Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7703–7707
Tetrahedron Letters

An easy three step synthesis of perfluoroalkylated amphetamines

Amit Tewari,[a] Martin Hein,[a,*] Alexander Zapf[b] and Matthias Beller[b,*]

[a]*Universität Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany*
[b]*Leibniz-Institut für Organische Katalyse an der Universittät Rostock e.V. (IfOK), Buchbinderstraße 5–6, D-18055 Rostock, Germany*

Received 2 June 2004; revised 13 August 2004; accepted 16 August 2004

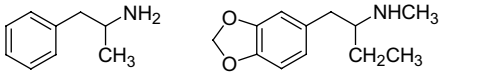
Abstract—A general synthesis of perfluoroalkylated amphetamines is presented. Initially, 1-aryl-1-iodo-2-(perfluoroalkyl)ethylenes are prepared by radical addition of perfluoroalkyl iodides to arylacetylenes. Key step of the reaction sequence is the following dehydroiodination in the presence of *n*-BuLi to give 1-perfluoroalkyl-2-arylacetylenes in situ, which are reacted with secondary amines to produce perfluoroalkylated enamines in a new one pot procedure. Final hydrogenation yields the desired products in good yields. By using *N*,*N*-dibenzylamine or *N*-benzylamines the corresponding primary and secondary perfluoroalkylated amines are easily available.

1. Introduction

2-Aminoprop-1-ylbenzene and its derivatives (amphetamines) belong to the class of sympathomimetic drugs (Fig. 1). They are of pharmacological interest due to their stimulating or inhibiting effect on the central nervous system, their anti-inflammatory activity and their ability to inhibit several enzymes.[1]

Classic methods for synthesizing amphetamines include reductive amination reactions of appropriate ketones,[2] reactions of aromatic aldehydes with nitroalkanes and subsequent reduction,[3] amidomercuration–demercuration of olefins[4] or *N*-alkylation of ammonia, primary and secondary amines.[5] Most of these reactions have significant drawbacks, because they require not easily available starting materials, they use stoichiometric amounts of toxic mercury salts or they produce at least one equivalent of a salt as a by-product.

In the past we demonstrated that simple styrenes are efficiently hydroaminated with amines in the presence of catalytic amounts of a base.[6] It is also possible to hydroaminate allylbenzenes directly to give the corresponding amphetamine derivatives via an isomerization–hydroamination sequence.[7]



Amphetamine — 2-(Methylamino)but-1-yl-(3,4-methylenedioxy)benzene (MBDB)

Figure 1. Biologically active amphetamines.

Based on this work we were interested in extending the methodology to prepare more functionalized, for example, fluorinated, amphetamines by hydroamination reactions.[8] Here, our studies toward a general synthesis of perfluoroalkylated amphetamine derivatives are described.

It is well established that the introduction of fluorine or fluoroalkyl groups into organic molecules changes their chemical and physical properties as well as their biological activity. Often fluorine has been used to replace hydrogen or hydroxyl groups, and CF_2 groups were introduced instead of carbonyl groups in order to obtain substances with similar sterical properties but with different reactivity or physicochemical behavior. A significant amount of partially fluorinated compounds is nowadays in use or at various stages of clinical trials as anticancer, antiviral, antibacterial, antimalarial, antifungal, or CNS active agents.[9] It is generally agreed on

Keywords: Amphetamines; Hydroamination; Alkynes; Perfluoroalkylation.
* Corresponding authors. Fax: +49 381 4986412 (M.H.); tel.: +49 381 466930; fax: +49 381 4669324 (M.B.); e-mail addresses: martin.hein@chemie.uni-rostock.de; matthias.beller@ifok.uni-rostock.de

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.08.080

that the introduction of fluorine or a short fluoroalkyl chain into specific parts of a molecule (e.g., aromatic cores) is advantageous because of the increase in the lipophilic character of the respective compound, which improves its in vivo transport and absorption behavior.[10] On the other hand fluorine atoms proved to be suitable markers for in vivo and in vitro ^{19}F NMR studies of the metabolism of drugs.[11]

Despite the importance of amphetamines on the one hand and fluorinated pharmaceuticals on the other hand until now, very little work has been done toward the synthesis of fluorinated analogues of amphetamines.[12]

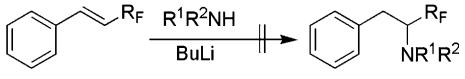
Although the introduction of longer perfluoroalkyl groups into amphetamine analogues seems less favorable from a pharmacological point of view, we decided to introduce perfluorohexyl and perfluorooctyl chains as model systems because of the lower volatility of the starting materials and intermediates, which do not require special equipment for handling.

2. Results and discussion

Our initial attempts to synthesize [2-amino-2-(perfluoroalkyl)ethyl]benzenes started from β-fluoroalkylated styrenes, which were prepared by radical addition of fluoroalkyl halides to styrene or related reactions and subsequent HX-elimination,[13] using a base-catalyzed hydroamination reaction (Scheme 1). Although base-catalyzed hydroaminations work reliably with a number of styrenes,[14] the reaction did not work in the case of β-fluoroalkylated styrenes. Here, only starting material was recovered from the reaction mixtures.

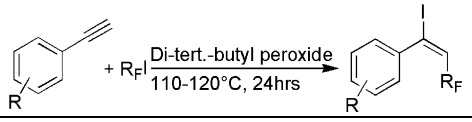
Alternatively, we explored the possibility of hydroamination reactions of 1-perfluoroalkyl-2-aryl-acetylenes.[15] Fluorinated acetylenes are conveniently synthesized by free radical addition of 1-iodoperfluoroalkanes to arylacetylenes. Thus, treatment of perfluoroalkyl iodides with three different arylalkynes in the presence of di-*tert*-butyl peroxide at 110–120 °C yielded 1-aryl-1-iodo-2-(perfluoroalkyl)ethylenes in 40–75% yield (Table 1). The addition of R_FI to arylacetylenes was also performed at lower temperature (0 °C–rt) using sodium dithionite as radical initiator. However, these reactions generally resulted in lower yields due to side reactions of dithionite.

In all cases the corresponding *E*-isomer is obtained exclusively. Similar conversions of non-aryl substituted olefines are known to give mixtures of *E*- and *Z*-olefins.[16] The reason for the high *E*-selectivity in case of arylacetylenes is unclear, but a correlation with the different radical geometry is supposed. The stereochemistry of the resulting iodinated olefins **1**–**4** was confirmed by X-ray crystallography[16] and NMR studies and is in agreement with the literature.[17]



Scheme 1. Hydroamination of β-(perfluoroalkyl)styrenes.

Table 1. Reaction of arylacetylenes with perfluoro-alkyl iodides



Entry	R	R_F	Product	Yield (%)
1	H	C_6F_{13}	**1**	75
2	H	C_8F_{17}	**2**	50
3	3-OMe	C_6F_{13}	**3**	45
4	4-CF_3	C_8F_{17}	**4**	40

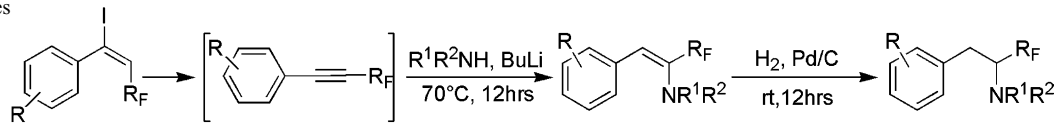
Next, we thought that olefins **1**–**4** should undergo in situ dehydroiodination to produce the corresponding alkynes, which might react with amines to give 2-aryl-1-perfluoroalkyl enamines. Indeed, in the presence of 2 equiv of *n*-BuLi immediate formation of 1-aryl-2-(perfluoroalkyl)alkynes is observed, which can be trapped directly with various secondary amines to yield the desired enamines **5**–**14** (Table 2).[18]

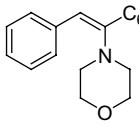
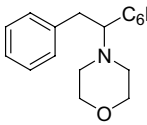
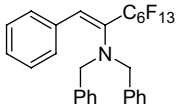
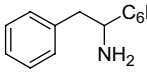
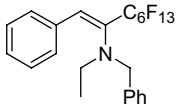
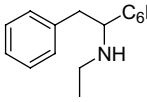
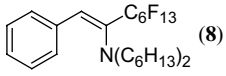
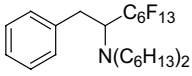
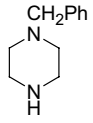
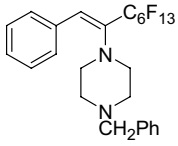
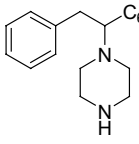
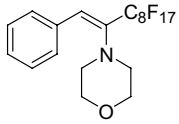
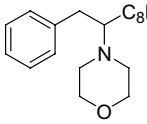
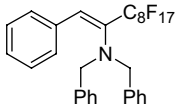
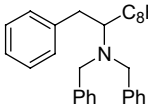
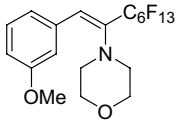
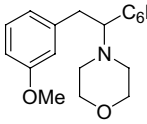
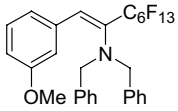
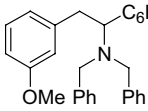
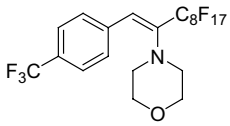
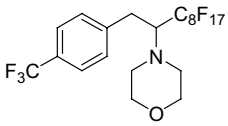
Interestingly, this novel two step one-pot reaction is not a simple nucleophilic substitution of the vinylic iodide and proceeds highly regio- and stereoselectively. The amine adds nearly exclusively (>95%) at the alkyne carbon, which is attached to the perfluoroalkyl group. Despite the electron-withdrawing character of the perfluoroalkyl group the negative charge is better stabilized in α-position to the aryl group. Hence, in all cases the 2-aryl-1-perfluoroalkylenamines are formed regioselectively. X-ray studies of product **10** (Table 2, entry 6) show the morpholine and phenyl ring on the same side of the resulting double bond confirming the (*Z*)-configuration for **10**. This stereochemical assignment for the enamines is also supported by NOE experiments. For example, in the case of *N*-[3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-1-(4-trifluoromethylphenyl)dec-1-en-2-yl]morpholine (**14**) (Table 2, entry 10) a correlation between the *ortho*-proton of the aromatic ring and N–CH_2 protons of the morpholine ring was observed, which confirms the (*Z*)-configuration.

Finally, the reduction of **5**–**14** was investigated with different reagents ($LiAlH_4$, $NaBH_4$, BH_3, $LiBH_4$/$ClSiMe_3$, and H_2 with Pd/C). Here, only the catalytic hydrogenation gave satisfactory results and the desired amines **15**–**24** could be isolated in good to excellent yields (70–95%).[19]

Noteworthy, in case of *N*-benzylated enamines **11** and **13** (Table 2, entries 7 and 9) a selective reduction of the double bond can be achieved applying shorter reaction times (6–12 h) and 5 mol% Pd/C, whereas enamine reduction and cleavage of the benzyl groups is observed using higher catalyst concentrations (10–15 mol%) and longer reaction times (2–3 days, see enamines **6**, **7**, **9**; Table 2, entries 2, 3, and 5). This allows the selective

Table 2. Hydroamination of in situ generated perfluoroalkylated arylacetylenes and subsequent reduction to amphetamine analogues



Entry	Starting material	Amine	Enamine	Yield (%)	Amphetamine derivative	Yield (%)
1	**1**		 (**5**)	50	 (**15**)	95
2	**1**		 (**6**)	51	 (**16**)	90
3	**1**		 (**7**)	52	 (**17**)	96
4	**1**	$NH(C_6H_{13})_2$	 (**8**)	40	 (**18**)	93
5	**1**		 (**9**)	52	 (**19**)	70
6	**2**		 (**10**)	53	 (**20**)	97
7	**2**		 (**11**)	63	 (**21**)	95
8	**3**		 (**12**)	55	 (**22**)	92
9	**3**		 (**13**)	56	 (**23**)	94
10	**4**		 (**14**)	20	 (**24**)	96

preparation of primary, secondary, and tertiary fluorinated amphetamines.

In conclusion, an easy and straightforward synthesis of fluorinated amphetamine analogues has been developed. Key step of the procedure is a novel two step one-pot hydroamination reaction of 1-aryl-1-iodo-2-(perfluoroalkyl)ethylenes. In situ dehydroiodination produced (perfluoroalkyl)arylacetylenes, which react with different amines to yield the corresponding enamines highly regio- and stereoselectively. Subsequent hydrogenation gives the desired fluoroalkylated amphetamine analogues in good yield.

Acknowledgements

The authors thank Prof. M. Michalik (IfOK), Prof. H. Reinke (University of Rostock) and Mrs. S. Buchholz (IfOK) for analytical assistance. This work was funded

by the Bundesministerium für Bildung und Forschung and the state of Mecklenburg–Vorpommern.

References and notes

1. (a) Pelletier, S. W. *Chemistry of Alkaloids*; Van Nostrand-Reinhold: New York, 1970; (b) Testa, B.; Salvesen, B. *J. Pharm. Sci.* **1980**, *69*, 497; (c) Laske, R.; Meindl, W.; Holler, E.; Schönenberger, H. *Arch. Pharm.* (*Weinheim, Germany*) **1989**, *322*, 297, 847.
2. (a) Glennon, R. A.; Smith, J. D.; Ismaiel, A. M.; El-Ashmawy, M.; Battaglia, G.; Fisher, J. B. *J. Med. Chem.* **1991**, *34*, 1094; (b) Nicols, D. E. *J. Med. Chem.* **1973**, *16*, 480; (c) Freifelder, M.; Stone, G. R. *J. Am. Chem. Soc.* **1958**, *80*, 5270; (d) Micovic, I. V.; Ivanovic, M. D.; Roglic, G. M.; Kiricojevic, V. D.; Popovic, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 265.
3. (a) Mori, A.; Ishiyama, I.; Akita, H.; Suzuki, K.; Mitsuoka, T.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 3449; (b) Iwai, I. *Chem. Pharm. Bull* **1965**, *13*, 118; (c) Fujii, M. *Chem. Lett.* **1992**, *6*, 933.
4. (a) Koziara, A.; Olejniczak, B.; Osowska, K.; Zwierzak, A. *Synthesis* **1982**, 918; (b) Barluenga, J.; Jiménez, C.; Nájera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 591; (c) Griffith, R. C.; Gentile, R. J.; Davidson, T. A.; Scott, F. L. *J. Org. Chem.* **1979**, *44*, 3580; (d) Barluenga, J.; Jiménez, C.; Nájera, C.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1981**, 670; (e) Larock, R. C. *Angew. Chem.* **1978**, *90*, 28; . *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27.
5. (a) Kirk-Othmer *Encyclopedia of Chemical Technology*, 4th ed.; John Wiley and Sons: New York, 1992; p 369; (b) Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G. *J. Med. Chem.* **1995**, *25*, 4929; (c) Glennon, R. A.; Yousif, M. Y.; Ismaiel, A. M.; El-Ashmawy, M. B.; Herndon, J. L.; Fischer, J. B.; Server, A. C.; Burke Howie, K. J. *J. Med. Chem.* **1991**, *34*, 3360.
6. (a) Kumar, K.; Michalik, D.; Garcia Castro, I.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746; (b) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M.; Trauthwein, H. *Angew. Chem.* **1998**, *110*, 3571; *Angew. Chem., Int. Ed.* **1998**, *38*, 3389; (c) Beller, M.; Breindl, C. *Tetrahedron* **1998**, *54*, 6359; (d) For amination of styrenes in the presence of stoichiometric amounts of base, see: Seijas, J. A.; Vázquez-Tato, M. P.; Entenza, C.; Martínez, M. M.; Ónega, M. G.; Veiga, S. *Tetrahedron Lett.* **1998**, *39*, 5073.
7. Hartung, C. G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* **2000**, *56*, 5157.
8. (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675; (b) For a personal account on hydroamination, see: Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579.
9. (a) Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93; (b) Hamprecht, G.; Würzer, B.; Witschel, M. *Chimia* **2004**, *58*, 117; (c) Heinrich, T.; Böttcher, H.; Bartoszyk, G. D.; Schwartz, H.; Anzali, S.; März, J.; Greiner, H. E.; Seyfried, C. A. *Chimia* **2004**, *58*, 143; (d) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha and Elsevier: Amsterdam, 1983.
10. *Biomedical Frontiers of Fluorine ChemistryACS Symposium Series*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; Vol. 639.
11. (a) Pandey, S. K.; Gryshuk, A. L.; Graham, A.; Ohkubo, K.; Fukuzumi, S.; Dobhal, M. P.; Zheng, G.; Ou, Z.; Zhan, R.; Kadish, K. M.; Oseroff, A.; Ramaprasad, S.; Pandey, R. K. *Tetrahedron* **2003**, *59*, 10059; (b) Martino, R.; Malet-Martino, M.; Gilard, V. *Curr. Drug Metabol.* **2000**, *1*, 271.
12. Uno, H.; Shiraishi, Y.; Shimokawa, K.; Suzuki, H. *Chem. Lett.* **1988**, 729.
13. (a) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Dolbier, W. R.; Pan, H.-Q. *J. Am. Chem. Soc.* **1993**, *115*, 1577; (b) Wu, F.-H.; Huang, B.-N.; Lu, L.; Huang, W.-Y. *J. Fluorine Chem.* **1996**, *80*, 91; (c) Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Sawada, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 627.
14. For a review on base-catalyzed hydroamination, see: Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.
15. For examples, of base-catalyzed hydroamination of arylalkynes, see: (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193; (b) Rodriguez, A.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem.* **2000**, *112*, 2607; (c) *Angew. Chem., Int. Ed.* **2000**, *39*, 2488; (d) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294.
16. X-ray analyses of **1** and **10** clearly show the supposed configurations of the compounds, but due to the disordered perfluoroalkyl chains the data are not suitable for publication.
17. Baum, K.; Bedford, C. D.; Hunadi, R. J. *J. Org. Chem.* **1982**, *47*, 2251.
18. A representative procedure is given for (*Z*)-*N*-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-phenyloct-1-en-2-yl)morpholine (**5**): To a stirred solution of morpholine (0.158 g, 1.82 mmol) in dry THF, 2 equiv of *n*-BuLi (3.6 mmol, 2.5 M in toluene) were added slowly at room temperature under argon and the reaction mixture was stirred for 10 min. Then a solution of (*E*)-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-iodooct-1-enyl)benzene (**1**) (1.0 g, 1.82 mmol) in THF was added dropwise. The reaction mixture was allowed to stir at 70 °C for 12 h. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed twice with water, dried over sodium sulfate, and concentrated in vacuo to give the crude product, which was purified by column chromatography (ethyl acetate/heptane 20:80) to yield 0.455 g (50%) **5**. ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 2.77 (t, $^{3}J_{HH}$ = 4.6 Hz, 4H, 2 morpholine N–CH_2), 3.53 (t, $^{3}J_{HH}$ = 4.6 Hz, 4H, 2 morpholine O–CH_2), 6.5 (s, 1H, Ph–C*H*), 7.26 (m, 5H, aromatic C*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 51.4 (2 morpholine N–*C*$_2$), 66.9 (2 morpholine O–*C*$_2$), 126.7 (t, $^{3}J_{CF}$ = 6.5 Hz, Ph–*C*H), 128.2 (2 aromatic *C*H), 128.2 (1 aromatic *C*H), 129.1 (2 aromatic *C*H), 134.3 (1 aromatic *C*), 136.4 (t, $^{2}J_{CF}$ = 21.9 Hz, *C*(NC$_4$H$_8$O)–CF$_2$). ^{19}F{^{1}H} NMR (235 MHz, $CDCl_3$): δ [ppm] = −125.9 (m, CF_2), −122.4 (m, CF_2), −121.5 (m, CF_2), −120.5 (m, CF_2), −108.8 (t, $^{3}J_{FF}$ = 14.5 Hz, C(NC$_4$H$_8$O)–CF_2), −80.6 (t, $^{3}J_{FF}$ = 10 Hz, CF_3). MS (EI, 70 eV): *m*/*z* (%) 507 (M^+, 85), 188 (100).
19. A representative procedure is given for (2-amino-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooct-1-yl)benzene (**16**): A mixture of (*Z*)-[2-(*N*,*N*-dibenzylamino)-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooct-1-en-1-yl]benzene (**6**) (0.50 g, 0.81 mmol) and 10 mol% Pd (86 mg, 10% Pd/C) in THF (10 mL) was stirred under an atmosphere of hydrogen (1 bar) at room temperature for 48 h. The mixture was then filtered through a bed of Celite. The filtrate was concentrated in vacuo to get the crude product which was further purified by column chromatography (ethyl acetate/heptane 30:70) to yield **16** as a white amorphous solid (0.32 g, 90%). ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 2.50 (dd, $^{2}J_{HH}$ = 13.9 Hz, $^{3}J_{HH}$ = 10.8 Hz, 1H, Ph–CH_a), 3.10 (d, $^{2}J_{HH}$ = 14.0 Hz, 1H, Ph–CH_b), 3.45–3.59 (m, 1H, C*H*–NH$_2$), 7.18–7.28 (m, 5H, 5 aromatic *H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ [ppm] = 35.8 (Ph–*C*$_2$), 54.5 (t,

$^2J_{CF}$ = 23.3 Hz, *C*H–NH_2), 127.0 (1 aromatic *C*H), 128.7 (2 aromatic *C*H), 129.2 (2 aromatic *C*H), 136.7 (1 aromatic *C*). $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ [ppm] = −125.9 (m, CF_2), −123.1 (dm, $^2J_{FF}$ = 290 Hz, CH–CF_a), −122.5 (m, CF_2), −121.7 (m, CF_2), −120.0 (m, CF_2), −119.4 (dm, $^2J_{FF}$ = 290 Hz, CH–CF_b), −80.5 (t, $^3J_{FF}$ = 10 Hz, CF_3). MS (EI, 70 eV): *m*/*z* (%) 439 (M^+, 2.7), 348 (100). HRMS calcd for $C_{14}H_{10}NF_{13}$ 439.06097, found 439.06058.