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Solvent controlled regioselective reaction of 1,2,3-benzotriazole (BtH) with pentafluorobenzene derivatives

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ABSTRACT

Regioselective reaction of 1,2,3-benzotriazole (BtH) with pentafluorobenzene derivatives under base conditions was investigated and its regioselectivity strongly depends on solvent, base, and electron-withdrawing group at 4-position on the perfluorophenyl ring. Several Bt(N1)-substituted perfluorobenzenes were prepared by using this method.

1. Introduction

Compounds with 1,2,3-benzotriazole (BtH) moiety are of great importance with regards to pharmaceuticals, agricultural pesticides, dyestuffs, photostabilizers, and dynamites.[1–8] Bt-containing compounds demonstrate excellent biological activities, such as antiviral, antibacterial, and plant growth regulation properties. For example, alizaprid is an antiemetic drug[9] and Tinuvin P is an efficient UV absorber.[10] Thus, new synthetic methods for preparation of Bt-substituted compounds are still desirable.

Fluorinated benzene derivatives have attracted considerable interests with respect to multi facetted chemical and NMR spectroscopic properties and potential applications in medicinal and material area.[11,12] Particularly, introduction of fluorine atom or fluorinated group (e.g., perfluorobenzene group) into organic compounds usually lead to the change of the biologic and physical properties.[13] However, scientists pay less attention on investigation of the reaction of BtH with pentafluorobenzene (PFB) halides since 1999.[14] In the connection with our study on fluorinated heterocyclic compounds, we envisioned that BtH may stereoselectively react with electron-withdrawing group substituted pentafluorobenzene to form a series of Bt(N1)-containing perfluorobenzenes. Herein, we report our preliminarily results.

2. Results and discussion

We began our investigation with a reaction of BtH with pentafluorobenzonitrile in the presence of triethylamine (Et_3N) in THF at refluxing. In general, using BtH as a prenucleophile, the nitrogen substitutions of BtH form a mixture of Bt (N1)-substituted product **3** and Bt(N2)-substituted product **4**.[2] After completion of the reaction, as expected, a mixture of **3**/**4** in 46% yield with a ratio of **3**/**4** in 3/1 was obtained (entries 1, Table 1). Using toluene gave the similar results (entry 2). Interestingly, the employment of MeCN instead of THF, 40% yields of **3** were obtained but trace amount of **4** were observed (entry 3). Unexpectedly, when ethyl alcohol was employed as solvent under the similar reaction conditions, opposing results were achieved (entry 4). These results strongly suggest that the regioselectivity of above reaction is solvent-controlled. Moreover, when K_2CO_3 was used as base other than Et_3N, **3** was obtained in 65% yield and along with trace amount of **4** was observed (entry 5). Consequently, a series of bases, such as pyridine(abbreviated to Py, following is the same), KF, and NaOAc were further examined under the similar conditions (entries 6–8, Table 1). KF and NaOAc gave **3** as the major product in 32% and 40% yield, respectively (entries 6 and 7). Py led to extremely poor results (entry 8). These results reveal that base also plays an important role for this regioselective reaction. It is worthy to note that considerable amount of the complex byproducts were observed in the course of the above-motioned reactions because pentafluorobenzonitrile are more active under the basic conditions at high temperature.[2]

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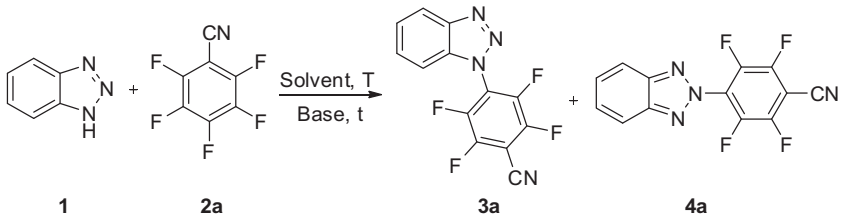
Table 1
Optimizing reaction condition for the reaction of BtH with PFB derivatives



1 **2a** **3a** **4a**

Entry	Base	Solvent	1/2	T,°C	*t* (h)	Yield of **3**, %[a]	Yield of **4**, %[a]
1	Et_3N	THF	1/1.2	Reflux	12	36	12
2	Et_3N	Toluene	1/1.2	80	12	37	9
3	Et_3N	$ClCH_2CH_2Cl$	1/1.2	80	12	50	10
4	Et_3N	MeCN	1/1.2	80	12	40	Trace
5	Et_3N	EtOH	1/1.2	80	4	Trace	70
6	K_2CO_3	MeCN	1/1.2	Reflux	12	41	10
7	KOH	MeCN	1/1.2	Reflux	12	33	8
8	K_2CO_3	EtOH	1/1.2	Reflux	4	65	Trace
9	KF	EtOH	1/1.2	Reflux	12	32	8
10	NaOAc	EtOH	1/1.2	Reflux	12	40	10
11	Py	EtOH	1/1.2	Reflux	12	4	2
12	Et_3N	MeCN	1/1.2	50	12	17	Trace
13	Et_3N	MeCN	1/1.2	rt	12	35	10
14	Et_3N	MeCN	1/2	rt	12	45	11
15	Et_3N	MeCN	1/3	rt	12	49	12
16	Et_3N	MeCN	2/1	rt	12	35	9

[a] Isolated yield.

With the optimal reaction conditions listed in entry 4 of Table 1, the scope of the reaction was then probed (Table 2). After completion of the reaction (12 h), **3a** was obtained in 40% yield from 2,3,4,5,6-pentafluorobenzonitrile and only trace amount of **4a** were observed (entry 1). 1,2,3,4,5-Pertafluoro-6-nitrobenze, containing a strong electron-withdrawing group NO_2 on the phenyl ring, was utilized as a substrate and it gave **3b** as major product in 24% yield along with 8% yield of **4b** (entry 2). 2,3,4,5,6-Pentafluorobenzaldehyde resulted in 32% yield of **3c** together with 13% yield of **4c** (entry 3). Notably, perfluorobenzene was employed as a substrate in above reaction and no desired product was observed by ^{19}F NMR (entry 4). 1-Chloro-2,3,4,5,6-pentafluorobenzene led to 60% yield of **3e** using K_2CO_3 instead of Et_3N in the absence of solvent (entry 5). 1-Bromo-2,3,4,5,6-pentafluorobenzene gave rise to **3f** in 40% yield using toluene as solvent (entry 6). 1,2,3,4,5-Pentafluoro-6-iodobenzene was used as substrate leading to **3g** in 35% yield and **4g** in 5% yield, respectively (entry 7).

To determine the molecular structures of **3** and **4**, two representative compounds **4a** and **3e** were crystallized from dichloromethane and *n*-hexane, and their X-ray diffraction analyses were performed. Their molecular structures were shown in Fig. 1 and Fig. 2, respectively.

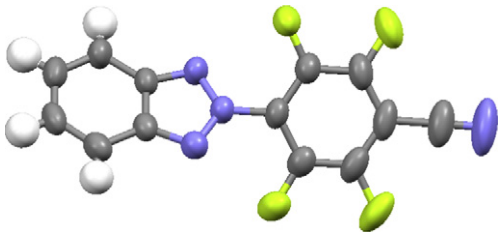
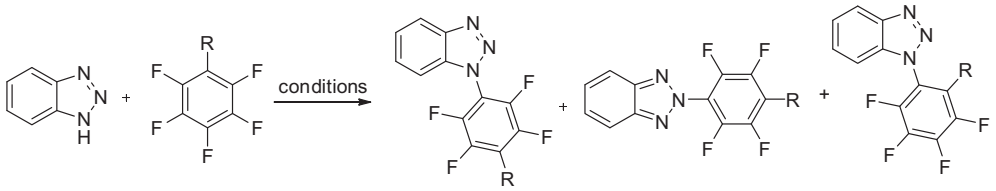


Fig. 1. Molecular structure of **4a**.

Table 2
Regio selective reaction of BtH with pentafluorobenzene derivatives



1 **2a-g** **3a-c, 3e-3g** **4a-c, 4g** **5b**

Entry	R	Base	Solvent	T,°C	*t*, h	**3**,%[c]	**4**, %[c]	**5**,%[c]
1	CN(**2a**)	Et_3N	CH_3CN	Reflux	12	40	Trace	—
2	NO_2(**2b**)	Et_3N	CH_3CN	80	0.5	24	8	10
3	CHO(**2c**)	Et_3N	CH_3CN	Reflux	24	32	13	—
4	F (**2d**)	K_2CO_3	—[b]	Reflux	24	NR	NR	—
5	Cl(**2e**)	K_2CO_3	—[b]	Reflux	10	60	—	—
6	Br(**2f**)	Et_3N	Toluene	Reflux	15	40	trace[a]	—
7	I(**2g**)	Et_3N	Toluene	Reflux	12	35	5	—

[a] Detected by ^{19}F NMR.
[b] Neat.
[c] Isolated yield.

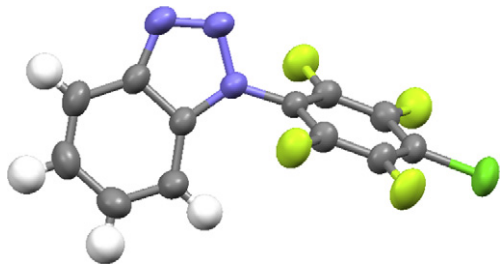


Fig. 2. Molecular structure of **3e**.

The UV analyses of **3a** and **4a** indicated that λ_{max} of Bt(N2)- and Bt(N1)-substituted perfluorobenzonitrile occurred at 297 nm. Comparing with λ_{max} of BtH, both **3a** and **4a** led to the red shift due to the introduction of perfluorobenzonitrile. Additionally, the absorption of **3a** is much stronger than that of **4a** (Fig. 3).

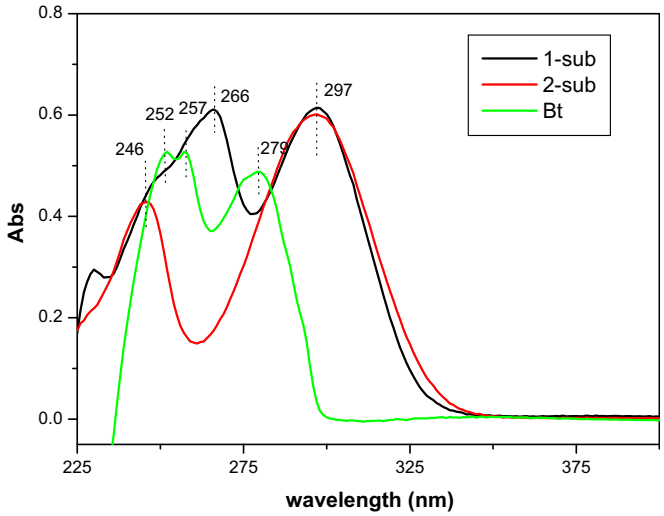


Fig. 3. UV–vis absorption curve of BtH, **3a** and **4a** in THF.

On the basis of the results achieved, a possible mechanism is proposed as illustrated in Scheme 1. The treatment of BtH (**1**) with base readily yields the resonance hybrids including two contributing structures (**I**) (more stable) and (**II**). Consequently, **I** undertakes the following nucleophilic substitution to produce **3**. The nucleophilic attack of **II** to pentafluorobenzene forms the corresponding **4**. When PFB halides react with BtH, the low reactivity only leads to the formation of **3**. Due to $p-\pi$ hyperconjugation,[15,16] **3** could transform to **V** under heat through a concerted process, which then could afford the product **4**. So the ratio of **3**:**4** increases along with the decrease of hyperconjugation effect in the order of iodine, bromine, and chlorine. **3b** and **5b** have almost no difference in polarity. We tried to separate them by column chromatography and recrystallization, however, both of these two common purification methods did not provide pure **3b** or **5b**.

3. Conclusion

We have developed a convenient method for synthesis of Bt (N1)-substituted perfluorobenzene derivatives and found that solvent and base have strong effect on the formation of Bt(N1)-substituted product. A possible reaction mechanism was explored as well. The further applications of Bt-containing fluorinated benzene derivatives are currently under way in our group.

4. Experimental

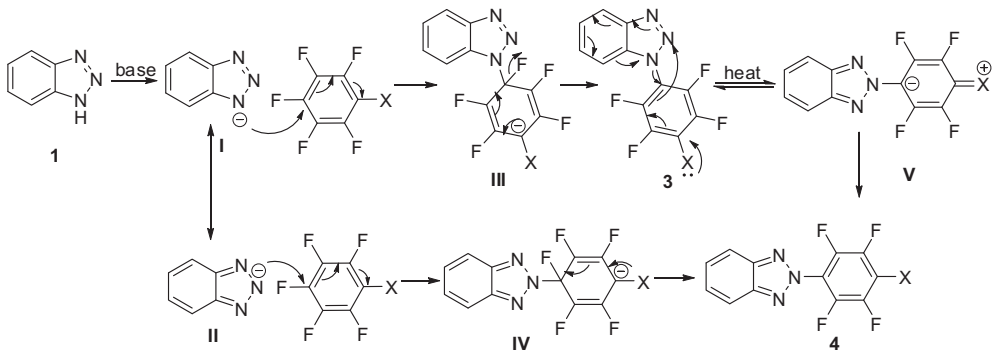
4.1. General

Melting points are measured on a Temp-Melt. Apparatus are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AM-300 instruments with Me_4Si and $CFCl_3$ as the internal and external standards, respectively. FT-IR spectra were obtained with a Nicolet AV-360 spectrometer. Low resolution mass spectra (LRMS) or high resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV), respectively. Elemental analyses were performed on a VARIO EL III elemental analyzer in the Analysis Department of this Institute. Single crystal X-ray structure analysis was performed on a Bruker P4 instrument.

4.2. General procedure of the reaction of 1,2,3-benzotriazole (BtH) and pentafluorobenzene derivatives

BtH 0.595 g (5 mmol) was dissolved in solvent 15 mL, and then the corresponding pentafluorobenzene derivative (6 mmol) and base (5 mmol) were added. The mixture was heated to reflux. According to TLC analysis, when the reaction completed, the solid was removed by filtration. Then the solvent was removed by a rotary evaporator under vacuum. The mixture was isolated on silica gel (petroleum/ethyl acetate=10/1) to afford products **3** and **4**.

4.2.1. 4-(1H-benzo[d][1,2,3]triazol-1-yl)-2,3,5,6-tetrafluorobenzonitrile ***3a***. White solid, mp: 128–130 °C. FT-IR (KBr) cm^{-1}: 2243, 1652, 1609, 1500, 1209, 993, 887, 812, 770, 757, 661. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (d, 1H, J=7.8 Hz), 7.65–7.24 (m, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ 129.1 (q, 2F, J=8.1 Hz), −140.0 (q, 2F, J=8.1 Hz). LR-EI-MS m/z (%): 292(M^+, 21), 264(79), 154(100), 124



Scheme 1. Possible mechanism.

(45). Anal. Calcd for $C_{13}H_4F_4N_4$ (%): C, 53.44; H, 1.38; N, 19.17. Found: C, 53.38; H, 1.66; N, 18.79.

4.2.2. 4-(2H-benzo[d][1,2,3]triazol-2-yl)-2,3,5,6-tetrafluorobenzonitrile ***4a***. White solid, mp: 137–140 °C. FT-IR (KBr) cm^{-1}: 2246, 1647, 1545, 1500, 1435, 1349, 1248, 1002, 865, 760. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.91 (dd, 2H, J=3.3, 6.9 Hz), 8.46 (dd, 2H, J=3.3, 6.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −129.5 (q, 2F, J=13.2 Hz), −141.3 (q, 2F, J=13.2 Hz). LR-EI-MS m/z (%): 292(100), 188(41), 90(28). Anal. Calcd for $C_{13}H_4F_4N_4$ (%): C, 53.44; H, 1.38; N, 19.17. Found: C, 53.66; H, 1.28; N, 19.30.

4.2.2.1. X-ray data of compound ***4a***. Empirical formula $C_{13}H_4F_4N_4$:FW=292.20; temperature 293 (K); monoclinic $P2(1)/c$; wavelength 0.71 Å; a=7.9074(8) Å, b=11.7360(12) Å, c=12.9927 (13) Å, α=90°, β=96.154(2)°, γ=90°. V=1198.8(2) $Å^3$; Z=4, Dc=1.619 mg/m^3; absorption coefficient 0.146 mm^{-1}; $F(000)$=584; size 0.480×0.423×0.396 mm; 2.34<θ<27.00; reflections collected 6932; Absorption correction Empirical; transmission 1.00max-0.763min; goodness of fit on F^2 0.966; final R indices $R1$=0.0436, $wR2$=0.1110. CCDC number is 705402.

4.2.3. Mixture of 1-(2,3,5,6-tetrafluoro-4-nitrophenyl)-1H-benzo[d][1,2,3]triazole ***3b*** *and 1-(2,3,4,5-tetrafluoro-6-nitrophenyl)-1H-benzo[d][1,2,3]triazole* ***5b***. White solid. FT-IR (KBr) cm^{-1}: 1645, 1561, 1501, 1350, 1163, 1051, 992, 779, 749. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.23(m, 1H), δ 7.73–7.45(m, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −139.4(m, 0.36F), −140.1(m, 2F), −142.8(m, 0.36F), −143.8(m, 2F), −145.6(m, 0.36F), −146.9(m, 0.36F). LR-EI-MS m/z (%): 312(M^+, 43), 238(100), 218(19), 188(12), 148(21). Anal. Calcd for $C_{12}H_4F_4N_4O_2$ (%): C, 46.17; H, 1.29; N, 17.95. Found: C, 46.23; H, 1.13; N, 17.79.

4.2.4. 2-(2,3,5,6-Tetrafluoro-4-nitrophenyl)-2H-benzo[d][1,2,3]triazole ***4b***. White solid, mp: 100–103 °C. FT-IR (KBr) cm^{-1}: 1632, 1554, 1493, 1345, 1232, 1014, 950, 876, 781, 754. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99(d, 1H, J=3.0 Hz), δ 7.96(d, 1H, J=3.0 Hz),δ 7.54(d, 1H, J=2.7 Hz),δ 7.52(d, 1H, J=3.0 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −141.5(m, 2F), δ −144.2(m.2F). LR-EI-MS m/z (%): 312(M^+, 100), 266(22), 162(23), 117(7.26). Anal. Calcd for $C_{12}H_4F_4N_4O_2$ (%): C, 46.17; H, 1.29; N, 17.95. Found: C, 45.95; H, 1.09; N, 17.77.

4.2.5. 4-(1H-benzo[d][1,2,3]triazol-1-yl)-2,3,5,6-tetrafluorobenzaldehyde ***3c***. White solid, mp: 107–109 °C. FT-IR (KBr) cm^{-1}:1710, 1648, 1521, 1497, 1370, 1274, 1052, 977, 961, 753, 622. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.43(s, 1H), δ 8.24–8.21(m, 1H), δ 7.69–7.44(m, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −142.72 to −172.86(m, 2F), δ −142.98 to −143.13(m. 2F). LR-EI-MS m/z (%): 295 (M^+, 37), 267(32), 238(100), 220(46), 189(21). Anal. Calcd for $C_{13}H_5F_4N_3O$ (%): C, 52.89; H, 1.71; N, 14.23. Found: C, 52.89; H, 1.43; N, 14.18.

4.2.6. 4-(2H-benzo[d][1,2,3]triazol-2-yl)-2,3,5,6-tetrafluorobenzaldehyde ***4d***. White solid, mp: 160–162 °C. FT-IR (KBr) cm^{-1}: 1706, 1648, 1498, 1242, 1153, 1045, 996, 953, 755, 633, 621. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.41(s, 1H), δ 8.01–7.96(m, 2H), δ 7.56–7.26(m, 2H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −143.57 to −143.73(m, 2F), δ −145.06 to −145.20(m.2F). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 181.5, 148.3 (m), 145.7, 143.6 (m), 141.0 (m), 128.7, 118.7, 115.7 (m). LR-EI-MS m/z (%): 295(M^+, 100), 191(12), 162(42), 118 (11), 113(31), 90(15). HR-EI-MS: Calcd mass for $C_{13}H_5N_3OF_4$: 295.0369. Found: 295.0373.

4.2.7. 1-(4-Chloro-2,3,5,6-tetrafluorophenyl)-1H-benzo[d][1,2,3]triazole ***3e*** *[3]*. White solid, mp: 119–121 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, 1H, J=8.4 Hz), 7.58–7.32 (m, 3H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −134.8 (d, 2F, J=9.0 Hz), −139.9 (d, 2F, J=9.0 Hz). LR-EI-MS m/z (%): 301(13), 238(100), 63(41).

4.2.7.1. X-ray data of compound ***3e***. Empirical formula $C_{12}H_4ClF_4N_3$:FW=301.63; temperature 293 (K); Triclinic P-1; wavelength 0.71 Å; a=6.5911(8) Å, b=7.5241(9) Å, c=12.2772(15) Å, α=76.975(2)°, β=86.409(2)°, γ=79.681(2)°. V=584.14(12) $Å^3$; Z=2, Dc=1.715 mg/m^3; absorption coefficient 0.371 mm^{-1}; $F(000)$=300; size 0.427×0.369×0.311 mm; 2.82<θ<27.00; reflections collected 3460; Absorption correction Empirical; transmission 1.00max-0.758min; goodness of fit on F^2 1.054; final R indices $R1$=0.0474, $wR2$=0.1360. CCDC number is 705403.

4.2.8. 1-(4-Bromo-2,3,5,6-tetrafluorophenyl)-1H-benzo[d][1,2,3]triazole ***3f***. White solid, mp: 138–139 °C. FT-IR (KBr) cm^{-1}: 1518, 1500, 1432, 1289, 1054, 974, 887, 796, 744, 632. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, 1H, J=7.5 Hz), 7.65 (t, 1H, J=7.5 Hz), 7.53 (t, 1H, J=7.5 Hz), 7.42 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −130.2 (q, 2F, J=9.0 Hz), −143.2 (q, 2F, J=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.5, 120.7, 125.0, 129.4, 133.4, 140.1–140.0(m), 143.3 (d, J=19.2 Hz), 146.1–145.5(m), 149.4–149.2(m). HR-ESI-MS m/z: 346, 348. Calcd mass for $C_{12}H_4N_3BrF_4$: 344.9525. Found: 344.9529.

4.2.9. 1-(2,3,5,6-Tetrafluoro-4-iodophenyl)-1H-benzo[d][1,2,3]triazole ***3g***. White solid, mp: 168–170 °C. FT-IR (KBr) cm^{-1}: 1514, 1480, 1288, 1054, 967, 787, 745. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.20 (d, 1H, J=7.5 Hz), 7.63 (t, 1H, J=7.5 Hz), 7.51 (t, 1H, J=7.5 Hz), 7.43–7.40 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −117.3 (q, 2F, J=12.4 Hz), −142.9 (q, 2F, J=12.4 Hz). LR-EI-MS m/z (%): 393(M^+, 22), 365(15), 238(100), 148(25). Anal. Calcd for $C_{12}H_4IF_4N_3$ (%): C, 36.67; H, 1.03; N, 10.69. Found: C, 36.65; H, 1.09; N, 10.70.

4.2.10. 2-(2,3,5,6-Tetrafluoro-4-iodophenyl)-2H-benzo[d][1,2,3]triazole ***4g***. White solid, mp: 173–174 °C. FT-IR (KBr) cm^{-1}: 1563, 1489, 1270, 1208, 975, 914, 805, 743, 621. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.98 (dd, 2H, J=3.0, 3.9 Hz), 7.52 (dd, 2H, J=3.0, 3.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −117.5 (q, 2F, J=8.2 Hz), −144.5 (q, 2F, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 89.0, 118.6, 128.3, 141.3, 145.5, 146.0, 153.6. LR-EI-MS m/z (%): 393(M^+, 100), 238(20), 162 (83), 148(13). HR-EI-MS: Calcd mass for $C_{12}H_4N_3IF_4$: 392.9386. Found: 392.9388.

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Supplementary data

Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.12.016. These data include MOL files and InChIKeys of the most important compounds described in this article.

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