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Mono- and trifluorination of the thiazole ring of 2,5-diarylthiazoles using N-fluorobenzenesulfonimide (NFSI)

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ABSTRACT

Fluorination of select 2,5-diarylthiazoles using the N–F reagent N-fluorobenzenesulfonimide (NFSI) has led to the formation of both the anticipated 4-fluorothiazole as well as a unique 4,4,5-trifluorothiazole. Selective monofluorination is best achieved using bromobenzene as solvent at 155 °C, while trifluorination is best achieved by performing the reaction without solvent at 135–140 °C. An X-ray crystal structure has been obtained on one of the trifluorinated products.

Introduction

The direct fluorination of aromatic compounds using N–F reagents (Fig. 1) has become increasingly common in recent years.[1–4] Due to the relative ease of handling and often improved chemoselectivity offered by N–F reagents, especially compared to elemental fluorine, many such reagents have been developed and their general reactivity toward aromatic compounds has been demonstrated.[5–12] However, the majority of work in this area has focused largely on the fluorination of benzene, or other carbocyclic, derivatives. In contrast, there have been fewer examples involving the direct fluorination of heteroaromatic compounds with N–F reagents.[13–17] These few examples have also shown variable success, with incomplete conversion to fluorinated product and/or low mass recovery often being observed, especially with nitrogen heterocycles, which may undergo N-fluorination or ring oxidation as a competing side reaction.[16,17] The application of this chemistry to heteroaromatics thus remains somewhat limited in scope.

To date, there have been only a few reports of the direct fluorination of thiazoles with N–F reagents. 2-Acetamidothiazole, an activated thiazole derivative, has been fluorinated at the 5-position in 48% yield using Selectfluor (**1**), although this reaction could not be driven to completion.[18] Similarly, a 2-amino-4-arylthiazole has also been fluorinated at the 5-position in 42% yield using Selectfluor (**1**).[19] However, a recent attempt to fluorinate a less activated 2-alkyl-4-arylthiazole at the 5-position reportedly failed (although the fluorination reagent used in this case was not disclosed).[20]

Previously, we have described the direct fluorination of some 2,4-diarylthiazoles at the 5-position by reaction with Accufluor (**2**).[21] That reaction proceeded rather selectively, but provided low to modest yields of the monofluorinated products (19–43%) due to incomplete consumption of starting material. In another study aimed at the direct fluorination of 3,5-diarylisoxazoles using Selectfluor (**1**), we obtained not only the anticipated 4-fluoroisoxazole derivatives, but also a unique 4,4,5-trifluoroisoxazole as a minor byproduct, which was shown to be formed by formal addition of F_2 to the monofluorothiazole.[22]

We have now explored the direct fluorination of some 2,5-diarylthiazoles, also using N–F reagents. As with the 3,5-diarylisoxazoles, but in contrast to our observations with the isomeric 2,4-diarylthiazoles, we have found that the 2,5-diarylthiazoles, depending on the aryl substituents, also undergo the unique 4,4,5-trifluorination reaction in addition to monofluorination.[23] Unfortunately, these mono- and trifluorinated thiazole products have proven quite difficult to separate by chromatography, which dramatically limits the isolated yield potential for each product. We have thus tried to optimize the reaction conditions with the goal of forming each product in a more selective manner, and this has led to modest improvements in both the mono- and trifluorination of the parent 2,5-diphenylthiazole. Herein, we wish to describe these results.[24] We also present a crystal structure of one of the unique 4,4,5-trifluorothiazole products.

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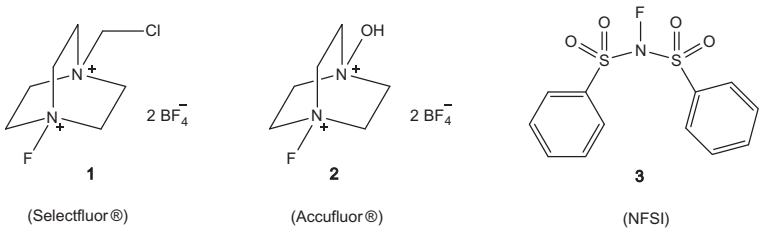


Figure 1. Structures of commonly used N–F reagents.

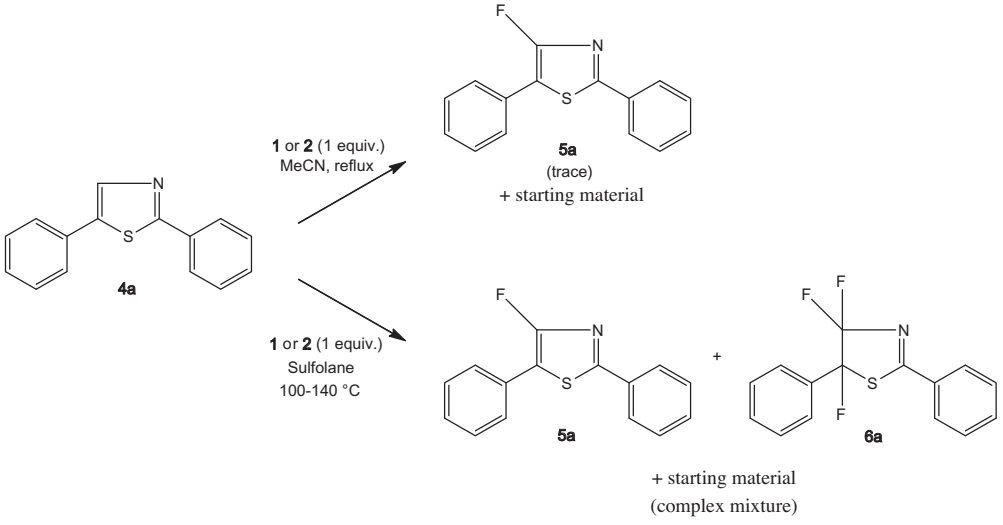
Results

Initially, we investigated the reaction of the parent 2,5-diphenylthiazole[25] (**4a**) with either Selectfluor (**1**) or Accufluor (**2**) (1.1 equiv), conditions we used successfully in our previous studies. Reaction with either of these N–F reagents in refluxing acetonitrile for several hours to overnight led to only minimal amounts of the 4-fluorothiazole according to TLC, with a large amount of starting material remaining unconsumed and some decomposition (Scheme 1). On the other hand, increasing the reaction temperature by heating in sulfolane[21] at various temperatures (100–140 °C) led to a complex mixture of the 4-fluorothiazole (**5a**), the 4,4,5-trifluorothiazole (**6a**), and unreacted starting material (Scheme 1). Thus, as with the 3,5-diarylisoxazoles,[22] trifluorination of the heterocyclic ring to give a non-aromatic product was observed. Since isolation of analytically pure products from this complex mixture using flash silica gel column chromatography was quite difficult, we did not determine isolated yields for these preliminary reactions. Instead, we pursued the development of other reaction conditions with the goal of improving the reaction selectivity.

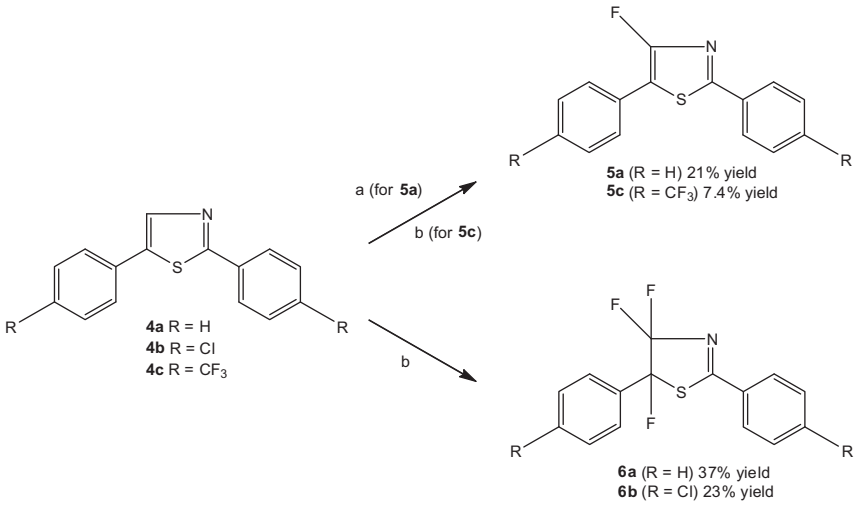
The reaction was next attempted using N-fluorobenzenesulfonimide (NFSI) (**3**), a less reactive fluorinating reagent that is most often used to fluorinate carbanions,[26] but which has also been used to fluorinate neutral aromatics.[14] Upon reaction of the parent 2,5-diphenylthiazole (**4a**) with NFSI (1.1 equiv) in sulfolane (at 140–150 °C), improved results were observed by TLC which included increased conversion of starting material and less decomposition. However, we were still left with a mixture of both mono- and trifluorinated products, along with unreacted starting material. Attempts to consume the starting material by using more equivalent of NFSI led to formation of more of the trifluorination product.

Considering that NFSI has good solubility in less polar solvents, we next tried refluxing toluene (bp 111 °C) as solvent. With this change, and by performing the reaction at relatively high dilution (~15 mL of solvent per mmole of thiazole), the reaction was quite selective for monofluorination, although a small amount of the trifluorinated product was still formed. However, the reaction appeared slow under these conditions. With a change of solvent to refluxing chlorobenzene (bp 132 °C), the reaction appeared faster, but still required several hours for maximum conversion according to TLC. With bromobenzene (bp 156 °C) as solvent, still under fairly dilute conditions, the reaction remained fairly selective for monofluorination and reached maximum conversion after about 3 h at 155 °C (Scheme 2). Considering this outcome was the best we had observed, we performed the reaction on preparative scale and obtained the 4-fluorothiazole **5a** in 21% isolated yield after flash column chromatography to remove residual starting material and minor traces of the trifluorinated product.[27]

We next turned our attention to maximizing the formation of the unique 4,4,5-trifluorothiazole product **6a**. We initially reacted the parent 2,5-diphenylthiazole (**4a**) with 3 equiv of NFSI in either *ortho*-dichlorobenzene or nitrobenzene at about 170–180 °C. Although these high-temperature conditions provided a larger amount of trifluoro product compared to monofluoro product according to TLC analysis, we eventually found that we could obtain a similar outcome by performing the reaction without solvent. This was possible since the melting point of NFSI is 110 °C, and thus a liquefied melt of the 2,5-diphenylthiazole **4a** and NFSI could be obtained upon heating the two reactants together at about 135 °C. After just 45 min at this temperature, a 37% isolated yield of the parent 4,4,5-trifluorothiazole **6a** was obtained following flash chromatography (Scheme 2).[28] Although still a fairly low yield, we were nonetheless pleased to be able to prepare a pure



Scheme 1. Original, unoptimized fluorination conditions. Purification not pursued to due limited product formation or formation of complex mixture.



Scheme 2. Reagents and conditions: (a) NFSI (1 equiv), bromobenzene (15 mL per mmole of thiazole), 155 °C, 3 h; (b) NFSI (3 equiv), 135–140 °C, 45 min, no solvent.

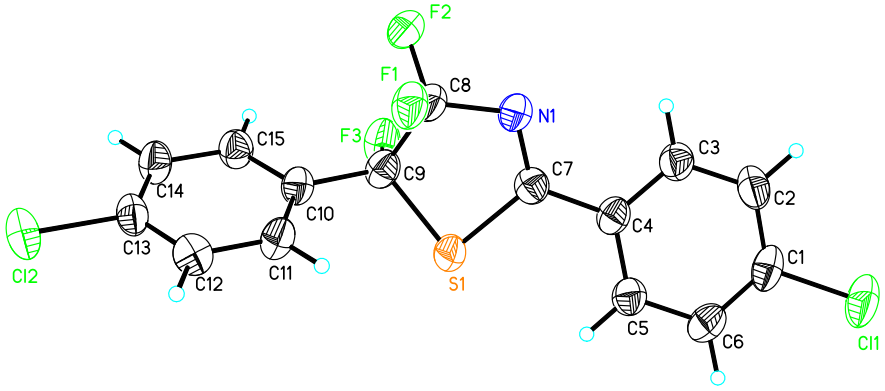


Figure 2. X-ray crystal structure of compound **6b**.

sample of the trifluorinated product. We were also pleased to find that NFSI is quite amenable to solvent-free fluorination reactions.[29]

To gain further insight into the unique trifluorination of the thiazole ring, we have briefly explored the effect of adding substituents to the phenyl rings of parent diphenylthiazole. Reaction of thiazole **4b** (R = Cl) with 3 equiv of NFSI in the absence of solvent (as with **4a**) led to the formation of trifluorinated product **6b** in 23% isolated yield (Scheme 2). However, when thiazole **4c** (R = CF_3) was subjected to these same conditions, only a small 7.4% isolated yield of monofluorinated product **5c** was obtained,[30] with no trifluorinated product being observed by TLC (a large amount of starting material remained). The lower reactivity of **4c** is attributed to the strong electron withdrawing effects of the two CF_3 substituents. Such a deactivating effect for the CF_3 group was also seen in our study on the fluorination of 3,5-diarylisoxazoles.[22]

Products in Scheme 2 have been characterized by mp, ^1H, ^{13}C and ^{19}F NMR, as well as HRMS.[27,28,30] As expected, the ^{19}F NMR of the monofluoro thiazoles (**5a** and **5c**) each showed one singlet for the lone fluorine, while the ^{19}F NMR of the trifluorothiazoles (**6a**–**b**) each showed three doublet of doublets ($^2J_{FF}$ = ~210 Hz; $^3J_{FF}$ = ~9 Hz) due to coupling of the three non-equivalent fluorines. The ^{13}C NMR spectra each revealed extended ^{13}C–^{19}F coupling. As for the fluorine-containing carbons, C-4 of the monofluoro thiazoles appeared as a doublet with a large coupling constant ($^1J_{FC}$ = ~250 Hz), while C-4 and C-5 of the trifluorinated thiazoles each appeared as a triplet of doublets, with both large and smaller coupling constants ($^1J_{FC}$ = ~235–255 Hz; $^2J_{FC}$ = ~25–45 Hz). In addition to spectral analysis, a crystal structure on trifluorothiazole **6b** was also obtained (Fig. 2).[31]

Conclusion

In conclusion, direct fluorination of 2,5-diphenylthiazole using N-fluorobenzenesulfonimide (NFSI) gives both the 4-fluorothiazole and the non-aromatic 4,4,5-trifluorothiazole upon heating. After some optimization of conditions, selective monofluorination was achieved in 21% isolated yield using bromobenzene as solvent at 155 °C under fairly dilute conditions, while trifluorination was achieved in 37% isolated yield by performing the reaction without solvent at 135–140 °C. Using the solvent-free fluorination conditions, the slightly deactivated 2,5-bis(4-chlorophenyl)thiazole was also trifluorinated in 23% isolated yield, however the more strongly deactivated 2,5-bis(4-trifluoromethylphenyl)thiazole was only monofluorinated in very low yield (7.4%). To our knowledge, this work represents the first example of the direct fluorination of thiazoles with NFSI. This work also illustrates the use of bromobenzene for high temperature reactions using NFSI, as well as the use of NFSI for solvent-free fluorinations.

Note added in proof

During the preparation of this Letter, a patent document from another group appeared online detailing the synthesis and

anti-cancer properties of some similar 4,5,5-trifluorothiazoles.[32] Those compounds were synthesized by direct fluorination of the thiazole ring with Selectfluor (2.4 equiv) in refluxing acetonitrile (3 h) in yields of 20–30%. Thus, the methodology we describe here for 4,5,5-trifluorination of the thiazole ring using NFSI without solvent represents an alternative synthetic method for the potential synthesis of these unique compounds.

Acknowledgments

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References and notes

1. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
2. Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31.
3. Nyffeler, P.; Duron, S.; Burkart, M.; Vincent, C.; Wong, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.
4. Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.
5. Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H.-N. *J. Am. Chem. Soc.* **1987**, *109*, 7194.
6. Umemoto, R.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
7. Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.
8. Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1999**, *40*, 2673.
9. Stavber, S.; Jereb, M.; Zupan, M. *ARKIVOC* **2001**, *v*, 98.
10. Adachi, K.; Ohira, Y.; Tomizawa, G.; Ishihara, S.; Oishi, S. *J. Fluorine Chem.* **2003**, *120*, 173.
11. Bluck, G. W.; Carter, N. B.; Smith, S. C.; Turnbull, M. D. *J. Fluorine Chem.* **2004**, *125*, 1873.
12. Heravi, M. R. P. *J. Fluorine Chem.* **2008**, *129*, 217.
13. Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron* **1996**, *52*, 11341.
14. (a) O'Neill, P. M.; Storr, R. C.; Park, B. K. *Tetrahedron* **1998**, *54*, 4615; (b) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.
15. (a) Baudoux, J.; Salit, A.-F.; Cahard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **2002**, *43*, 6573; (b) Sloop, J. C.; Jackson, J. L.; Schmidt, R. D. *Heteroat. Chem.* **2009**, *20*, 341.
16. Lange, K.; Hysell, M.; Druelinger, M. *Abstract CHED-562*. 213th National Meeting of the American Chemical Society, Apr, 1997.
17. Fields, S. C.; Lo, W. C.; Brewster, W. K.; Lowe, C. T. *Tetrahedron Lett.* **2010**, *51*, 79.
18. Briner, P. H.; Fyfe, M. C. T.; Martin, P.; Murray, P. J.; Naud, F.; Procter, M. J. *Org. Process Res. Dev.* **2006**, *10*, 346.
19. Antipas, A. S.; Blumberg, L. C.; Brissette, W. H.; Brown, M. F.; Casavant, J. M.; Doty, J. L.; Driscoll, J.; Harris, T. M.; Jones, C. S.; McCurdy, S. P.; McElroy, E.; Mitton-Fry, M.; Munchhof, M. J.; Reim, D. A.; Reiter, L. A.; Ripp, S. L.; Shavnya, A.; Smeets, M. I.; Trevena, K. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4069.
20. Cohen, F.; Koehler, M. F. T.; Bergeron, P.; Elliott, L. O.; Flygare, J. A.; Franklin, M. C.; Gazzard, L.; Keteltas, S. F.; Lau, K.; Ly, C. Q.; Tsui, V.; Fairbrother, W. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2229.
21. Campbell, T. F.; Stephens, C. E. *J. Fluorine Chem.* **2006**, *127*, 1591.
22. Stephens, C. E.; Blake, J. A. *J. Fluorine Chem.* **2004**, *125*, 1939.
23. For a related example of 2,5,5-trifluorination of thiazoles by electrolysis, see: Riyadh, S. M.; Fuchigami, T. *J. Org. Chem.* **2002**, *67*, 9379.
24. *This Work was Presented in Preliminary Form at the 19th International Symposium on Fluorine Chemistry*; Hatfield, J. M.; Stephens, C. E. Abstract 244, 2009.
25. The 2,5-arylthiazoles (**4a**–**c**) used in this study were prepared by the Pd-catalyzed Heck arylation of thiazole with 2 equiv of a bromobenzene: Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2003**, *59*, 5685.
26. Taylor, S. D.; Kotoris, G. Tetrahedron 1999, 55, 12431. b) Yamada, S.; Gavryushin, A.; Knochel, P *Angew. Chem. Int. Ed.* **2010**, *49*, 2215.
27. *Synthesis and analytical data for* ***5a***: A mixture of 2,5-diphenylthiazole (0.24 g, 1.0 mmol) and NFSI (0.35 g, 1.1 mmol) in bromobenzene (15 mL) was heated at 155 °C (oil bath temp) under N_2 for 3 h. The dark yellow solution was diluted with water and extracted with EtOAc. The extract was evaporated onto silica gel and subjected to flash chromatography on silica using hexanes as eluent to give monofluoro thiazole **5a** (0.055 g, 21% yield) as a yellow solid. Recrystallization from MeOH gave a fluffy yellow solid, mp 72.5–74 °C. IR (ATR): 3053, 2921, 1599, 1572, 1547, 1361, 1332, 1040, 1023, 907, 754, 686, 674 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.38–7.40 (m, 1H), 7.45–7.52 (m, 5H), 7.61 (d, J = 8.0 Hz, 2H), 7.89–7.92 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 113.6 (d, J = 26.2 Hz), 125.7 (s), 127.2 (d, J = 5.0 Hz), 128.4 (d, J = 5.0 Hz), 128.9 (s), 129.8 (s), 129.8 (s), 131.6 (s), 132.2 (s), 155.5 (d, J = 248 Hz), 161.2 (d, J = 19.1 Hz). ^{19}F NMR (282 MHz, DMSO-d_6, C_6F_6 internal standard): 55.7 (s). HRMS (ESI^+) calcd for $C_{15}H_{11}FNS$: 256.0596; found: 256.0594.
28. *Synthesis and analytical data for* ***6a***: A mixture of 2,5-diphenylthiazole (0.24 g, 1.0 mmol) and NFSI (3.0 mmol) was heated without solvent at 135 °C (oil bath temp) under N_2 for 3 h. Upon cooling, the resulting orange solid was dissolved in EtOAc, evaporated onto silica gel, and then subjected to flash chromatography on silica eluting with hexanes to give a pale yellow oil (0.108 g, 37%) which, after standing overnight, became solid, mp 61–64 °C. IR (ATR): 3063, 2925, 2850, 1595, 1575, 1449, 1263, 1194, 1162, 1108, 1000, 994, 960, 889, 760, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.42–7.57 (m, 5H), 7.62–7.68 (m, 1H), 7.69–7.76 (m, 2H), 8.01 (dd, J = 1.6, 0.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): 111.8–113.9 (ddd, J = 235, 44.6, 27.0 Hz), 127.1 (dd, J = 6.5, 1.5 Hz), 128.6 (s), 129.1 (s), 129.1 (s), 130.3–133.9 (ddd, J = 254, 250, 28.5 Hz), 130.6 (d, J = 24.2 Hz), 130.6 (s), 131.0 (s), 134.4 (s), 175.4 (dd, J = 18.8, 11.3 Hz). ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6 internal standard): 31.1–31.2 (dd, J = 9.3, 9.0 Hz), 57.9–58.7 (dd, J = 209, 9.3 Hz), 82.0–82.8 (dd, J = 208, 9.0 Hz). HRMS (ESI^+) calcd for $C_{15}H_{11}F_3NS$: 294.0564; found: 294.0550.
29. For use of selectfluor and accufluor under solvent-free conditions, see: Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2007**, *48*, 2671.
30. *Analytical data for* ***5c***: Mp 102–103 °C (hexanes). IR: 2923, 2851, 1615, 1548, 1508, 1407, 1363, 1320, 1289, 1163, 1108, 1065, 1039, 835 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): 7.83 (s, 4H), 7.87 (d, J = 8.3 Hz, 2H), 8.10 (d, J = 8.2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): 113.4 (d, J = 26.7 Hz), 123.8 (q, J = 272 Hz), 123.9 (q, J = 272 Hz) 126.2 (s), 126.3 (m, 2C), 127.5 (d, J = 5.2 Hz), 128.5 (q, J = 38.1 Hz), 130.8 (q, J = 32.2 Hz), 131.9 (d, J = 6.5 Hz), 135.1 (d, J = 1.4 Hz), 157.1 (d, J = 251 Hz), 160.0 (d, J = 19.8 Hz). ^{19}F NMR (282 MHz, DMSO-d_6, C_6F_6 internal standard): 58.7 (s), 101.1 (s, 3F), 101.3 (s, 3F). HRMS (ESI^+) calcd for $C_{17}H_9F_7NS$: 392.0344; found: 392.0349.
31. Good quality crystals of **6b** (mp 88–89 °C) were obtained by recrystallization from hexanes. *Crystal data*: monoclinic, a = 6.1553(3), b = 9.8572(6), c = 24.6607(15) Å, α = 90°, β = 93.703(3)°, γ = 90°. V = 1493.14(15) $Å^3$, space group $P2(1)/n$, Z = 4, D_{calcd} = 1.611 mg/m^3, abs coeff = 5.484 mm^{-1}, $F(000)$ = 728. Crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication no. CCDC 815178. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
32. Santano, J. G.; Grifols, R. L.; Palomera, F. A.; Perarnau, A. P.; Gallego, S. P.; Girones, D. G.; Iglesias-Serret, D.; Albalate, R. R. WO2012028757, 2012.