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Discovery of 4-*tert*-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity

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Abstract: Versatile, safe, shelf-stable, and easy-to-handle fluorinating agents are strongly desired in both academic and industrial arenas, since fluorinated compounds have attracted considerable interest in many areas, such as drug discovery, due to the unique effects of fluorine atoms when incorporated into molecules. This article describes the synthesis, properties, and reactivity of many substituted and thermally stable phenylsulfur trifluorides, in particular, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead, **1k**), as a crystalline solid having surprisingly high stability on contact with water and superior utility as a deoxofluorinating agent compared to current reagents, such as DAST and its analogues. The roles of substiuents on **1k** in thermal and hydrolytic stability, fluorination reactivity, and the high-yield fluorination mechanism it undergoes have been clarified. In addition to fluorinations of alcohols, aldehydes, and enolizable ketones, **1k** smoothly converts non-enolizable carbonyls to CF_2 groups, and carboxylic groups to CF_3 groups, in high yields. **1k** also converts C(=S) and $CH_3SC(=S)O$ groups to CF_2 and CF_3O groups, respectively, in high yields. In addition, **1k** effects highly stereoselective deoxofluoro-arylsulfinylation of diols and amino alcohols to give fluoroalkyl arylsulfinates and arylsulfinamides, with complete inversion of configuration at fluorine and the simultaneous, selective formation of one conformational isomer at the sulfoxide sulfur atom. Considering the unique and diverse properties, relative safety, and ease of handling of **1k** in addition to its convenient synthesis, it is expected to find considerable use as a novel fluorinating agent in both academic and industrial arenas.

Introduction

Fluorine has an increasingly important role in medicinal chemistry and drug design, as it often imparts enhanced biological activity, metabolic stability, binding interaction, or other desirable changes in physical properties to drug molecules.[1] Therefore, extensive studies have been conducted on fluorination, and thus many fluorinating agents have been developed so far.[2] Among them, deoxofluorinating agents that replace an oxygen atom in a molecule with a fluorine atom(s) are particularly useful because an endless number of natural and synthetic oxygen-containing compounds such as alcohols, aldehydes, ketones, and carboxylic acids are available.

Initially, in 1960, sulfur tetrafluoride (SF_4) was used successfully for deoxofluorination of aldehydes, ketones, and carboxylic acids, giving $-CF_2H$, $-CF_2-$, and $-CF_3$, respectively.[3] However, its strongly toxic and gaseous nature has prevented its widespread use as a reagent among synthetic organic chemists. In the 1970s, reactive and liquid dialkylaminosulfur trifluorides, represented by diethylaminosulfur trifluoride (Et_2NSF_3, or DAST), were developed as an alternative to gaseous SF_4.[4] Since then, although it fumes in air and reacts explosively on contact with water, DAST has been used widely due to its excellent capability for deoxofluorination of alcohols, aldehydes, and ketones.[5,6] However, one serious defect of DAST is that it is thermally unstable, and its explosive nature has precluded applications in elevated temperature reactions and large-scale reactions, in addition to requiring necessary shipping

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(1) (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: New York, 2009. (b) Bégué, J.-P., Bonnet-Delpon, D., *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: New York, 2008. (c) Tressaud, A.; Haufe, G. *Fluorine and Health—Molecular Imaging, Biomedical Materials and Pharmaceuticals*; Elsevier: Amsterdam, 2008.
(2) (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1755. (b) Kirsch, P. *Modern Fluoroorganic Chemistry—Synthesis, Reactivity, Applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004. (c) *Advances in Organic Synthesis*, Vol. 2; Atta-Ur-Rahman, Laali, K. K., Eds.; Bentham Science Publishers Ltd.: Oak Park, IL, 2006. (d) *New Fluorinating Agents in Organic Syntheses*; German, L., Zemskov, S., Eds.; Springer-Verlag: New York, 1989.
(3) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, *82*, 543–551.
(4) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578. (b) Markovsku, L. N.; Pashinnik, V. E.; Kirsanov, A. V. *Synthesis* **1973**, 787–789.
(5) Reviews: (a) Hudlický, M. *Org. React.* **1988**, *35*, 513–637. (b) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561–2578. (c) Singh, R. P.; Meshri, D. T.; Shreeve, J. M. In *Advances in Organic Synthesis Vol. 2, Modern Organofluorine Chemistry—Synthetic Aspects*; Atta-Ur-Rahman, Laali, K. K., Eds.; Bentham Science Publishers Ltd.: Hilversum, Netherlands, 2006; pp 291–326.
(6) For recent papers, see ref S1 in the Supporting Information.

restrictions.[7] Moreover, with DAST it is difficult to fluorinate certain ketones such as non-enolizable ketones,[8] and it does not convert carboxylic acids to $-CF_3$. An analogue, bis(methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor reagent, Air Products and Chemicals, Inc.), with enhanced thermal stability, has been developed.[9,10] It is a liquid which fumes in air and has reactivity similar to that of DAST. A continuous process using a microreactor was recently developed for hazardous reactions with DAST or Deoxo-Fluor.[11] Most recently, crystalline dialkylamidodifluorosulfinium tetrafluoroborate ($[R_2N^+{=}SF_2]BF_4^-$), which does not fume and is more thermally stable than DAST and Deoxo-Fluor, has been recognized as a useful deoxofluorinating agent when combined with triethylamine tris(hydrogen fluoride) ($Et_3N(HF)_3$).[12] However, the actual reactive species might in fact be dialkylaminosulfur trifluoride, which can be formed by the reaction of F^- in $Et_3N(HF)_3$ $[Et_3NH^+F^-(HF)_2]$ with the amidodifluorosulfinium salt, since $Et_3N(HF)_3$ has a pH close to neutral and is a weak nucleophile and fluoride donor.[13,14]

Many other deoxofluorinating agents are known. Fluoroamine reagents such as Et_2NCF_2CFHCl (Yarovenko reagent),[15] $Et_2NCF_2CFHCF_3$ (Ishikawa reagent),[16] 2,2-difluoro-*N,N′*-dimethylimidazolidine (DFI),[17] 1,1,2,2-tetrafluoroethyl-*N,N*-dimethylamine,[18] and *N,N*-diethyl-α,α-difluoro-(*m*-methylbenzyl)amine[19] are useful for fluorination of alcohols. However, these fluoroamine reagents have limited scope because of limited applicability to the fluorinations of carbonyl functions. In addition, Ph_3PF_2[20] and a method using *n*-perfluorobutanesulfonyl fluoride/DBU[21] have been developed for fluorination of alcohols.

In 1960, shortly after the report of fluorination with SF_4, liquid phenylsulfur trifluoride ($PhSF_3$) was synthesized and its reactivity evaluated, showing that $PhSF_3$ was useful for arylaldehydes such as benzaldehyde but not effective for alkylaldehydes, ketones, and carboxylic acids due to low reactivity and yields.[22] Since the discovery of DAST as mentioned above, phenylsulfur trifluoride has been mostly ignored, except for a report in 1981 that it fluorinated chlolesterol in good yield under certain limited reaction conditions, as it proceeded via a specific homoallyl cation intermediate.[23] However, *p*-nitrophenylsulfur trifluoride did not give any fluorinated products, but rather an ether product.[23]

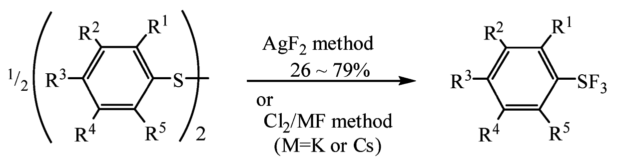
The recent developing need for a safe, reactive, and selective fluorinating agent for use by non-fluorine organic chemists in many areas stimulated us to develop a new deoxofluorinating agent with both high reactivity and high stability, properties which are generally in conflict. Thermal analysis studies of DAST and related R_2NSF_3 compounds[7b] indicate that decomposition of these aminosulfur trifluorides occurs in two stages. A slow reaction is seen at 90 °C with evolution of gaseous SF_4 and formation of a bis(dialkylamino)sulfur difluoride ($(R_2N)_2SF_2$) by a disproportionation reaction. On heating to higher temperatures, the samples explode or detonate, resulting in a black tar and unidentified gaseous products. The enhanced thermal stability of Deoxo-Fluor is rationalized on the basis of conformational rigidity imposed by coordination of the alkoxyl groups with the electron-deficient sulfur atom of the trifluoride. However, the stability of Deoxo-Fluor is not significantly better than that of DAST. The onset of decompostion is almost the same for both compounds (~140 °C), but DAST degrades much more rapidly and with larger heat evolution (1700 vs 1100 J/g for Deoxo-Fluor), and Deoxo-Fluor shows a more gradual exotherm over a wider temperature range. These results indicate that Deoxo-Fluor is more stable than DAST but without significant improvements.

In our attempt to develop new and upgraded deoxofluorinating agents, we desired to prepare arylsulfur trifluorides that would not yield significant gaseous byproducts on thermal decomposition. Compared to aminosulfur trifluoride, arylsulfur trifluorides have several prominent advantages. First, the C−S bond (714 ± 1.2 kJ/mol) is much stronger than the N−S bond (464 ± 21 kJ/mol).[24] This would make arylsulfur trifluoride more stable than aminosulfur trifluoride, as the N−S bond cleavage accounts for the decomposition of aminosulfur trifluoride.[7b] Second, arylsulfur trifluorides are more easily tunable by altering the substituents on the aryl ring. The stability and reactivity of arylsulfur trifluorides may be controlled by employing different substituents on the phenyl ring. The reactivity of phenylsulfur trifluoride may be increased with addition of electron-donating substituents.

This article now describes the clues that led us to the discovery of a new, reactive deoxofluorinating agent and its synthesis, high thermal stability, unexpected resistance to water, high fluorinating capability, and extensive potential applications, including direct conversion of carboxyl groups to trifluoromethyl

(7) (a) Cochran, J. *Chem. Eng. News* **1979**, *57* (March 19), 4. (b) Messina, P. A.; Mange, K. C.; Middleton, W. J. *J. Fluorine Chem.* **1989**, *42*, 137–143.
(8) (a) Chang, Y.; Tewari, A.; Adi, A.-I.; Bae, C. *Tetrahedron* **2008**, *64*, 9837–9842. (b) Kirsh, P.; Bremer, M.; Huber, F.; Lannert, H.; Ruhl, A.; Lieb, M.; Wallmichrath, T. *J. Am. Chem. Soc.* **2001**, *123*, 5414–5417. (c) Kiryanov, A. A.; Seed, A. J.; Sampson, P. *Tetrahedron* **2001**, *57*, 5757–5767.
(9) (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *Chem. Commun.* **1999**, 215–216. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054. (c) Lal, G. S.; Lobach, E.; Evans, A. *J. Org. Chem.* **2000**, *65*, 4830–4832.
(10) For other papers, see ref S2 in the Supporting Information.
(11) Negi, D. S.; Köppling, L.; Lovis, K.; Abdallah, R.; Geisler, J.; Budde, U. *Org. Process Res. Dev.* **2008**, *12*, 345–348.
(12) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050–5053. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401–3411.
(13) (a) Saluzzo, C.; Alvernhe, G.; Anker, D. *J. Fluorine Chem.* **1990**, *47*, 467–479. (b) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31–35.
(14) The ^{19}F NMR peak of SF_3 of DAST was not observed in the presence of $Et_3N(HF)_3$ because of rapid equilibrium between conformations: A broad peak at 26 ppm due to SF_3 was observed in ^{19}F NMR (300 MHz) of DAST in anhydrous $CDCl_3$, but the broad peak was not observed in ^{19}F NMR of a 1:1 mole ratio mixture of DAST and $Et_3N(HF)_3$ in anhydrous $CDCl_3$.
(15) Yarovenko, N. N.; Raksha, M. A.; Shemanina, V. N.; Vasileva, A. S. *J. Gen. Chem. USSR* **1957**, *27*, 2246.
(16) Takaoka, A.; Iwakiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377–3380.
(17) Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618–1619.
(18) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. *J. Fluorine Chem.* **2001**, *109*, 25–31.
(19) Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron* **2004**, *60*, 6923–6930.
(20) Kobayashi, Y.; Akashi, C. *Chem. Pharm. Bull.* **1968**, *16*, 1009–1013.
(21) (a) Bennua-Skalmowski, B.; Vorbrüggen, H. *Tetrahedron Lett.* **1995**, *36*, 2611–2614. (b) Decréau, R. A.; Marson, C. M. *Synth. Commun.* **2004**, *34*, 4369–4385. (c) Yin, J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. K. *Org. Lett.* **2004**, *6*, 1465–1468.
(22) (a) Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751–4752. (b) Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3058–3063.
(23) Wei-Yuan, H.; Cai-Yun, G. *Acta Chim. Sin.* **1981**, *39*, 63–68.
(24) *CRC Handbook of Chemistry and Physics*, 85th ed.; CRC Press, LLC: Boca Raton, FL, 2004−2005.

Scheme 1



2 → 1

a; $R^{1\sim5}$=H
b; $R^{1,2,4,5}$=H, R^3=CH_3
c; $R^{1,3}$=CH_3, $R^{2,4,5}$=H
d; $R^{1,4}$=CH_3, $R^{2,3,5}$=H
e; $R^{1,5}$=CH_3, $R^{2\text{-}4}$=H
f; $R^{1,3,5}$=CH_3, $R^{2,4}$=H
g; $R^{1,2,4,5}$=H, R^3=$C(CH_3)_3$
h; $R^{1,2,4,5}$=H, R^3=F
i; $R^{1,2,4,5}$=H, R^3=Cl
j; $R^{1,4,5}$=H, R^2=CH_3, R^3=Cl
k; $R^{1,5}$=CH_3, $R^{2,4}$=H, R_3=$C(CH_3)_3$
l; $R^{1,5}$=CH_3, R^2=Cl, R^3=$C(CH_3)_3$, R^4=H
m; $R^{1,5}$=CH_3, $R^{2,4}$=Cl, R^3=$C(CH_3)_3$
n; $R^{1,3,5}$=$CH(CH_3)_2$, $R^{2,4}$=H
o; $R^{1,5}$=CH_2OCH_3, $R^{2\sim4}$=H
p; $R^{1,5}$=CH_2OCH_3, $R^{2,4}$=H, R^3=$C(CH_3)_3$
q; $R^{1,5}$=$CH_2OC_2H_5$, $R^{2,4}$=H, R^3=$C(CH_3)_3$
r; $R^{1,5}$=$CH_2OCH(CH_3)_2$, $R^{2,4}$=H, R^3=$C(CH_3)_3$
s; $R^{1,5}$=$CH_2OCH_2CF_3$, $R^{2,4}$=H, R^3=$C(CH_3)_3$
t; $R^{1,5}$=$CH_2OCH(CF_3)_2$, $R^{2,4}$=H, R^3=$C(CH_3)_3$

groups and new, stereoselective deoxofluoro-arylsulfinylations of diols and amino alcohols.

Results and Discussion

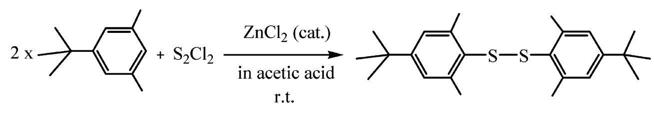
Synthesis of Substituted Phenylsulfur Trifluorides. There are several methods for the synthesis of arylsulfur trifluorides. All of them employ the oxidation of diaryl disulfide or arylthiol by various oxidative reagents, such as F_2/N_2,[25,26] AgF_2,[22] XeF_2,[27] or the Cl_2/KF method.[28] To investigate our hypothesis that phenylsulfur trifluoride may be activated by an electron-donating substituent(s) on the phenyl ring, we synthesized a number of new substituted phenylsulfur trifluorides, **1c**−**t**, in addition to the known **1a**,**b** by two procedures, one employing AgF_2 and the other using Cl_2/KF or CsF method as shown in Scheme 1.

First, we synthesized a series of arylsulfur trifluorides by the reaction of aryl disulfides **2** with a suspension of AgF_2 in 1,1,2-trichlorotrifluoroethane in a fluoropolymer bottle. The substituent on the phenyl ring affects the reaction rate. Generally, an electron-donating group accelerates the reaction rate, and an electron-withdrawing group retards it. For example, the reaction of diphenyl disulfide (**2a**) with AgF_2 is complete in 1 h, and the mono- and multi-alkyl-substituted diaryl disulfides **2b**−**g**,**k**−**n** react faster than **2a**. As expected, bis(4-chlorophenyl) disulfide (**2j**) reacts slower and needs 2 h for complete reaction. Bis(4-fluorophenyl) disulfide (**2h**) has the same reaction rate as **2a**, because the fluorine contributes electron density through p−π conjugation. It seemed that methoxymethyl derivatives **2o**,**p** reacted with AgF_2 almost similarly to **2a**. Fluoroalkoxy derivatives **2s**,**t** reacted with AgF_2 very slowly.

The arylsulfur trifluorides were also prepared by reaction of diaryl disulfides with Cl_2 in the presence of KF[28] or CsF. Thus, Cl_2 gas was introduced into a mixture of a disulfide and a metal fluoride in acetonitrile at ice bath temperature to room temperature. With Cl_2 flowing, the color of the reaction mixture changed from white to orange, and then yellow, and finally white. By the Cl_2/KF or CsF method, diaryl disulfides **2** provided the corresponding expected products **1** except that bis(3-methylphenyl) disulfide gave an unexpected product, 4-chloro-

(25) Chambers, R. D.; Holling, D.; Spink, R. C. H.; Sandford, G. *Lab Chip* **2001**, *1*, 132–137.
(26) Chamberlain, D. L.; Kharasch, N. *J. Am. Chem. Soc.* **1955**, *77*, 1041–1045.
(27) Ou, X.; Janzen, A. F. *J. Fluorine Chem.* **2000**, *101*, 279–283.
(28) Pashinnik, V. E.; Martyniuk, E. G.; Tabachuk, M. R.; Shermolovich, Y. G.; Yagupolskii, L. M. *Synth. Commun.* **2003**, *33*, 2505–2509.

Scheme 2



2k

3-methylphenylsulfur trifluoride (**1j**), which was produced by simultaneous chlorination at the 4-position by Cl_2. This is probably due to the activation of the 4-position by the electron-donating 3-methyl group. Reaction on bis(4-methoxyphenyl) disulfide and bis[4-(*N*,*N*-dimethylamino)phenyl] disulfide failed. The methoxy substituent resulted in formation of a complex mixture, and the strongly electron-donating dimethylamino substituent led to a different complex reaction, possibly an oxidation reaction, as strong coloring was observed.

The procedure involving Cl_2/KF or CsF requires a rigorously dry atmosphere and conditions due to the use of an acetonitrile solvent which absorbs moisture readily, in contrast to the AgF_2 method which uses a hydrophobic fluoro solvent. If the reaction mixture or sample is contaminated with moisture or traces of hydrolyzed impurity, it may show a bluish color.

Most arylsulfur trifluorides are moisture-sensitive, colorless liquids that are stable when stored at room temperature in a container made of an inert material such as fluoropolymer. By careful exclusion of moisture, the preparation and distillation of arylsulfur trifluorides may be carried out in Pyrex glass equipment.

As mentioned below, we found that **1k** was the best fluorinating agent from the viewpoint of reactivity and stability of the arylsulfur trifluorides synthesized. Its large-scale production was successfully conducted by the economical Cl_2/KF method using a 20 L glass reactor, applying the small-scale conditions to a large-scale production. White crystalline powder **1k** was obtained in 82% yield from 1.0 kg of starting material **2k**. All procedures and handling were done under a rigorously dry atmosphere.

Preparation of Diaryl Disulfides 2 as Starting Materials. We found that bulky, multi-alkylated diaryl disulfides such as bis(4-*tert*-butyl-2,6-dimethylphenyl) disulfide (**2k**) and bis(2,4,6-triisopropylphenyl) disulfide (**2n**) are directly and simply prepared in high yields from aromatic hydrocarbons and sulfur monochloride (S_2Cl_2). As shown in Scheme 2, 1-*tert*-butyl-3,5-dimethylbenzene reacted with an equivalent amount of S_2Cl_2 in acetic acid at room temperature in the presence of a catalytic amount of $ZnCl_2$ for 4 h to produce **2k** in 79% isolated yield. The similar catalytic reaction of 1,3,5-triisopropylbenzene with S_2Cl_2 in acetic acid at 60 °C gave **2n** in 70% yield.

It is known that trimethylbenzenes or more multi-methylated benzenes react with S_2Cl_2 in ether at room temperature to give a mixture of the corresponding diaryl di-, tri-, and/or tetrasulfides [Ar−$(S)_n$−Ar, $n = 2,3,4$] owing to easy cleavage of a S−S bond.[29] Reaction of 1,3,5-mesitylene with S_2Cl_2 in the presence of a Lewis acid produced dimesityl monosulfide (Ar−S−Ar) as the main product.[30] Therefore, it is noteworthy that the $ZnCl_2$-catalyzed reactions of bulky multi-alkylated benzenes and S_2Cl_2 produce diaryl disulfides in high yields.

^{19}F and ^{1}H NMR of Arylsulfur Trifluorides. The structure of SF_3 in arylsulfur trifluorides has been determined to be trigonal-bipyramidal (Figure 1) by ^{19}F NMR analysis of (pentafluo-

(29) Ariyan, Z. S.; Wiles, L. A. *J. Chem. Soc.* **1961**, 4510–4514.
(30) Yoshifuji, M.; Tanaka, S.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2607–2608.

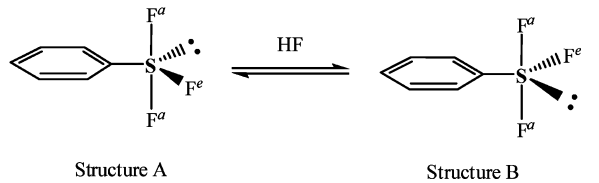
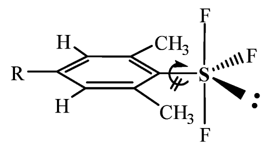


Figure 1



R=H (**1e**), CH_3 (**1f**), *t*-Bu (**1k**)

Figure 2

rophenyl)sulfur trifluoride.[31] It has been reported that broad singlets of SF_3 of phenylsulfur trifluoride in chloroform appear as a doublet and a triplet of intensity 2:1 on cooling.[22b] We found that the solvent has a strong effect on the NMR spectra of arylsulfur trifluorides. For example, when we add a fraction of anhydrous diethyl ether into the NMR tube (giving CD_3CN/Et_2O, 3/1 v/v), the two broad peaks (53 ppm 2F and −57 ppm 1F) of **1k** in CD_3CN become sharp and give a prominent split of a doublet and a triplet. This shows the trigonal-bipyramidal structure of SF_3 which exists in equilibrium between structures A and B with two apical fluorine atoms (F^a) and an equatorial fluorine atom (F^e), as can be seen in Figure 1.

Apparently, the electron-donating ability of lone-pair electrons of oxygen in diethyl ether or THF accounts for this phenomenon. The oxygen in ether binds with traces of contaminating HF, which may catalyze the exchange between structures A and B,[31c] or coordinates with an electron-deficient sulfur atom of arylsulfur trifluoride, fixing the fast equilibrium. Thus, two nonequivalent *ortho*-methyl groups and two *meta*-hydrogen atoms of **1e**, **1f**, and **1k** were observed in the ^1H NMR spectra (CD_3CN/THF-d_8). This also indicates that rotation of the C−S bond is hindered (Figure 2).

Thermal Stability of Arylsulfur Trifluorides. Thermal stabilities of a series of arylsulfur trifluorides were examined by differential scanning calorimetry (DSC). Phenylsulfur trifluoride (**1a**) has much higher decomposition temperature and smaller exothermal heat ($-\Delta H$) than DAST or Deoxo-Fluor. **1a** has decomposition temperature 305 °C and $-\Delta H = 826$ J/g, whereas DAST has ∼140 °C and 1700 J/g, and Deoxo-Fluor has ∼140 °C and 1100 J/g.[9a] The high stability of phenylsulfur trifluoride probably results from the strong C−S bond compared to the weak N−S bond of DAST and Deoxo-Fluor. The stability of phenylsulfur trifluoride **1a** (305 °C) changes with substitution on the phenyl ring. Substitution with a methyl group lowers the decomposition temperature, as seen in the 4-methyl derivative **1b** (273 °C), 2,6-dimethyl **1e** (222 °C), and 2,4,6-trimethyl **1f** (209 °C). Substituents such as isopropyl and methoxymethyl groups also result in a lowering of the decomposition temperature, as seen in 2,4,6-triisopropyl **1n** (215 °C) and 2,6-bis(methoxymethyl) **1o** (175 °C). On the contrary, it is significant that a *tert*-butyl group increases the stability, as seen in 4-*tert*-butyl **1g** (319 °C) compared to unsubstituted **1a** (305 °C), in 4-*tert*-butyl-2,6-dimethyl **1k** (232 °C) compared to 2,6-dimethyl **1e** (222 °C), and in 4-*tert*-butyl-2,6-bis(methoxymethyl) **1p** (214 °C) compared to 2,6-bis(methoxymethyl) **1o** (175 °C). The destabilization by methyl, isopropyl, and methoxymethyl groups at the *o*- or *p*-position can be explained by possible dehydrofluorination to an *o*- or *p*-quinoid compound **3** at high temperatures, as exemplified in Scheme 3. The increased high thermal stability imparted by a *tert*-butyl group can be explained by its lack of an α-proton and its steric bulkiness. The absence of an α-proton prevents a quinoid decomposition process, and the bulkiness may retard decomposition such as polymerization of the aromatic rings, as will be discussed below. Remarkably, a bulky group such as isopropoxymethyl **1r** (259 °C) and electron-withdrawing groups such as trifluoroethoxymethyl **1s** (224 °C) and hexafluoroisopropoxymethyl **1t** (241 °C) increase the stability.

(31) (a) Sheppard, W. A.; Foster, S. S. *J. Fluorine Chem.* **1972/73**, *2*, 53–62. (b) Sheppard, W. A.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 1919–1923. (c) Meakin, P.; Ovenall, D. W.; Sheppard, W. A.; Jesson, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 522–528.

Scheme 3. Possible Decomposition Mechanism of Arylsulfur Trifluorides

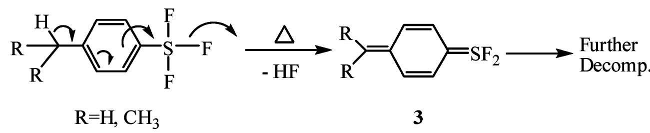
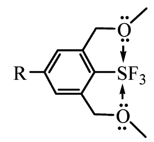


Chart 1. Fluolead on Water

Stability of Arylsulfur Trifluorides on Contact with Water. Arylsulfur trifluorides react with water to form hydrolysis products such as arylsulfinyl fluorides and their further hydrolyzed compounds. The relative stabilities were examined by observing the change when a few drops or solid (20−50 mg) of an arylsulfur trifluoride were dropped onto water (with no stirring). When a drop of DAST or Deoxo-Fluor was added onto water, reaction was instant and very vigorous, accompanied by a loud sound and a lot of fuming. When phenylsulfur trifluoride (**1a**) and its 4-methyl analogue **1b** were contacted with water similarly, they reacted vigorously, with moderate sound and fuming. However, surprisingly, when 4-*tert*-butyl-2,6-dimethyl **1k** (Fluolead) was dropped onto water, nothing happened apparently, as shown in Chart 1. The hydrolysis reaction was slow, as no evident reaction was observed in 10 min. The bulky *tert*-butyl group at the 4-position has a significant role, because 4-*tert*-butyl **1g** did not change for about 1 min after it was dropped onto water and the hydrolysis was slow. Rapid reaction between 2,4,6-trimethyl **1f** and water started after several seconds. Therefore, the surprisingly high stability of **1k** against water can be explained by steric protection of SF_3 by a



R=H **1o**
=*t*-Bu **1p**

Figure 3

Table 1. Fluorination of Benzyl Alcohol with $ArSF_3$[a]

$$PhCH_2OH + ArSF_3 \xrightarrow[\text{in } CH_2Cl_2]{\text{rt, 2 h}} PhCH_2F + ArS(O)F$$

run	$ArSF_3$	yield[b] (%) of $PhCH_2F$[c]
1	**1a**	25
2	**1b**	19
3	**1d**	46
4	**1e**	40
5	**1f**	38
6	**1g**	52
7	**1i**	37
8	**1k**	88
9	**1m**	90
10	**1n**	46
11	**1o**	95
12	**1p**	90
13	**1q**	78
14	**1r**	83
15	**1s**	58
16	**1t**	56

[a] Fluorination was conducted in a dilute solution ($PhCH_2OH$ 0.2 mmol/1 mL of solvent). [b] Yields were determined by ^{19}F NMR. [c] Reference 4.

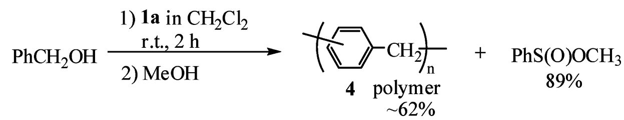
hydrophobic *tert*-butyl and two dimethyl groups.[32] 2,4,6-Triisopropyl **1n** also showed high stability, similar to **1k**.

2,6-Bis(methoxymethyl) **1o** showed a significant stability on contact with water, as hydrolysis started only after ca. 45 s. This suggests that the two ether oxygen atoms stabilize an electron-deficient SF_3 by coordination, as shown in Figure 3. This kind of effect was suggested to explain the improved thermal stability of Deoxo-Fluor.[9b] 4-*tert*-Butyl-2,6-bis(methoxymethyl) **1p** showed additional stability due to the hydrophobic *tert*-butyl group. Its hydrolysis was observed after ca. 5 min.

Fluorination Reactivity of Arylsulfur Trifluorides. Relative fluorination reactivities of the arylsulfur trifluorides synthesized were examined by reaction with benzyl alcohol at room temperature for 2 h, as shown in Table 1. Unsubstituted **1a** and 4-methyl derivative **1b** gave very low yields of benzyl fluoride (25% and 19%). Interestingly, these reaction solutions became strongly colored. Dimethyl derivatives **1d** and **1e** gave better yields (46, 40%), but 2,4,6-trimethyl derivative **1f** gave no improvement (run 5, 38%). However, 4-*tert*-butyl **1g** gave a much better yield (52%) than 4-methyl **1b** (19%). This suggested to us that a bulky substituent is important. Thus, 4-*tert*-butyl-2,6-dimethyl **1k** provided a high yield (88%) of benzyl fluoride. It is clear that a bulky 4-*tert*-butyl group has a significant role, in addition to the methyl groups at the 2- and 6-positions. Fully substituted **1m** provided a similarly high yield (run 9, 90%). 2,4,6-Triisopropyl **1n** gave a lower yield (run 10, 46%) than **1k** and **1m**, probably due to slow reaction because of the steric hindrance around SF_3. Both 2,6-bis(methoxymethyl) **1o** and 4-*tert*-butyl-2,6-bis(methoxymethyl) derivative **1p** gave high yields of the product (runs 11 and 12). This is quite different from the case of 2,6-dimethyl **1e** and 4-*tert*-butyl-2,6-dimethyl **1k**, in which **1e** gave much lower yield than **1k** (runs 4 and 8). The high yield with **1o** can be explained by the lone-pair electrons of oxygen atoms of the methoxymethyl groups, which may block the cationic benzylation to the phenyl ring followed by polymerization, as will be discussed below.

(32) ***Caution!*** Water should never be added into a large amount of solid **1k**. Heat generated by partial hydrolysis may induce vigorous decomposition of the rest of **1k**.

Scheme 4. Reaction of $PhSF_3$ (**1a**) and Benzyl Alcohol



As shown in Scheme 4, the reaction of unsubstituted **1a** with benzyl alcohol was found to produce a large amount of polymeric compound (solid) and methyl phenylsulfinate after treatment with methanol. ^{19}F NMR of the solid showed no fluorine, and its ^{1}H NMR showed broad peaks at 6.6−7.4 and 3.6−4.1 ppm. As the former peak was assigned to aromatic protons and the latter to benzyl-type protons, the solid product was identified as a polymer having a main unit of ($-C_6H_4CH_2-$).

Formation of the polymer from **1a** strongly suggests that the high yield of fluorination with **1k** is largely due to the *tert*-butyl group of **1k**, because the bulky substituent inhibits the participation of the activated phenyl ring in the polymerization reaction, as shown as route *b* in Scheme 5. In addition, the electron-donating effect of the *tert*-butyl and two methyl groups should contribute to the formation of ionic intermediate **8** rather than **7**. The sulfur-cationic intermediate **8** results in easy formation of the fluorination product, as shown as route *a*. The two methyl groups may interfere with formation of **10**, which may lead to an ether byproduct, through some steric hindrance (route *c*). An ether byproduct was reported to be formed as a main product in the reaction of a steroidal alcohol with 4-nitrophenylsulfur trifluoride rather than phenylsulfur trifluoride (**1a**).[23] It is thus less likely that the intermediate **7** or **8** of multi-alkylated phenylsulfur trifluoride **1k** reacts with benzyl alcohol to give an ether byproduct (route *d*). Dibenzyl ether was detected in a trace amount by GC-MS from the reaction of benzyl alcohol with **1k**. It is clear that both the 4-*tert*-butyl and 2,4-dimethyl groups of **1k** make significant contributions, sterically and electronically, to the high yields of the fluorinated products observed.

Fluorinations of Various Kinds of Organic Compounds with 1k.[33] We have selected **1k** as a particularly useful deoxofluorinating agent among many arylsulfur trifluorides synthesized and extensively examined its fluorinating capability. Table 2 shows typical examples of fluorination reactions with **1k**. Fluorination of *trans*-4-hydroxyprolinonitrile **11** with **1k** produced *cis*-4-fluoroprolinonitrile **12** in high yield (run 1). This clearly indicates that the fluorination proceeds in an inversion manner. The reaction of D-glucopyranose **13** produced 96:4 mixtures of α- and β-fluoro products **14** (run 2). It has been reported that treatment of **13** with DAST[34] and Deoxo-Fluor[9a] produced a 11:89 and 28:72 mixture of α- and β-isomers of **14**, respectively. Cyclohexanone **15** was fluorinated with **1k** in the presence of HF−pyridine to give a 99:1 mixture of di-F product **16** and mono-F-olefin **17** in high yield (run 3). DAST

(33) See the Supporting Information for detailed results and discussion.
(34) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5–8.

Scheme 5. Reaction Mechanism of Benzyl Alcohol with **1k**

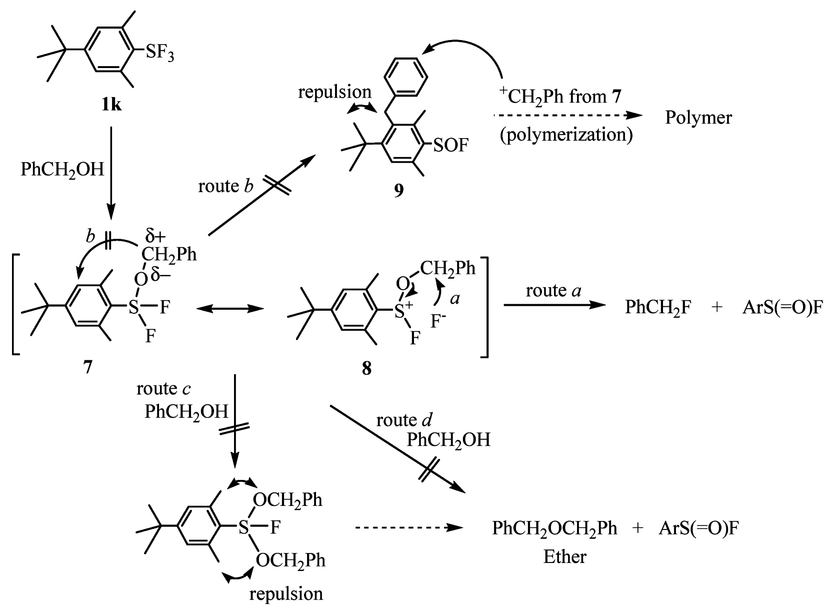
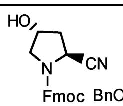
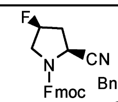
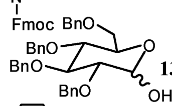
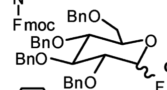
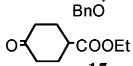
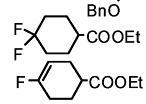
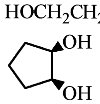
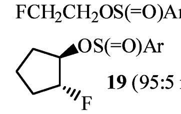
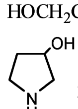
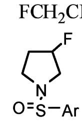


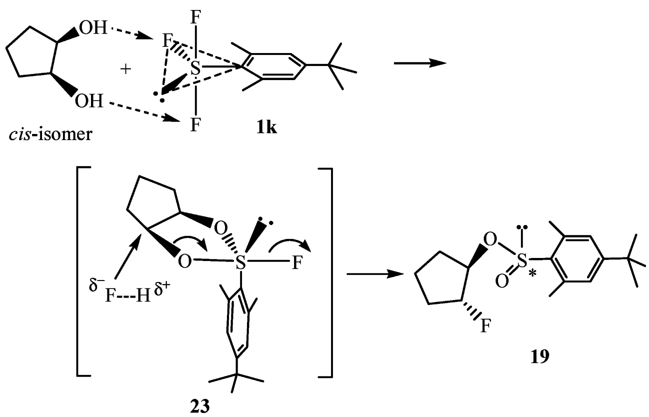
Table 2. Fluorination of Various Compounds with **1k**

Run	Substrate	$ArSF_3$(eq)[a]	Additive (eq)[a]	Conditions[b]	Products[c]	Y(%)[d]
1	 **11**[f]	**1k**(1.5)	-	in DCM, 0 °C 1 h->r.t. 60 h	 **12**	85
2	 **13**[g]	**1k**(1.5)	-	in DCM, r.t. 2 h	 **14**[h] α/β=96/4	84(99[e])
3	 **15**	**1k**(1.5)	HF-py(0.4)	in DCM, 0 °C->r.t. 3 h	 **16**[i](99) **17**[i](1)	81
4	Fluorenone	**1k**(1.5)	HF-py(1.7)	in DCM, r.t. 24 h	9,9-Difluorofluorene[j]	70
5	PhCOCOPh	**1k**(2.5)	HF-py(0.8)	in DCM, r.r. 24 h	$PhCF_2CF_2Ph$[k]	88
6	n-$C_{11}H_{23}COOH$	**1k**(3)	HF-py(2.9)	50 °C, 24 h	n-$C_{11}H_{23}CF_3$[l]	91
7	PhCOOH	**1k**(3)	-	100 °C, 3 h	$PhCF_3$	100[e]
8	Cinnamic acid	**1k**(3)	-	100 °C, 3 h	*trans*-PhCH=CHCF$_3$[m]	75
9	$HOCO(CH_2)_8COOH$	**1k**(6)	-	100 °C, 8 h	$CF_3(CH_2)_8CF_3$[l]	95
10	n-$C_{10}H_{21}OC(=S)SMe$	**1k**(3)	$SbCl_3$(0.05)	in DCM, 0 °C->r.t. 1 h	n-$C_{10}H_{21}OCF_3$[n]	90
11	PhOC(=S)SMe	**1k**(5)	$SbCl_3$(0.05)	in DCM, 65 °C 20 h[o]	$PhOCF_3$	100[e]
12	$HOCH_2CH_2OH$	**1k**(1)	Et_3N(2)	in DCM, r.t. 15 h	$FCH_2CH_2OS(=O)Ar$ **18**	91
13		**1k**(1)	-	in DCM, -60 °C->0 °C 2 h ->reflux 17 h	 **19** (95:5 mixture)[p]	95
14	$HOCH_2CH_2NHCH_3$	**1k**(1)	*Step 1:* $Et_3N(HF)_3$(0.5) in DCE, 75 °C 5 min; *Step 2*: Et_3N(3.6) in DCE, r.t. 1 h		$FCH_2CH_2N(CH_3)S(=O)Ar$ **20**	65(70[e])
15	 **21**[q]	**1k**(1.3)	*Step 1*: HF-py(0.8) in DCM, r.t. 4 h; *Step 2*: Et3N(22) in DCM, r.t. 2 h		 **22**[r] (1:1 mixture)[p]	85(100[e])
16	**21**[q]	**1k**(1)	Et_3N(2)	in DCM, reflux 10 h	**22** (1:0.66 mixture)[p]	72

[a] The amount used of $ArSF_3$ or an additive is shown relative to substrate. HF-py (density 1.1, available from Sigma-Aldrich) was a 7:3 w/w mixture of anhydrous HF and pyridine, and its molecular weight was regarded to be 263, formulated as $C_5H_5N(HF)_{9.2}$. [b] rt, room temperature; DCM, dichloromethane; DCE, 1,2-dichloroethane. [c] Ar, 4-*tert*-butyl-2,6-dimethylphenyl. The figures in parentheses are formation ratios. [d] Isolated yields except for the ones indicated by *e*. [e] Yields determined by ^{19}F NMR. [f] (2*S*,4*R*)-*N*-Fmoc-4-hydroxyprolinonitrile. [g] 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose. [h] Posner, G. H.; Halnes, S. R. *Tetrahedron Lett.* **1985**, *26*, 1823−1826. [i] Reference 35. [j] Marko, Z.; Zvonko, B.; Stojan, S. *Bull. Chem. Technol. Macedonia* **1994**, *13*, 97−98. [k] Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 6263−6267. [l] Reference 3. [m] Fuchikami, T.; Yatabe, M.; Ojima, I. *Synthesis* **1981**, 365−366. [n] Kuroboshi, M.; Suzuki, K.; Hiyama, T. *Tetrahedron Lett.* **1992**, *33*, 4173−4176. [o] A sealed fluoropolymer reactor was used. [p] Mixture of diastereomers. [q] Racemic 3-hydroxypyrrolidine. [r] NMR chart no. **22a**.

and Deoxo-Fluor produced 2.6:1 and 1.5:1 mixtures of **16** and **17** in 79% and 94% yield, respectively.[35] **1k** fluorinated non-enolizable ketones and diketones such as fluorenone and benzil under very mild conditions, giving high yields of the difluoro and tetrafluoro products (runs 4 and 5). It is noteworthy that **1k** has an excellent ability to convert a carboxyl group to a CF_3 group, as there have been no useful reagents for direct conversion of a carboxyl group to a CF_3 group, except for SF_4[3]

Scheme 6



and MoF_6.[36] As seen in runs 6−9, carboxylic acids were converted to the CF_3 compounds in high yields. Aliphatic and aromatic dithiocarbonates were smoothly fluorinated with **1k** in the presence of $SbCl_3$ as a catalyst, giving the respective CF_3O compounds in high yield (runs 10 and 11).

Remarkably, **1k** reacted with ethylene glycol at room temperature to produce a fluoroethyl arylsulfinate **18** in high yield (Run 12). The reaction with *cis*-cyclopentane-1,2-diol gave *trans*-2-fluoro-1-(arylsulfinyloxy)cyclopentane **19**, which was demonstrated to be a 95:5 mixture of two diasteromers on the basis of the conformation of the sulfoxide sulfur atom. This high stereoselectivity can be explained by a mechanism via intermediate **23**, as shown in Scheme 6.

When an amino alcohol was treated by a two-step method, treatment with **1k** and $Et_3N(HF)_3$ followed by treatment with Et_3N, *N*-arylsulfinyl fluoro product **20** was obtained in good yield (run 14). Hydroxypyrrolidine **21** was treated with **1k** by the two-step method using HF−pyridine instead of $Et_3N(HF)_3$ to give product **22** as a 1:1 mixture of diastereomers in high yield (run 15), while **21** was reacted with **1k** in the presence of triethylamine (2 equiv) to directly give **22** as a 1:0.66 mixture of the diastereomers in 72% yield (run 16). The latter one-step method can be rationalized if the reaction proceeds via a cyclic intermediate like **23**.

Conclusion

We have synthesized many variously substituted phenylsulfur trifluorides and clarified their stability, reactivity, and fluorination mechanism as a function of the steric and electronic nature of substituents and their positions and combinations on the phenyl ring. Thus, we have discovered and characterized 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (**1k**) and related compounds which have versatile fluorination capability as deoxofluorinating agents in addition to possessing high thermal stability and unusual resistance to aqueous hydrolysis. **1k** fluorinates alcohols, aldehydes, ketones, diketones, keto esters, keto amides, and carboxylic acids to give the corresponding monofluoro, difluoro, and trifluoro products. **1k** also successfully fluorinates various thiocarbonyl compounds. Furthermore, **1k** undergoes new, stereoselective deoxofluoro-arylsulfinylation with diols and amino alcohols, which provides fluoroalkyl arylsulfinates and arylsulfinamides having specified stereochemistry at both the fluorine atom and the sulfur atom. In addition, **1k** can be produced in only two steps from 5-*tert*-butyl-*m*-xylene, a commodity chemical. Therefore, **1k** is expected to have wide utility as a safe, easy-to-handle, reactive, and selective fluorinating agent for a wide variety of substrates in many diverse fields.

Acknowledgment. We thank UBE Industries, Ltd. in Japan for research funds for this work. We thank Lloyd Garrick for technical contribution. We thank Dr. Hideya Yoshitake and Dr. Shigeyoshi Nishino of UBE Industries, Ltd. for support of this project.

Supporting Information Available: Fluorination reactions of various compounds with **1k** along with some results with **1n**, **1o**, **1p**, **1s**, and **1t**; some applications of the fluorinated products; full experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) Fukumura, K.; Sonoda, H.; Hayashi, H.; Kusumoto, M. U.S. Patent 6,686,509 B2, Feb 3, 2004.

(36) (a) Van DerPuy, M. *J. Fluorine Chem.* **1979**, *13*, 375. (b) Shustov, L. D.; Nikolenko, L. N.; Senchenkova, T. M. *Zh. Obshch. Kim* **1983**, *53*, 103; *Chem. Abstr.* **1983**, *98*, 143326v.