Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 5795–5798

TETRAHEDRON LETTERS

A new family of delocalized lipophilic cations

Marielouise Henrich,[a] Albrecht Marhold,[a] Alexander A. Kolomeitsev,[b,*] Natalya Kalinovich[c] and Gerd-Volker Röschenthaler[c]

[a]*BCH-FCH-RD Fluorchemie, D-51368 Bayer AG, Leverkusen, Germany*
[b]*Institute of Organic Chemistry, Ukrainian National Academy of Sciences, Murmanskaya 6, 02094 Kiev, Ukraine*
[c]*Institut für Anorganische & Physikalische Chemie, Universität Bremen, Leobener Strasse, D-28334 Bremen, Germany*

Received 11 April 2003; accepted 7 June 2003

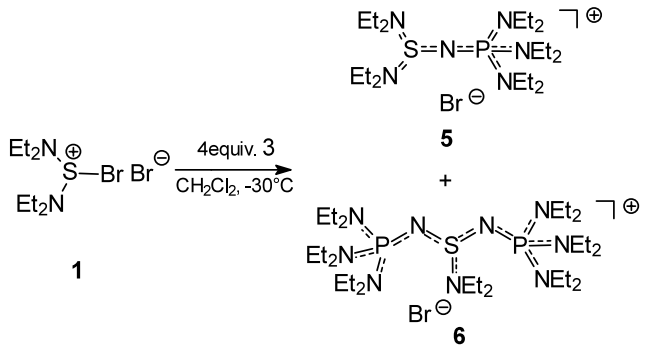
Abstract—A new family of delocalized lipophilic cations containing one to three carbimino, sulfimino and phosphinimino units with Cl^-, Br^-, HF_2^- and $Me_3SiF_2^-$ as counterions has been designed. The compounds synthesized demonstrate high performance and thermal stability in the 'Halex' fluorination reactions. For the first time sulfur tetrachloride pregenerated at −78°C was successfully applied in reactions with *N*-nucleophiles to afford straightforwardly sulfonium chlorides with three S–N bonds.

There is a growing interest in salts containing delocalized lipophilic cations (DLCs) due to their stability and high performance in numerous phase-transfer (PT) organic reactions proceeding under extreme conditions (e.g. high temperature, strongly basic media, powerful nucleophiles).[1,2] A new important aspect of their application is connected with the ability of some DLCs to selectively target mitochondria of carcinoma cells resulting in their selective killing. It is a novel and effective strategy intensely studied presently for the treatment of cancer.[3] Solid–liquid PT halogen exchange ('Halex' process) with alkaline fluorides is one of the two main techniques to produce selectively fluorinated aromatics on an industrial scale, complementary to diazotation of anilines in hydrogen fluoride or Schiemann reaction.[4,5] Potassium fluoride presenting an optimal ratio between cost and reactivity is the most widely used reagent for the industrial synthesis of fluoroaromatics. In most of the Halex-type reactions, the rate-determining step is the fluoride anion/substrate reaction to generate the anionic Meisenheimer complex. The sparing solubility of potassium fluoride in aprotic solvents or aromatic substrates even at elevated temperatures results in low fluorination rates and formation of by-products. To overcome this problem, the range of PT catalysts, conventional tetraalkylammonium, phosphonium, pyridinium salts, 18-crown-6 and polyethylene glycol were proposed.[5–7] Unfortunately, most of them show shortcomings, especially at elevated temperatures (ca. 200°C), that restrict their application on an industrial scale. Tetrakis(dialkylamino)phosphonium halides,[8] however, with the robust and lipophilic phosphonium cation, were evaluated as powerful catalysts for some Cl/F exchange reactions.[9] There are no universal catalysts of halogen exchange reactions; so far, the choice depends strongly on the chloroaromatic substrate used and the degree of halogen activation. There is still a growing need to create robust, easily recyclable, cheap and highly effective catalysts for this very important industrial process.

To improve the 'Halex' fluorination process, we have synthesized a range of new salts with symmetrical and nonsymmetrical backbones (C-N-P^+, C-N-S^+ and S-N-P^+), all fully substituted with dialkylamino groups.[10] Among these new salts and already known aminodiphosphazenium[11] and 2-azaallenium[12] halides, novel catalysts of high potential for solid–liquid PT halogen exchange with KF in chloroaromatic compounds were evaluated.[10] The present paper discloses the design of a new family of delocalized lipophilic halides for catalytic fluorination and furthermore hydrogen difluorides and difluorotrimethylsilicates as fluorinating reagents and Lewis bases easily soluble in aprotic solvents of general interest in organic and organofluorine chemistry. The key point of our route to thermally stable salts stable towards the highly basic fluorides for the 'Halex' process, was the consideration that the guanidyl and phosphoroaniminyl substituents being more effectively

Keywords: delocalized lipophilic cations; halogen exchange fluorination; aminosulfonium salts.
* Corresponding author. Fax: +49 421 2184267; e-mail: alex@chemie.uni-bremen.de

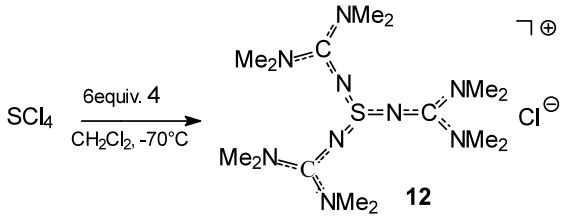
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01422-9



Scheme 1.

electron donating than the dialkylamino moieties,[13] should reduce the electrophilicity at carbon, sulfur and phosphorus and thus increase the stability of the respective onium salts under basic conditions. On this basis, the main building blocks used in the reaction with electrophilic halosulfonium halides, sulfur tetrachloride, chloroformamidinium chlorides and bis(dialkylamino)difluoromethanes were the cheap tetramethylguanidine and easily available tris(diethylamino)phosphazene.[14] For comparison, the respective reactions with diethylamine were also studied. Thus, we started reacting bis(diethylamino)bromosulfonium bromide (**1**) bis(diethylamino)chlorosulfonium chloride (**2**) pregenerated at −30°C with an excess of tris(diethylamino)phosphazene (**3**) (Scheme 1) and tetramethylguanidine (**4**) in methylene chloride (Table 1).

For (**1**) and tris(diethylamino)phosphazene (**3**) the conversion was quantitative during 2 h. After warming up to ambient temperature followed by basic work-up, a 1:4 mixture of bis-(diethylamino)-tris[(diethylamino)-phosphazeno)]sulfonium bromide (**5**) and diethylaminobis{tris[(diethylamino)phosphazeno)]}sulfonium bromide (**6**) has been obtained. Similarly, a 1:4 mixture of tetramethylguanido-substituted sulfonium chlorides (**7**, **8**) has been observed for the reaction of (**2**) with tetramethylguanidine (**4**) (Table 1). In contrast, (**1**) and diethylamine gave tris(diethylamino)sulfonium bromide (**9**) as the only reaction product. The yields of (**5–9**) were 93–97% based on bis(diethylamino)sulfur. Interestingly, but unfortunately, not only chlorine or



Scheme 2.

bromine, but also the dialkylamino function at the sulfonium center could be substituted by the phosphazo- and guanido- group, showing their high nucleophilicity. Sulfur tetrachloride (**10**), considered to be thermally unstable, is however, easily generated from sulfur dichloride and chlorine in 1:1 ratio at lower temperatures.

SCl_4 (**10**) and (**3**, **4**) and also diethylamine at −70°C react to give the tris[tris(diethylamino)phosphazeno]- (**11**), tris(tetramethylguanido)- (**12**),[15] and tris(diethylamino)sulfonium (**13**) chlorides in 95–97% isolated yields after basic workup (Scheme 2, Table 1). Recently SF_4, a toxic gas demanding special handling, has been used for the synthesis of tris(dialkylamino)sulfonium difluorotrimethylsilicates.[16] To the best of our knowledge there is no example of SCl_4 application for the synthesis of sulfonium salts. These methods could also simplify the synthesis of chiral triaminosulfonium salts recently developed for catalytic asymmetric anionic trifluoromethylation of carbonyl compounds.[17]

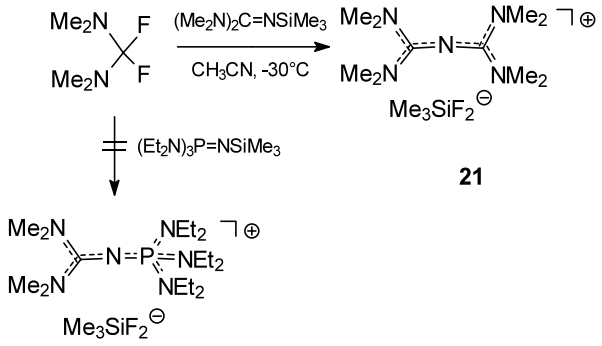
To accelerate the 'Halex' process, one should provide a high concentration of fluoride in solution by an anion exchange process. Most fluorides soluble in organic solvents (even in toluene, THF or dimethoxyethane) contain at least one phosphorus atom.[9,11,18–20] As far as salts $(Alk_2N)_4P^+Cl(Br)^-$ have proved to be effective 'Halex' catalysts, one can assume that substitution of the Alk_2N group at phosphorus for tetramethylguanidyl will not only increase the thermal and chemical stability of the phosphonium salt, but can also induce a more effective delocalization of the positive charge in $(Alk_2N)_3PNC(NAlk_2)_2^+$ as compared to $(Alk_2N)_4P^+$ $Cl(Br)^-$. Beside the increased cation stability

Table 1.

Entry	Substrate	Reagents	Products		Yield[a] (%)
1[b]	**1**	4 equiv. **3**	$(Et_2N)_2S[NP(NEt_2)_3]^+Br^-$	**5**	93
			$[(Et_2N)_3PN]_2S(NEt_2)^+Br^-$	**6**	**5**+**6**
2[b]	**2**	4 equiv. **4**	$(Et_2N)_2S[NC(NMe_2)_2]^+Cl^-$	**7**	95
			$(Et_2N)S[NC(NMe_2)_2]_2^+Cl^-$	**8**	**7**+**8**
3[b]	**1**	2 equiv. Et_2NH	$(Et_2N)_3S^+Br^-$	**9**	97
4[c]	**10**	3 equiv. **3** 4.5 equiv. Et_3N	$S[NP(NEt_2)_3]_3^+Cl^-$	**11**	95
5[c]	**10**	6 equiv. **4**	$S[NC(NMe_2)_3]_3^+Cl^-$	**12**	97
6[c]	**10**	6 equiv. Et_2NH	$(Et_2N)_3S^+Cl^-$	**13**	95

[a] Isolated yields.
[b] Reaction conditions for entries 1–3: CH_2Cl_2, −30°C, 2 h, then 20°C, 0.5 h.
[c] Reaction conditions for entries 4–6: CH_2Cl_2, −70°C, warming up to 20°C within 2 h.

under strongly basic 'Halex' conditions, these delocalized cations do much better to stabilize the intermediate Meisenheimer complex, thus increasing the rate of aromatic fluorination. It was found that tetramethylchloro-formamidinium (**14**) and 2-chloro-1,3-dimethylimidazolidinium (**15**) chlorides react smoothly in methylene chloride at −20 to 20°C with 2 equiv. of tris(diethylamino)phosphazene (or 1 equiv. $(Et_2N)_3P{=}NH$ and 1.5 equiv. of Et_3N) to afford the target carbophosphazenium salts (**16**, **17**) in 97 and 99% isolated yield, respectively, after treating the reaction mixtures with sodium methoxide and separation of tris(diethylamino)phosphazene or triethylamine (Table 2). The 2-azaallenium chlorides, $(Alk_2N)_2CNC(NAlk_2)_2^+Cl^-$,[12] also proved to be catalysts of choice for the 'Halex' reaction.[10] Bis(dimethylamino)difluoromethane (**18**) and 2,2-difluoro-1,3-dimethyl-imidazoline[21] (**19**), recently successfully used for the synthesis of hexaalkyl guanidinium difluorotrimethylsilicates,[22] could be also used for designing salts with $(Alk_2N)_3PNC(NAlk_2)_2^+$ and $(Alk_2N)_2CNC(NAlk_2)_2^+$ cations. Indeed, *N*-trimethylsilyl guanidine (**20**) smoothly reacted with (**18**) and (**19**) at −30 to 20°C in CH_3CN to give difluorotrimethylsilicates (**21**, **22**) (Table 2).[23] These compounds enrich the class of tris(dialkylamino)sulfonium- and hexaalkylguanidinium difluorotrimethylsilicates, known as useful fluorinating agents and applied also for the synthesis of perfluoroalkyloxy- and perfluoroalkylthiosubstituted organic compounds.[16,22] *N*-Trimethylsilyl-tris(diethylamino)phosphazene surprisingly does not react with 2,2-difluoro-1,3-dimethyl- imidazoline or bis(dimethylamino)difluoromethane even on heating in various aprotic solvents (Scheme 3). Tris(diethylamino)phosphazene (**3**), however reacts with (**18**, **19**) to afford carbophosphazenium hydrogen difluorides (**23**, **24**)[24] as the only reaction products (Table 2).

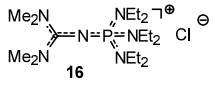
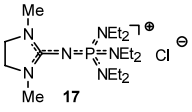
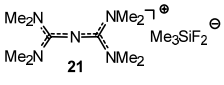
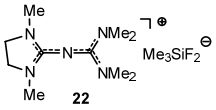
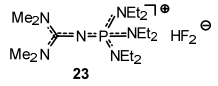
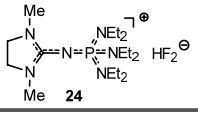


Scheme 3.

The onium hydrogen difluorides with lipophilic cations, i.e., $Bu_4P^+HF_2^-$, $(Alk_2N)_4P^+HF_2^-$ or $Bu_4N^+HF_2^-$, are known as effective and mild fluorinating agents.[1,18,19] Compound (**23**), presumably, is a very important reactive intermediate responsible for the catalytic action of $(Et_2N)_3PNC(NMe_2)_2^+Cl^-$ by the 'Halex' process performed in C–H acidic aprotic solvents (i.e. DMSO is the solvent of choice for 'Halex'). It could be generated in situ from $(Et_2N)_3PNC(NMe_2)_2^+F^-$, produced by ion exchange reaction from $(Et_2N)_3PNC(NMe_2)_2^+Cl^-$ and KF at elevated temperature, in the course of the 'Halex' reaction followed by the solvent deprotonation with the highly basic fluoride ion.

In summary, we have found a simple synthesis of a new family of robust 'Halex' catalysts and new fluorinating agents with DLCs of potential interest as PT catalysts in general organic and for the use in medicinal chemistry. Detailed studies of the application of these new salts for the synthesis of weakly solvated fluorides with new DLCs are in progress.

Table 2.

Entry	Substrate	Reagents	Products	Yield [a] (%)
7[b]	**14**	1 equiv. **3** 1.5 equiv. Et_3N	 **16**	97
8[b]	**15**	"	 **17**	99
9[c]	**18**	1 equiv. **20**	 **21**	98
10[c]	**19**	"	 **22**	95
11[d]	**18**	1 equiv. **3**	 **23**	92
12[d]	**19**	"	 **24**	95

[a] Isolated yields. [b] Reaction conditions for entries 7, 8: CH_2Cl_2, -20°C, 2 h, then 20°C, 0.5 h. [c] Reaction conditions for entries 9, 10: CH_3CN, -30°C, then 20°C, 2 h. [d] Reaction conditions for entries 11, 12: CH_2Cl_2, -30°C, 2 h, then 20°C, 0.5 h.

Acknowledgements

Natalya Kalinovich thanks the Friedrich Ebert Foundation for a fellowship.

References

1. (a) Albanese, D.; Landini, D.; Maia, A.; Penso, M. *Ind. Eng. Chem. Res.* **2001**, *40*, 2396–2401; (b) Albanese, D.; Landini, D.; Maia, A.; Penso, M. *J. Mol. Catal. A: Chem.* **1999**, *150*, 113–131; (c) Mąkosza, M.; Bujok, R. *Tetrahedron Lett.* **2002**, *43*, 2761–2763.
2. Dehmlow, E. V.; Knufinke, V. *J. Chem. Res. (A)* **1989**, 224–225.
3. (a) Fantin, V. R.; Berardi, M. J.; Scorrano, L.; Korsmeyer, S. J.; Leder, P. *Cancer Cell* **2002**, *2*, 29–42; (b) Modica-Napolitano, J. S.; Aprille, J. R. *Adv. Drug Deliv. Rev.* **2001**, *49*, 63–70.

4. Langlois, B.; Gilbert, L.; Forat, G. In *Industrial Chemistry Library*; Desmurs, J.-R.; Ratton, S., Eds.; Elsevier: Amsterdam, 1996; Vol. 8, pp. 244–292.
5. (a) Clark, H. J.; Wails, D.; Bastock, T. W. *Aromatic Fluorinations*; CRC Press: New York, 1996; (b) For recent developments see: Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225–231.
6. Sasson, Y.; Negussie, S.; Royz, M.; Mushkin, N. *J. Chem. Soc., Chem. Commun.* **1996**, 297–298.
7. Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. *J. Am. Chem. Soc.* **1990**, *112*, 7619–7625.
8. (a) Issleib, K.; Lischewski, M. *Synth. Inorg. Met. Org. Chem.* **1973**, *3*, 255–264; (b) Koidan, G. N.; Marchenko, A. P.; Kudryavtsev, A. A.; Pinchuk, A. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1982**, *52*, 1779–1787; (c) Marchenko, A. P.; Koidan, G. N.; Povolotskii, M. I.; Pinchuk, A. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 1364–1368.
9. (a) Pazenok, S. V.; Kolomeitsev, A. A. Pat. WO 98, 05, 610 (to Aventis Research & Technologies GmbH & Co), February, 12, 1998; *Chem. Abstr.* **1998**, *128*, 252250a; (b) Kolomeitsev, A. A.; Yagupolskii, Y. L.; Yagupolskii, L. M.; Pazenok, S. V.; Appel, W. K.; Pfirmann, R.; Wessel, T. *12th European Symposium on Fluorine Chemistry*, Berlin, Germany, **1998**, Abstract PII-83; (c) Kolomeitsev, A. A.; Kirij, N. V.; Pazenok, S. V.; Appel, W. K.; Röschenthaler, G.-V. *14th Winter Fluorine Conference*; St. Petersburg, Florida, **1999**, Abstract 37, p. 26.
10. (a) Henrich, M.; Marhold, A.; Kolomeitsev, A. A.; Röschenthaler, G.-V. DE 10129057/EP 1266904 (to Bayer AG), December, 18, 2002; (b) Simultaneously to this patent application, the use of symmetrical and nonsymmetrical diphosphazenium salts as highly effective PT catalysts for halogen exchange aromatic fluorination has been claimed: Schanen, V.; Cristau, H.-J.; Taillefer, M. WO 02092226 (to Rhodia Chimie), November, 21, 2002.
11. (a) Marchenko, A. P.; Koidan, G. N.; Pinchuk, A. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 583–589; (b) Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honnert, D.; Limbach, H. H.; Männle, F. *Angew. Chem.* **1991**, *103*, 1376–1378.
12. Hamed, A.; Mueller, E.; Jochims, J. C. *Tetrahedron* **1986**, *42*, 6645–6656.
13. Koppel, I. A.; Schwesinger, R.; Breuer, T.; Burk, P.; Herodes, K.; Koppel, I.; Leito, I.; Mishima, M. *J. Phys. Chem. A* **2001**, *105*, 9575–9586.
14. Marchenko, A. P.; Koidan, G. N.; Kudryavtsev, A. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1979**, *50*, 679–680.
15. *Tris(tetramethylguanido)sulfonium chloride* (**12**). To a stirred solution of sulfur dichloride (10.0 g, 97.1 mmol) in dichloromethane (100 mL) at −78°C was condensed chlorine (6.9 g, 97.1 mmol) and the mixture was stirred for 5 min at this temperature. Then the tetramethylguanidine (69.0 g, 600 mmol) was added in portions to keep the reaction temperature below −70°C. The reaction mixture was allowed to warm to room temperature within 2 h. The solvent was pumped off in vacuo, the residue cooled to 0°C, treated with sodium methoxide (15.7 g, 291.3 mmol) in methanol (120 mL) and the reaction mixture allowed to warm to 22°C. The solvent and tetramethylguanidine were removed in vacuo (0.05 Torr). Dissolving the residue in methylene chloride followed by the filtration from sodium chloride and evaporation of the solvent in vacuo gave (**12**) (38.6 g, 97%, mp 115–116°C, purity 96.5%). Recrystallization from THF/ether at −30°C led in 92% yield to the analytically pure compound. ^{1}H NMR (200.13 MHz, $CDCl_3$, ppm): δ 2.8 (s, 18H,). ^{13}C NMR (50.33 MHz, $CDCl_3$): δ 40.9 (CH_3, CH_3N), 165.0 (C=N). HRMS m/z 374,28257 (M^+, calcd for $C_{15}H_{36}N_9S$: 374,28144).
16. Middleton, W. J. US 3940402 (to E. I. Du Pont de Nemours & Co), February, 24, 1976; *Chem. Abstr.* **1976**, *85*, 6388j.
17. Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231–8234.
18. (a) Seto, H.; Qian, Z.; Yoshioka, H.; Uchibori, Y.; Umeno, M. *Chem. Lett.* **1991**, 1185–1188; (b) Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953–955.
19. Kolomeitsev, A. A.; Bissky, G.; Lork, E.; Movchun, V. N.; Rusanov, E.; Kirsch, P.; Röschenthaler, G.-V. *J. Chem. Soc., Chem. Commun.* **1999**, 1017–1019.
20. Grushin, V. *Angew.Chem.* **1998**, *110*, 1042–1044.
21. Sonoda, H.; Okada, K.; Goto, K.; Fukumura, K.; Naruse, J.; Nagata, T.; Takanashi, A. EP 949226 (to Mitsui Chemicals, Inc.), October, 13, 1999; *Chem. Abstr.* **1999**, *131*, 271696c.
22. Kolomeitsev, A. A.; Bissky, G.; Barten, J.; Kalinovich, N.; Lork, E.; Röschenthaler, G.-V. *Inorg. Chem.* **2002**, *41*, 6118–6124.
23. *N - [Bis(dimethylamino)methylene][bis - (dimethylamino)]-methane-iminium difluorotrimethylsilicate* (**21**). To a stirred solution of *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-(trimethylsilyl)-guanidine (0.74 g, 4 mmol) in CH_3CN (5 mL) kept at −30°C was added 0.55 g (4 mmol) of 2,2-difluoro-1,3-dimethylimidazolidine. The mixture was allowed to warm to 22°C and stirred for 2 h at the ambient temperature. The solvent was pumped off in vacuo (0.05 Torr) till dryness and the residue washed two times with diethyl ether (2×5 mL) to leave a colorless solid, which was dried in vacuo 0.05 mbar for 0.5 h at 0°C to give 1.27 g (98.0%) of (**21**), which contained 4.9% impurity of *N*-[bis(dimethyl-amino)-methylene] - [bis(dimethylamino)] - methane-iminium-hydrogendifluoride. Recrystallization from CH_3CN/ether at −30°C gave 1.1 g (85%) of analytically pure (**21**) mp 74–75°C. ^{1}H NMR (200.13 MHz, CD_3CN): δ 0.29 (s, 9H), 2.9 (s, CH_3, 24H). ^{19}F NMR (188.31 MHz, CD_3CN): δ −61.1 (s, Me_3SiF_2, 2F). ^{13}C NMR (50.33 MHz, CD_3CN): δ 6.7 (s, Me_3SiF_2), 40.3 (s, CH_3), 165.7 (s, C^+). MS FAB (+): 214 (M^+, 100). Anal. calcd for $C_{13}H_{33}F_2N_5Si$: C, 47.97; H, 10.22; N, 21.52. Found: C, 47.49; H, 10.02; N, 21.85.
24. *3,3,3-Tris(diethylamino)-2,6-dimethyl-2,4,6-triaza-3-phosphonia-4-heptenhydrogendifluoride* (**23**). To a solution of *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexaethylphosphonimidic triamide (0.91 g, 3.48 mmol) in dichloromethane (3 mL) cooled to −30°C was added portionwise 0.48 g (3.48 mmol) of bis(dimethylamino)difluoromethane. The mixture was allowed to warm up to 22°C and stirred for 5 h at ambient temperature. Removal of the solvent (vacuo 0.05 Torr) followed by washing of the residue with diethyl ether (2×5 mL) gave 1.28 g (92%) of (**23**) as a pale yellow solid. Mp 36–37°C. ^{1}H NMR (200.13 MHz, CD_3CN): δ 1.1 (t, $^{3}J_{HH}$=7.0 Hz, 18H), 2.9 (s, 12H), 3.1 (dq, $^{3}J_{HH}$=7.0 Hz, $^{3}J_{HP}$=11.0 Hz, 12H), 16.0 (br.s, 1H). ^{19}F NMR (188.31 MHz, CD_3CN): δ −149.6 (d, $^{2}J_{FH}$=120.3 Hz, 2F). ^{13}C NMR (50.33 MHz, CD_3CN): δ 13.3, 39.8, 47.0, 160.9. ^{31}P NMR (81.00 MHz, CD_3CN): δ 20.4 (s, 1P). MS FAB (+): 361 (M^+, 100). Anal. calcd for $C_{17}H_{43}F_2N_6P$: C, 50.98; H, 10.82; N, 20.98. Found: C, 50.59; H, 10.89; N, 20.85.