Tetrahedron Letters 51 (2010) 6150–6152

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nucleophilic (phenylsulfonyl)difluoromethylation of alkyl halides using $PhSO_2CF_2SiMe_3$: preparation of *gem*-difluoroalkenes and trifluoromethyl compounds

Lingui Zhu, Ya Li, Yanchuan Zhao, Jinbo Hu *

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-ling Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 13 August 2010
Revised 14 September 2010
Accepted 17 September 2010
Available online 22 September 2010

Keywords:
Fluorine
(Phenylsulfonyl)difluoromethylation
Difluoroalkene
Trifluoromethylation
Nucleophilic substitution
Fluoroalkylation

ABSTRACT

Nucleophilic (phenylsulfonyl)difluoromethylation of both alkyl iodides and bromides was successfully accomplished by using CsF/15-crown-5 as an initiating system in DME, and the amount of 15-crown-5 was found to be critical to the yield of the product. The prepared (phenylsulfonyl)difluoromethylated alkanes were converted into *gem*-difluoroalkenes by a base-mediated 1,2-elimination reaction, and the latter species could be further transformed into trifluoromethyl compounds in the presence of KF/18-crown-6 or TBAF.

Selective incorporation of fluorine atom(s) or fluorine-containing moieties into organic molecules can often bring about many profound changes in their physical, chemical, and biological properties.[1,2] Among the fluorine-containing moieties, *gem*-difluorovinyl group is of particular interest owing to its high electrophilicity, isosteric property as a carbonyl group,[3,4] as well as its critical role in some enzyme inhibitors.[5] Moreover, *gem*-difluoroalkenes are also important synthetic precursors to prepare other fluorinated compounds and polymers.[6]

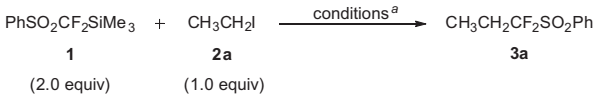
At present, there are several methods to prepare *gem*-difluoroalkenes,[7] including Wittig-type reactions,[8] elimination reactions,[9] and Julia–Kocienski olefination.[10] Previously, Prakash et al. reported the preparation of *gem*-difluoroalkenes by a substitution-elimination method using primary alkyl halides and difluoromethyl phenyl sulfone ($PhSO_2CF_2H$).[11] Due to the use of a strong base such as *t*-BuOK, this method is not compatible with activated alkyl halides such as benzyl bromides.[11] On the other hand, as an alternative reagent to $PhSO_2CF_2H$, [(phenylsulfonyl)difluoromethyl]trimethylsilane ($PhSO_2CF_2SiMe_3$, **1**) was successfully applied by us in the nucleophilic (phenylsulfonyl)difluoromethylation of some base-sensitive substrates such as enolizable aldehydes under mild conditions.[12] Recently, fluoride-initiated cross-coupling reactions between alkyl halides and R_fSiMe_3 ($R_f = CF_3$, C_2F_5, $PhSCF_2$) reagents were reported by Tyrra et al.[13a] and us.[13b] Inspired by these results, we envisioned that a nucleophilic substitution reaction between an alkyl halide and $PhSO_2CF_2SiMe_3$ reagent in the presence of a fluoride ion source could also be possible. More importantly, the prepared $PhSO_2CF_2$-containing alkanes could be further transformed into trifluoromethyl compounds through *gem*-difluoroalkene intermediates.[14]

First of all, we examined the reaction conditions of the nucleophilic (phenylsulfonyl)difluormethylation reaction with $PhSO_2CF_2$-SiMe (**1**) by using iodoethane (**2a**) as a model substrate. The results are shown in Table 1. It was found that, when tetrabutylammonium (triphenylsilyl)-difluorosilicate (TBAT) was used as an initiating system in THF,[15] the (phenylsulfonyl)difluormethylation reaction between reagent **1** and substrate **2a** hardly proceeded (Table 1, entry 1). When KF (2.0 equiv)/DMF or CsF (2.0 equiv)/15-crown-5 (4.0 equiv)/1,2-dimethoxyethane (DME) was used,[13a] product **3a** was obtained in 23% and 84% yield, respectively (Table 1, entries 2 and 3). Although the yield of **3a** was satisfactory, the amount of 15-crown-5 was still too high (4.0 equiv relative to **2a**). Therefore, we decided to explore the effect of the amount of 15-crown-5 on the yield of the product. After testing various amounts from 1.0 to 4.0 equiv (Table 1, entries 3–7), we found that the amount of 15-crown-5 was critical to the yield of the product. As shown in Table 1, when the amount of 15-crown-5 was below 2.0 equiv, the yields linearly increased with the amounts of 15-crown-5; however, when the amount of 15-crown-5 was above 2.0 equiv, the yields almost kept intact.

* Corresponding author. Tel.: +86 21 54925174; fax: +86 21 64166128.
E-mail address: jinbohu@sioc.ac.cn (J. Hu).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.068

Table 1
The optimization of reaction condition



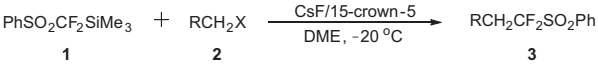
Entry	Conditions	15-Crown-5 (equiv)	Yield[b] (%)
1	TBAT/THF/0 °C	None	<10
2	KF/DMF/−20 °C	None	23
3	CsF/DME−20 °C	4.0	84
4	CsF/DME/−20 °C	3.0	85
5	CSF/DME/−20 °C	2.0	85
6	CSF/DME/−20 °C	1.5	65
7	CSF/DME/−20 °C	1.0	44
8	CsF/DME/−78 °C	2.0	77
9	CsF/DME/0 °C	2.0	24
10	CsF/DME/−20 °C	2.0	34[c]
11	CsF/DME/−20 °C	2.0	<10[d]

[a] In all cases, the amount of fluoride source was 2.0 equiv relative to that of **2a**.
[b] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.
[c] CH_3CH_2Br was used as a substrate instead of **2a**.
[d] CH_3CH_2OTs was used as a substrate instead of **2a**.

Furthermore, an investigation on reaction temperature indicated that the reaction proceeded best at −20 °C (Table 1, entries 5, 8, and 9). In addition, when bromoethane and ethyl tosylate were used as substrates instead of iodoethane, the product yields were sharply decreased (Table 1, entries 10 and 11). Finally, the optimal reaction condition was chosen as follows: using CsF/15-crown-5 as an initiating system in DME solvent and running the reaction at temperatures ranging from −20 °C to ambient temperature (Table 1, entry 5).[16]

By using the optimized condition as standard, we extended the reaction scope to a variety of alkyl halides to give corresponding (phenylsulfonyl)difluoromethylated products **3**. As illustrated in Table 2, not only could primary alkyl iodides bearing different chain length afford products **3a**–**f** in moderate to good yields (Table 2, entries 1–6), activated bromides such as allyl bromide and benzyl bromides could also give the corresponding products **3g** and **3i**–**m** in similar yields (Table 2, entries 7 and 9–13). However, the reactions with alkyl halides bearing strong electron-withdrawing groups, such as ethyl 2-bromoacetate and *p*-nitrobenzyl bromide, were not successful (Table 2, entries 8 and 14). It should be mentioned that, in all cases as shown in Table 2, no formation of *gem*-difluoroalkenes was observed probably owing to the weak basicity of CsF.

Table 2
Nucleophilic (phenylsulfonyl)difluormethylation of alkyl halides **2**



Entry	RCH_2X (2)	$RCH_2CF_2SO_2Ph$ (3)	Yield[a] (%)
1	CH_3CH_2I (2a)	$CH_3CH_2CF_2SO_2Ph$ (3a)	79
2	$CH_3CH_2CH_2I$ (2b)	$CH_3CH_2CH_2CF_2SO_2Ph$ (3b)	65
3	$CH_3(CH_2)_2CH_2I$ (2c)	$CH_3(CH_2)_2CH_2CF_2SO_2Ph$ (3c)	62
4	$CH_3(CH_2)_4CH_2I$ (2d)	$CH_3(CH_2)_4CH_2CF_2SO_2Ph$ (3d)	71
5	$CH_3(CH_2)_5CH_2I$ (2e)	$CH_3(CH_2)_5CH_2CF_2SO_2Ph$ (3e)	72
6	$C_6H_5(CH_2)_2CH_2I$ (2f)	$C_6H_5(CH_2)_2CH_2CF_2SO_2Ph$ (3f)	73
7	CH_2=$CHCH_2Br$ (2g)	CH_2=$CHCH_2CF_2SO_2Ph$ (3g)	57
8	$EtOOCCH_2Br$ (2h)	$EtOOCCH_2CF_2SO_2Ph$ (3h)	0
9	$C_6H_5CH_2Br$ (2i)	$C_6H_5CH_2CF_2SO_2Ph$ (3i)	84
10	4-MeO-$C_6H_4CH_2Br$ (2j)	4-MeO-$C_6H_4CH_2CF_2SO_2Ph$ (3j)	83
11	4-Ph-$C_6H_4CH_2Br$ (2k)	4-Ph-$C_6H_4CH_2CF_2SO_2Ph$ (3k)	79
12	1-Naphth-CH_2Br (2l)	1-Naphth-$CH_2CF_2SO_2Ph$ (3l)	77
13	4-Br-$C_6H_4CH_2Br$ (2m)	4-Br-$C_6H_4CH_2CF_2SO_2Ph$ (3m)	51
14	4-O_2N-$C_6H_4CH_2Br$ (2n)	4-O_2N-$C_6H_4CH_2CF_2SO_2Ph$ (3n)	Trace

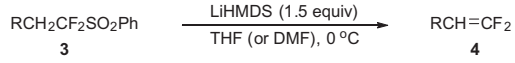
[a] Isolated yield.

Having achieved nucleophilic substitution of alkyl halides with $PhSO_2CF_2SiMe_3$, we turned our interest into the preparation of *gem*-difluoroalkenes by a base-mediated 1,2-elimination reaction from product **3**. According to the modified procedure using LiHMDS as a base,[17] *gem*-difluoroalkenes **4a**–**e** were obtained in moderate to excellent yields from **3f** and **3j**–**m** (Table 3).

With *gem*-difluoroalkenes **4** in hand, their further transformations were taken into account. In the presence of wet KF and 18-crown-6,[18] *gem*-difluoroalkenes such as **4b**–**e** gave trifluoromethylated products **5b**–**e** in moderate yields, but *gem*-difluoroalkene-containing aliphatic chain **4a** failed to give the CF_3-containing product **5a** (Table 4, entries 1–5). Considering that tetrabutylammonium fluoride (TBAF) can act both as a good nucleophilic fluorinating agent and as a phase-transfer catalyst (PTC), we applied TBAF to replace wet KF/18-crown-6 system in the reaction. Much to our delight, it was found that in the presence of TBAF, the transformation could smoothly proceed at ambient temperature to afford the desired products **5b**–**e** in satisfactory yields (Table 4, entries 2–5).[19]

In conclusion, an improved protocol to prepare *gem*-difluoroalkenes has been achieved by (phenylsulfonyl)difluoromethylation of alkyl halides using $PhSO_2CF_2SiMe_3$ (**1**) and subsequent base-mediated 1,2-elimination. Taking CsF/15-crown-5 as an initiating system in DME, (phenylsulfonyl)difluoromethylation of both simple alkyl iodides and activated alkyl bromides smoothly proceeded. It was found that the amount of additive 15-crown-5 was critical to the yield of the product. The prepared (phenylsulfonyl)difluoromethylated alkanes were converted into *gem*-difluoroalkenes by a base-mediated elimination reaction, and the latter species could be further transformed into trifluoromethyl compounds in the presence of wet KF/18-crown-6 or TBAF reagent.

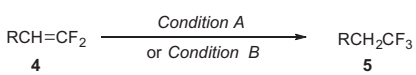
Table 3
Preparation of *gem*-difluoroalkenes **4a**–**e**



Entry	$RCH_2CF_2SO_2Ph$ (3)	RCH=CF_2 (4)	Yield[a] (%)
1	$C_6H_5(CH_2)_2CH_2CF_2SO_2Ph$ (3f)	$C_6H_5(CH_2)_2CH$=CF_2 (4a)	68[b]
2	4-MeO-$C_6H_4CH_2CF_2SO_2Ph$ (3j)	4-MeO-C_6H_4CH=CF_2 (4b)	78[b]
3	4-Ph-$C_6H_4CH_2CF_2SO_2Ph$ (3k)	4-Ph-C_6H_4CH=CF_2 (4c)	90
4	1-Naphth-$CH_2CF_2SO_2Ph$ (3l)	1-Naphth-CH=CF_2 (4d)	76
5	4-Br-$C_6H_4CH_2CF_2SO_2Ph$ (3m)	4-Br-C_6H_4CH=CF_2 (4e)	77

[a] Isolated yield.
[b] The reactions were carried out in DMF.

Table 4
Further transformations of *gem*-difluoroalkenes **4**



Condition A: KF, 18-crown-6, DMF(*wet*), 80–140 °C
Condition B: TBAF, THF, rt

Entry	RCH=CF_2 (4)	RCH_2CF_3 (5)	Yield[a] (%)
1	$C_6H_5(CH_2)_2CH$=CF_2 (4a)	$C_6H_5(CH_2)_2CH_2CF_3$ (5a)	0 (0)
2	4-MeO-C_6H_4CH=CF_2 (4b)	4-MeO-$C_6H_4CH_2CF_3$ (5b)	57[b] (56)
3	4-Ph-C_6H_4CH=CF_2 (4c)	4-Ph-$C_6H_4CH_2CF_3$ (5c)	58 (66)
4	1-Naphth-CH=CF_2 (4d)	1-Naphth-CH_2CF_3 (5d)	60 (55)
5	4-Br-C_6H_4CH=CF_2 (4e)	4-Br-$C_6H_4CH_2CF_3$ (5e)	64[b] (61[b])

[a] Isolated yield obtained by using either *condition A* or *condition B* (data in parentheses).
[b] Determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

Therefore, in certain cases, the (phenylsulfonyl)difluoromethyl functionality (in combination of an additional fluoride ion source) can be considered as a synthetic equivalent of trifluoromethyl group.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (20502029, 20772144, 20825209, 20832008) and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for financial support.

Supplementary data

Supplementary data (experimental procedures and spectroscopic data for all isolated new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.068.

References and notes

1. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991; (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity and Applications*; Wiley-VCH: Weinheim, 2004; (c) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, 2008.
2. (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–643; (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886; (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369; (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321; (e) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discov. Devel.* **2008**, *11*, 793–802.
3. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Biological Chemistry*; Wiley: New York, 1991; (b)*Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*; Chambers, R. D., Ed.; Springer: New York, 1997; (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006; (d) Ichikawa, J. In *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005.; (e) Ichikawa, J. In *Current Fluoroorganic Chemistry*; Soloshonok, V. A., Mikami, K., Yamazaki, T., Welch, J. T., Honek, J. F., Eds.; ACS Symposium Series 949; American Chemical Society: Washington, DC, 2007.
4. Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1437–1439.
5. (a) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS Symposium Series 456; American Chemical Society: Washington, DC, 1991.; (b) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360–361.; (c) Weintraub, P. M.; Holland, A. K.; Gates, C. A.; Moores, W. R.; Resvick, R. J.; Beye, P.; Peet, N. P. *Bioorg. Med. Chem.* **2003**, *11*, 427–431.
6. (a) Taguchi, T.; Kodama, Y.; Kanazawa, M. *Carbohydr. Res.* **1993**, *249*, 243–252; (b) Yamazaki, T.; Ueki, H.; Kitazume, T. *Chem. Commun.* **2002**, 2670–2671; (c) Ichikawa, J.; Miyazaki, H.; Sakoda, K.; Wada, Y. *J. Fluorine Chem.* **2004**, *125*, 585–593.
7. (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683; (b) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257–263.
8. (a) Naae, D. G.; Burton, D. J. *J. Fluorine Chem.* **1971**, *1*, 123–125; (b) Naae, D. G.; Burton, D. J. *Synth. Commun.* **1973**, *3*, 197–200.
9. (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186–193; (b) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *Tetrahedron Lett.* **1995**, *36*, 5003–5006; (c) Shi, G.-Q.; Huang, X.-H. *Tetrahedron Lett.* **1996**, *37*, 5401–5404.
10. Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444–1447.
11. Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5203–5206.
12. (a) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273–8277; (b) Liu, J.; Ni, C.; Wang, F.; Hu, J. *Tetrahedron Lett.* **2008**, *49*, 1605–1608.
13. (a) Tyrra, W.; Naumann, D.; Quadt, S.; Buslei, S.; Yagupolskii, Y. L.; Kremlev, M. M. *J. Fluorine Chem.* **2007**, *128*, 813–817; (b) Li, Y.; Hu, J. *J. Fluorine Chem.* **2008**, *129*, 382–385.
14. Previously, $PhSO_2CF_2$ group was known to act as synthetic equivalents of difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$) and difluoromethylidene ($=CF_2$) functionalities. See reviews: (a) Hu, J. *J. Fluorine Chem.* **2009**, *130*, 1130–1139; (b) Prakash, G. K. S.; Hu, J. *Acc. Chem. Soc.* **2007**, *40*, 921–930; (c) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465–7478.
15. Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Synlett* **2001**, 77–78.
16. *Typical experimental procedure for nucleophilic substitution of alkyl halides with* $PhSO_2CF_2SiMe_3$ (**1**): The reaction was carried out in a Schlenk flask under a nitrogen atmosphere. A solution of CsF (205 mg, 1.349 mmol) and 15-crown-5 (300 mg, 1.36 mmol) in DME (2 mL) was cooled to −20 °C (ice-sodium chloride) after stirring at room temperature for 10 min, then a mixture of $PhSO_2CF_2SiMe_3$ (**1**) (356 mg, 1.347 mmol) and ethyl iodide (105 mg, 0.675 mmol) in DME (1.2 mL) was slowly added to the reaction flask. The reaction temperature was allowed to warm to room temperature. When the reaction was completed by TLC, water (5 mL) was added to the mixture and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (EtOAc/PE = 1:50) to give product **3a** as colorless oil, 79% yield (117 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 2.4 Hz, 2H), 7.80−7.75 (m, 1H), 7.66−7.61 (m, 2H), 2.48−2.49 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.0 (t, J = 19.2 Hz, 2F) lit.[10]
17. Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 786–789.
18. (a) Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758–7764; (b) Lee, C.-C.; Lin, S.-T. *J. Chem. Res. (S)* **2000**, 142–144.
19. *Typical procedure for the preparation of compound* **5**: *Condition A*: A mixture of **4d** (151 mg, 0.794 mmol), KF (140 mg, 2.547 mmol), and 18-crown-6 ether in DMF (3 mL) containing water (0.15 mL) was stirred in sealed tube and heated at 140 °C for 10 h. The reaction mixture was poured into water and extracted with Et_2O. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether) to afford **5d** as white solid, 60% yield (100 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 1H), 7.90−7.86 (m, 2H), 7.60−7.46 (m, 4H), 3.86 (q, J = 10.7 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −65.1 (t, J = 10.3 Hz, 3F).
Condition B: Under N_2 atmosphere, to a solution of **4c** (109 mg, 0.500 mmol) in THF (3.8 mL) was added a solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 1.50 mL, 1.50 mmol) at room temperature and stirred for 24 h. The reaction was quenched with saturated NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether) to afford **5c** as white solid, 66% yield (78 mg). Mp: 80−81 °C. IR (film): 3000, 1568, 1490, 1411, 1363, 1251, 1147, 1073, 908, 853, 813, 763, 736, 691, 651 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.36 (m, 9H), 3.41 (q, J = 8.1 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, J = 10.9 Hz, 3F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 140.5, 130.55, 130.54, 120.1 (q, J = 2.8 Hz), 128.8, 127.5, 127.4, 127.1, 125.8 (q, J = 275.2 Hz), 39.8 (q, J = 29.5 Hz). MS (EI, m/z, %): 236 (M^+, 78), 167 (100). Anal. Calcd for $C_{14}H_{11}F_3$: C, 71.18; H, 4.69. Found: C, 71.17; H, 4.58.