonding of compounds **1a**, **2a**, and **3a** also caused their C^5–H signal to split, which coalesced into one singlet upon addition of polar DMSO-d_6.[17b] The coupling constant (J=3.5 Hz) of **2a** is notably larger than that (J=2.6 Hz) of **3a** and its signal shifted to the more downfield area, both implying that the intramolecular hydrogen bonding formed by **2a** was stronger than that of **3a**. This observation is in agreement with the above chemical shifting change. The formation of a relatively weak intramolecular hydrogen bonding on the N-1 side may be attributed to the higher electronegativity of nitrogen relative to carbon, which should reduce the capacity of the *ortho*-halogen atoms on the benzene rings in acting as hydrogen bonding donors.

Upon dilution from 10 mM to 1 mM, the C^5–H signal of all the twelve compounds in the ^1H NMR spectrum in chloroform-*d* displayed no significant shifting (<0.01 ppm), indicating that both the possible intermolecular bifurcated C^5–H···$N^{2/3}$ hydrogen bonding and the intermolecular aromatic stacking were weak in this solvent.[25b,29] This result further supported that the above difference of the chemical shifting of the C^5–H signal exhibited by the same series of compounds was mainly caused by the different strength of the discrete intramolecular C^5–H···X hydrogen bonding. Considering that chloroform is a weak hydrogen bonding donor and acceptor, however, this result does not exclude that this intermolecular hydrogen bonding may form in solvents of even lower polarity. Actually, it is observed in the crystal structure of compounds **4a**, **4b**, and **4c** (Fig. 5, vide infra).

The crystal structures of compounds **1a**–**4a**, **3b**, **4b**, and **4c** were obtained. The crystal structure of **1a** is shown in Fig. 2. Probably due to the structural symmetry, the molecules were arranged alternately in the crystal. As a result, the N-1 and C-4 atoms appeared at two identical positions with 50% probability.[30] Similar phenomenon was also observed in the crystals of compounds **4a**–**4c** (Fig. 5, vide infra). It can be found that both fluorine atoms of **1a** were

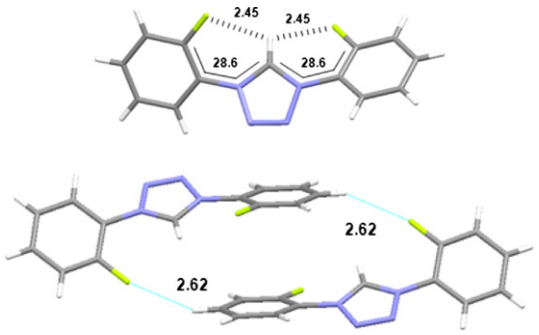


Fig. 2. The crystal structures of compound **1a**, highlighting the intramolecular six-membered C^5–H···F hydrogen bonding (upper) and intermolecular H···F hydrogen bonding (down).

engaged in the intramolecular six-membered C^5–H···F hydrogen bonding. The two hydrogen bonds had the identical H···F distance as a result of the special alternate arrangement of the molecules. The neighboring molecules also formed a dimeric structure, which was stabilized by two weak intermolecular C–H···F hydrogen bonds.

Crystal structures of compounds **2a** and **3a** are provided in Fig. 3. Both compounds also displayed the expected intramolecular six-membered C^5–H···F hydrogen bonding. However, the H···F distance of **2a** was pronouncedly shorter than that of **3a**, which is consistent with the fact that the benzene ring on the C-4 side had an obviously smaller torsion angle. These results are also in accordance with the above ^{1}H NMR observations, again indicating that the hydrogen bonding formed on the C-4 side is stronger than that formed on the N-1 side. The different torsions of the two benzene rings from the triazole unit also induced the two molecules to adopt two different space groups, that is, the triclinic P-1 and monoclinic P2(1)/*c* ones, respectively. For both compounds, the C^5–H proton was not engaged in any intermolecular contacts.

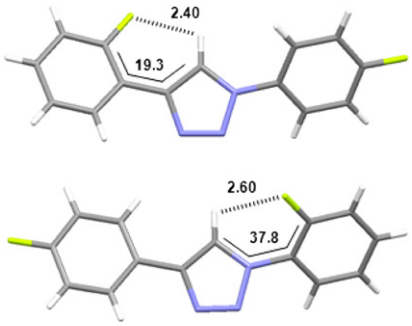


Fig. 3. The crystal structure of compounds **2a** (upper) and **3a** (down).

Compound **3b** formed a weak six-membered C^5–H···Cl hydrogen bond on the N-1 side in the crystal structure (Fig. 4). The benzene ring on this side was distorted remarkably from the triazole unit for the *ortho*-Cl to give rise to a weak intermolecular Cl···N halogen bond with the N-3 atom of the neighboring molecule in another stacking layer. Similar F···N contact was not exhibited in the crystal structure of compound **3a**, which may be rationalized by considering that the C–H···F hydrogen bonding is stronger than the C–H···Cl hydrogen bonding, while the F···N halogen bonding is weaker than the Cl···N halogen bonding.[31]

The crystal structures of compounds **4a**, **4b**, and **4c** are presented in Fig. 5. All the compounds adopted the monoclinic space

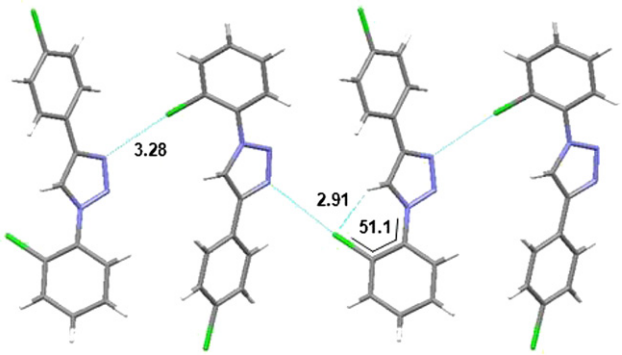


Fig. 4. Crystal structure and stacking pattern of compound **3b**, highlighting the weak intramolecular C^5–H···Cl hydrogen bonding and the intermolecular N···Cl halogen bonding.

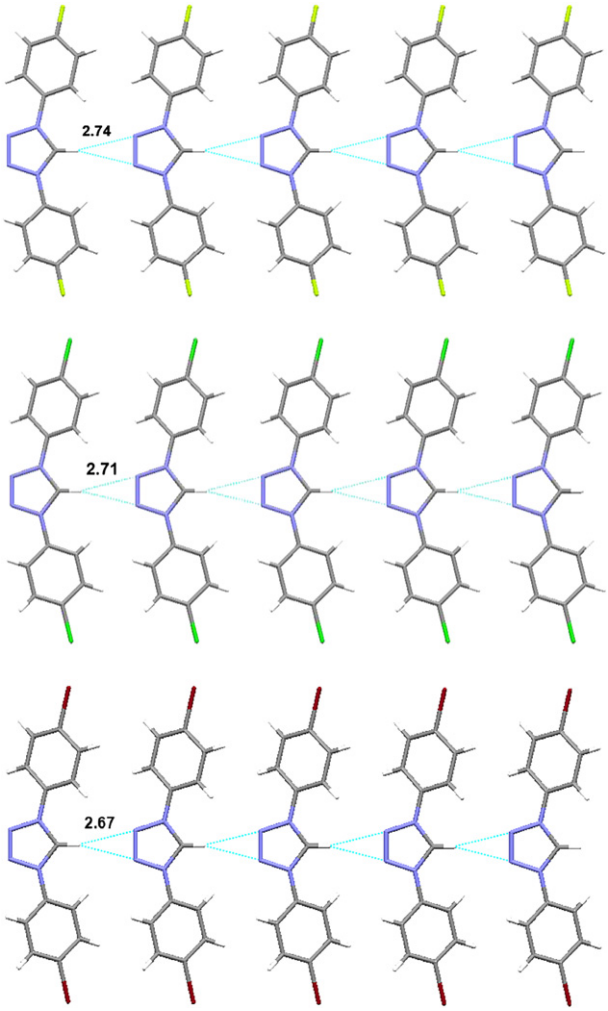


Fig. 5. The crystal structure and stacking pattern of compounds **4a** (upper), **4b** (middle), and **4c** (down).

group C2/*c* and the neighboring molecules all formed two intermolecular bifurcated C^5–H···N hydrogen bonds. The corresponding H···N distance decreases slightly from **4a** to **4b** and to **4c** due to the increased distortion of the two benzene rings from the central triazole unit. This distortion is expected to reduce possible spatial hindrance and thus favors the intermolecular hydrogen bonding. Probably also as a result of the high structural symmetry, for all the three compounds, opposite arrangement of the molecular framework was observed, which caused the N-1 and C-4 atoms of the central triazole to orientate alternately.[30] In consequence, the two intermolecular C^5–H···X (X=F, Cl, Br) hydrogen bonds have the identical H···X distance for all the three compounds. Similar intermolecular C^5–H···N hydrogen bonding was not observed in the crystal structures of **1a**–**3a** and **3b**, implying that their intramolecular C^5–H···F/Cl hydrogen bonding was stronger.

The highly symmetric conformation of compounds **1a** and **4a**–**4c** in crystals prompted us to investigate the conformation of compound **5**, the triazole, of which is attached with two pentafluorophenyl groups. The crystal structure of **5** is provided in Fig. 6. Different from that of compounds **4a**–**4c**, **5** formed a strong intramolecular C^5–H···F hydrogen bonding on the C-4 side, while another pentafluorophenyl unit was distorted remarkably from the triazole plane, excluding the possibility of forming similar intramolecular hydrogen bonding. Although intermolecular stacking might promote the coplanarity of the two pentafluorobenzene rings with the triazole unit, these results again supported that the

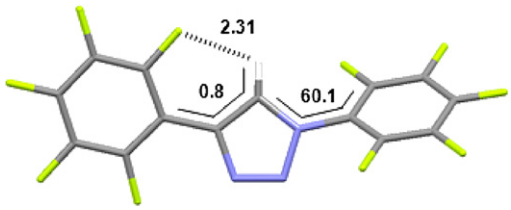


Fig. 6. The crystal structure of compound **5**, showing the formation of an intramolecular C^5—H···F hydrogen bonding on the C-4 side of the triazole unit.

ortho-halogen of the benzene ring on the C-4 side has a larger tendency of forming intramolecular hydrogen bonding.

DFT calculations were further performed for compounds **2a**–**c** and **3a**–**c**. The energy profiles for different torsions of their 2-substituted benzene ring from the triazole unit, with the 4-substituted benzene ring being constrained to be co-planar with the triazole unit, were obtained (Fig. 7). It can be found that the minimum-energy conformation of **2a**–**c** and **3a** is that with the 2-substituted benzene ring being co-planar with the triazole unit. These four compounds also gave rise to two high-energy conformations, the rotated benzene rings, of which had a torsion angle of about 90 or 180°. The minimum-energy conformation should be stabilized by the expected intramolecular six-membered C^5—H···X hydrogen bonding, while the two high-energy conformations can be rationalized by considering the complete breaking of the conjugativity between the benzene and triazole units and the electrostatic repulsion between the 2-halogen and the N-2 or N-3 atoms of the *syn* co-planar conformation. Compounds **3b** and **3c** also displayed the similar high-energy shoulder or peak. However,

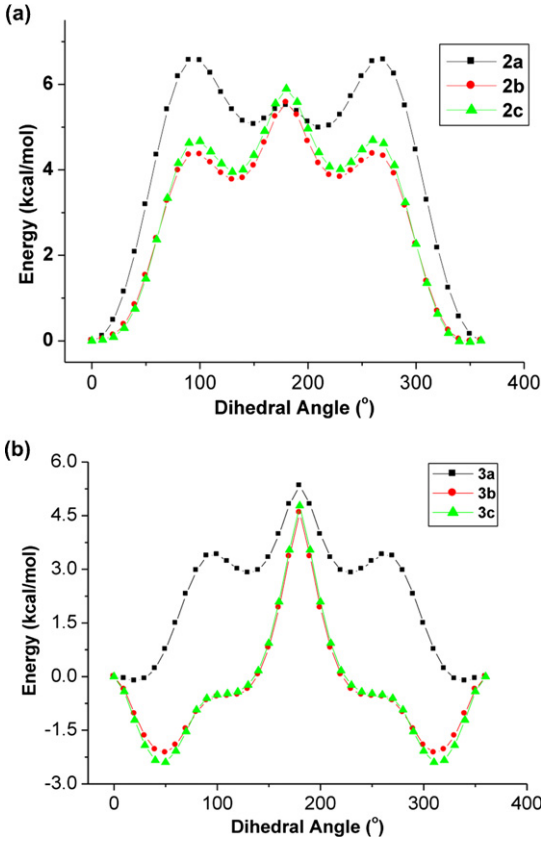


Fig. 7. The torsion energies of compounds (a) **2a**–**c** and (b) **3a**–**c** for turning the 2-substituted phenyl rings out of the plane of the triazole unit by incremental steps of 10°.

the minimum-energy conformation of these two compounds appeared at the torsion of about 45° for the benzene ring on N-1, again reflecting the weakness of the *ortho*-Cl and Br atoms on this benzene ring in forming the intramolecular six-membered hydrogen bonding. This result is well consistent with the above ^{1}H NMR and X-ray crystallographic observations. Similar low-energy deviation had been revealed from the DFT calculation for 1,4-bis(2-fluorophenyl)-1,2,3-triazole.[24] A potential explanation involved the formation of a stabilizing HOMO–LUMO interaction occurring in the twisted geometry.

3. Conclusions

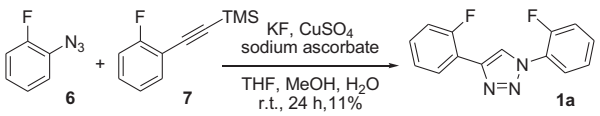
This work provides a systematic investigation on the stability of the intramolecular six-membered C^5—H···X (X=F, Cl, Br) hydrogen bonding formed by 1,4-diphenyl-1,2,3-triazole derivatives. We demonstrate that, for all the three halogen atoms, the hydrogen bonding on the C-4 side of the triazole unit is more stable and only fluorine forms relatively stable hydrogen bonding on the N-1 side of the triazole. We also reveal that, although weak in solution, in the absence of intramolecular hydrogen bonding, the intermolecular bifurcated C^5—H···$N^{2,3}$ (triazole) hydrogen bonding is the most important non-covalent force for this kind of triazole derivatives in the solid state. Although the results presented in this work are based on a limited data set and should be taken with caution, the two intramolecular C^5—H···F hydrogen bonds are quite strong to form a typical three-center hydrogen bonding pattern, which may find applications in the design of new triazole-based foldamers or other structures that require a control of the molecular conformation.

4. Experimental section

4.1. General methods

All reagents and chemicals were obtained from commercial sources and used without further purification. The solvents were purified by standard procedures before use. Silica gel (10–40 m) was used for all column chromatography. The NMR spectra were recorded on Bruker Avance 300 MHz spectrometer in the indicated solvent. Chemical shifts are expressed in parts per million using residual proton resonances of the deuterated solvents as the internal standards. All the precursors for the 1,3-dipolar cycloadditions were prepared according to the reported procedures. The crystals for X-ray analysis were grown from different solvents by slow evaporation of the solvent (**1a**: acetone/petroleum ether, **2a**, and **3a**: dichloromethane/*n*-pentane, **4a**: DMSO/ethyl acetate, **3b**: dichloromethane/petroleum ether/ethyl acetate, **4b**: dichloromethane/DMF, **4c**: dichloromethane/1,4-dioxane, and **5**: dichloromethane/methanol). The DFT (b31yp/6-31g(d,p)) calculations on the rotation barrier and relative stability of the *syn* and *anti* conformations of compounds **2a**–**c** and **3a**–**c** were performed in the gas phase. CCDC-882615–882622 (**1a**–**4a**, **3b**, **4b**, **4c**, and **5**) contain the supplementary crystallographic data for this paper, which can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.2. Preparation and characterizations



4.2.1. Compound ***1a***. A mixture of compounds **6** (0.15 g, 1.09 mmol), **7** (0.20 g, 1.04 mmol), potassium fluoride dihydrate (0.23 g, 3.94 mmol), copper sulfate pentahydrate (28 mg, 0.11 mmol), and sodium ascorbate (49 mg, 0.22 mmol) in THF (5 mL), methanol (5 mL), and water (2 mL) was stirred at room temperature for 24 h and then concentrated with a rotavapor. The resulting slurry was triturated with dichloromethane (10 mL). The organic phase was washed with water (5 mL×2) and brine (5 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the resulting residue was subject to column chromatography (petroleum ether/AcOEt 4:1) to give compound **1a** as a white solid (30 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (t, J_1=3.0 Hz, 1H), 8.37 (t, J_1=7.8 Hz, 1H), 8.00 (t, J_1=7.5 Hz, 1H), 7.46–7.43 (m, 1H), 7.38–7.34 (m, 4H), 7.18 (t, J_1=10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.63, 158.16, 154.81, 152.30, 141.70, 130.37, 130.29, 129.68, 129.60, 128.06, 128.02, 125.38, 125.30, 125.27, 125.06, 124.72, 124.68, 124.40, 123.94, 123.85, 123.81, 123.72, 118.31, 118.18, 117.23, 117.04, 115.91, 115.70. ^{19}F NMR (300 MHz, $CDCl_3$): δ −115.4 (s, 1 F), −124.3 (s, 1 F). MS (ESI): *m*/*z* 258.0 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}F_2N_3$ $[M+H]^+$: 258.0840. Found: 258.0837.

All other 1,4-diphenyltriazoles were prepared according to the procedures similar to that described for the preparation of compound **1a**.

4.2.2. Compound ***1b***. White solid in 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.35 (d,d, J_1=7.8 Hz, J_2=1.5 Hz, 1H), 7.70 (t, J_1=5.7 Hz, 1H), 7.62 (t, J_1=4.5 Hz, 1H), 7.51–7.40 (m, 4H), 7.34 (t,d, J_1=7.5 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.86, 134.93, 131.43, 130.88, 130.32, 130.03, 129.28, 128.93, 128.86, 127.98, 127.86, 127.27, 125.25. MS (ESI): *m*/*z* 290.0 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_3$ $[M]^+$: 290.0260. Found: 290.0246.

4.2.3. Compound ***1c***. White solid in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.22 (d, J_1=6.6 Hz, 1H), 7.80 (d, J_1=8.1 Hz, 1H), 7.67 (t, J_1=9.3 Hz, 2H), 7.55–7.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.03, 136.48, 133.98, 133.63, 131.22, 130.89, 130.72, 129.55, 128.54, 128.21, 127.77, 125.10, 121.33, 118.63. MS (ESI): *m*/*z* 379.9 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Br_2N_3$ $[M+H]^+$: 377.9248. Found: 377.9236.

4.2.4. Compound ***2a***. White solid in 14% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (t,d, J_1=7.5 Hz, J_2=2.1 Hz, 1H), 8.35 (d, J_1=3.3 Hz, 1H), 7.82–7.78 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.28 (m, 2H), 7.24–7.18 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.73, 161.24, 160.55, 158.08, 141.94, 133.27, 129.76, 129.67, 127.97, 127.93, 124.76, 124.72, 122.61, 122.53, 120.91, 120.78, 118.11, 117.98, 116.89, 116.66, 115.86, 115.65. ^{19}F NMR (300 MHz, $CDCl_3$): δ −112.1 (s, 1 F), −114.6 (s, 1 F). MS (ESI): *m*/*z* 258.2 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}F_2N_3$ $[M+H]^+$: 258.0843. Found: 258.0837.

4.2.5. Compound ***2b***. White solid in 35% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.32 (d,d, J_1=6.0 Hz, J_2=1.2 Hz, 1H), 7.78 (d,t, J_1=6.6 Hz, J_2=1.5 Hz, 2H), 7.55 (d,t, J_1=6.9 Hz, J_2=1.8 Hz, 2H), 7.49 (d,d, J_1=6.30 Hz, J_2=1.2 Hz, 1H), 7.42 (t,d, J_1=5.7 Hz, J_2=1.2 Hz, 1H). 7.32 (t,d, J_1=6.0 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.17, 144.81, 135.45, 134.65, 131.29, 130.31, 129.98, 129.95, 129.44, 128.61, 127.31, 121.80, 121.05, 98.73. MS (ESI): *m*/*z* 290.1 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_3$ $[M+H]^+$: 290.0254. Found: 290.0246.

4.2.6. Compound ***2c***. Pale yellow solid in 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.18 (d, J_1=5.7 Hz, 1H), 7.70 (t, J_1=7.8 Hz, 5H), 7.45 (t, J_1=5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.19, 135.95, 133.64, 132.94, 130.70, 129.70, 127.81, 122.50, 122.02, 121.22, 120.78. MS (ESI): *m*/*z* 379.9 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Br_2N_3$ $[M+H]^+$: 377.9245. Found: 377.9236.

4.2.7. Compound ***3a***. White solid in 17% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J_1=2.7 Hz, 1H), 8.03 (t,d, J_1=8.1 Hz, J_2=1.5 Hz, 1H), 7.90 (t,d, J_1=5.7 Hz, J_2=3.3 Hz, 2H), 7.51–7.44 (m, 1H), 7.39–7.31 (m, 2H), 7.17 (t, J_1=8.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.10, 161.64, 154.51, 152.01, 147.28, 130.32, 130.25, 127.74, 127.66, 126.26, 125.38, 125.34, 124.82, 120.54, 120.45, 117.18, 116.98, 116.08, 115.86. ^{19}F NMR (300 MHz, $CDCl_3$): δ −112.1 (s, 1 F), −114.6 (s, 1 F). MS (ESI): *m*/*z* 258.2 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}F_2N_3$ $[M+H]^+$: 258.0843. Found: 258.0837.

4.2.8. Compound ***3b***. White solid in 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.87 (d,t, J_1=6.3 Hz, J_2=1.5 Hz, 2H), 7.69–7.67 (m, 1H), 7.63–7.60 (m, 1H), 7.51–7.48 (m, 2H), 7.45 (d,t, J_1=6.3 Hz, J_2=1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.25, 130.89, 130.86, 129.17, 128.68, 128.56, 128.03, 127.76, 127.16, 121.64. MS (ESI): *m*/*z* 290.1 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_3$ $[M+H]^+$: 290.0254. Found: 290.0246.

4.2.9. Compound ***3c***. Yellow solid in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.82–7.78 (m, 3H), 7.61–7.58 (m, 3H), 7.52 (t, J_1=7.5 Hz, 1H), 7.43 (t, J_1=7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.51, 136.41, 133.97, 132.07, 131.31, 129.15, 128.57, 128.16, 127.40, 122.33, 121.75, 118.52. MS (ESI): *m*/*z* 380.0 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Br_2N_3$ $[M+H]^+$: 377.9244. Found: 377.9236.

4.2.10. Compound ***4a***. White solid in 26% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.88 (t,d, J_1=5.1 Hz, J_2=3.9 Hz, 2H), 7.79–7.75 (m, 2H), 7.27 (t, J_1=9.6 Hz, 2H), 7.16 (t, J_1=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.21, 163.83, 161.74, 161.34, 147.71, 133.32, 127.80, 127.72, 126.28, 126.25, 122.70, 122.62, 117.79, 116.99, 116.76, 116.18, 115.96, 96.15. ^{19}F NMR (300 MHz, $CDCl_3$): δ −112.0 (s, 1 F), −114.0 (s, 1 F). MS (ESI): *m*/*z* 258.1 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}F_2N_3$ $[M+H]^+$: 258.0842. Found: 258.0837.

4.2.11. Compound ***4b***. White solid in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.84 (d, J_1=8.4 Hz, 2H), 7.74 (d, J_1=8.7 Hz, 2H), 7.53 (d, J_1=8.7 Hz, 2H), 7.44 (d, J_1=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.63, 135.44, 134.77, 134.44, 130.06, 129.24, 128.51, 127.14, 121.71, 117.53. MS (ESI): *m*/*z* 290.0 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_{10}Cl_2N_3$ $[M+H]^+$: 290.0256. Found: 290.0246.

4.2.12. Compound ***4c***. Yellow solid in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.78 (d, J_1=8.4 Hz, 2H), 7.69 (s, 4H), 7.60 (d, J_1=8.7 Hz, 2H). MS (ESI): *m*/*z* 380.0 $[M+H]^+$. HRMS (MALDI): calcd for $C_{14}H_{10}Br_2N_3$ $[M+H]^+$: 377.9230. Found: 377.9236.

4.2.13. Compound ***5***. White solid in 36% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 144.0, 143.1, 142.0, 141.2, 140.0, 139.6, 137.0, 135.5, 125.2, 112.4, 105.3. ^{19}F NMR (300 MHz, $CDCl_3$): δ −139.1, −145.2, −148.8, −152.7, −158.8, −161.1. MS (ESI): *m*/*z* 402.1 $[M+H]^+$. HRMS (ESI): calcd for $C_{14}H_2F_{10}N_3$ $[M+H]^+$: 402.01010. Found: 402.00836.

4.3. Crystal data

4.3.1. Compound ***1a***. $C_{14}H_9F_2N_3$, *M*=257.24, Monoclinic, Space group C2/*c*, *a*=14.0890(15), *b*=12.1866(13), *c*=7.2514(8) Å, β=112.174(2), *V*=1153.0(2) Å^3, *T*=293 K, *Z*=4, D_c=1.482 g cm^{-3}, μ=0.114 mm^{-1}, *F*(000), 528, R_1=0.0482, wR_2=0.1198 ($I>2\sigma$ (I)),

R_1=0.0511, wR_2=0.1166 (all data). Reflections collected/unique: 3087/1130 (R_{int}=0.0934), GOF=1.094.

4.3.2. Compound ***2a***. $C_{14}H_9F_2N_3$, M=257.24, Triclinic, Space group P-1, a=5.8208(10), b=7.3728(12), c=13.821(2) Å, β=96.202(3), V=569.78(16) Å^3, T=293 K, Z=2, D_c=1.499 g cm^{-3}, μ=0.115 mm^{-1}, F(000), 264, R_1=0.0553, wR_2=0.1638 ($I>2\sigma$ (I)), R_1=0.0590, wR_2=0.1573 (all data). Reflections collected/unique: 3109/2187 (R_{int}=0.0257), GOF=1.048.

4.3.3. Compound ***3a***. $C_{14}H_9F_2N_3$, M=257.24, Monoclinic, Space group P2(1)/c, a=13.417(2), b=11.5535(19), c=7.5275(12) Å, β=90.189(3), V=1166.8(3) Å^3, T=293 K, Z=4, D_c=1.464 g cm^{-3}, μ=0.113 mm^{-1}, F(000), 528, R_1=0.0635, wR_2=0.1723 ($I>2\sigma$ (I)), R_1=0.0770, wR_2=0.1619 (all data). Reflections collected/unique: 5949/2167 (R_{int}=0.1534), GOF=0.993.

4.3.4. Compound ***4a***. $C_{14}H_9F_2N_3$, M=257.24, Monoclinic, Space group C2/c, a=27.993(4), b=5.6987(8), c=7.3154(10) Å, β=103.827(2), V=1133.2(3) Å^3, T=293 K, Z=4, D_c=1.508 g cm^{-3}, μ=0.116 mm^{-1}, F(000), 528, R_1=0.0498, wR_2=0.1690 ($I>2\sigma$ (I)), R_1=0.0533, wR_2=0.1647 (all data). Reflections collected/unique: 3041/1169 (R_{int}=0.0220), GOF=1.130. Disorders at N-1 and C-4 were found.

4.3.5. Compound ***3b***. $C_{14}H_9Cl_2N_3$, M=290.14, Monoclinic, Space group P2(1)/n, a=4.0145(18), b=27.862(12), c=11.598(5) Å, β=92.220(6), V=1296.3(10) Å^3, T=293 K, Z=4, D_c=1.487 g cm^{-3}, μ=0.488 mm^{-1}, F(000), 592, R_1=0.0749, wR_2=0.1898 ($I>2\sigma$ (I)), R_1=0.1032, wR_2=0.1736 (all data). Reflections collected/unique: 5524/2479 (R_{int}=0.0364), GOF=0.992.

4.3.6. Compound ***4b***. $C_{14}H_9Cl_2N_3$, M=290.54, Monoclinic, Space group C2/c, a=30.701(5), b=5.6709(9), c=7.3915(12) Å, β=98.819(5), V=1271.7(4) Å^3, T=293 K, Z=4, D_c=1.518 g cm^{-3}, μ=0.498 mm^{-1}, F(000), 592, R_1=0.0486, wR_2=0.1538 ($I>2\sigma$ (I)), R_1=0.0549, wR_2=0.1383 (all data). Reflections collected/unique: 3428/1374 (R_{int}=0.0597), GOF=1.085. Disorders at N-1 and C-4 were found.

4.3.7. Compound ***4c***. $C_{14}H_9Br_2N_3$, M=379.06, Monoclinic, Space group C2/c, a=32.028(6), b=5.6282(10), c=7.4518(13) Å, β=98.685(3), V=1327.8(4) Å^3, T=293 K, Z=4, D_c=1.896 g cm^{-3}, μ=6.093 mm^{-1}, F(000), 740, R_1=0.0704, wR_2=0.1885 ($I>2\sigma$ (I)), R_1=0.0784, wR_2=0.1829 (all data). Reflections collected/unique: 3440/1303 (R_{int}=0.1054), GOF=1.011. Disorders at N-1 and C-4 were found.

4.3.8. Compound ***5***. $C_{14}HF_{10}N_3$, M=401.18, Monoclinic, Space group P2(1)/c, a=14.2193(12), b=10.5291(9), c=9.0845(8) Å, β=91.433(2), V=1359.7(2) Å^3, T=293 K, Z=4, D_c=1.960 g cm^{-3}, μ=0.216 mm^{-1}, F(000), 784, R_1=0.0436, wR_2=0.1167 ($I>2\sigma$ (I)), R_1=0.0504, wR_2=0.1117 (all data). Reflections collected/unique: 6928/2526 (R_{int}=0.0925), GOF=1.038.

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