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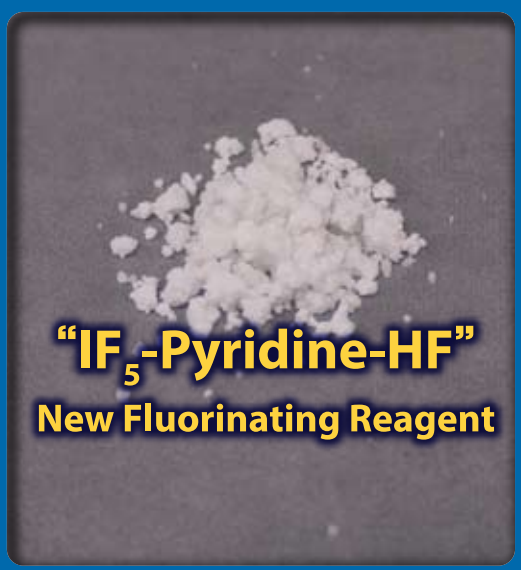

CONTENTS

TCI

Research Article

A New Air-stable Fluorinating Reagent, IF_5-pyridine-HF

Shoji Hara

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1. Introduction

Hypervalent iodine fluorides have been used as oxidants as well as fluorinating reagents. Among them, iodotoluene difluoride (*p*-TolIF_2), is the most popular fluorinating reagent because it can be prepared without hazardous F_2 gas, and stable enough to be used without special knowledge and techniques.[1]

On the other hand, iodine pentafluoride (IF_5) is not as popular as *p*-TolIF_2 because F_2 gas is used in its preparation and it decomposes in air by moisture emitting corrosive HF. Therefore, we studied fluorination reactions using the hypervalent iodine reagent *p*-TolIF_2.[1b,1e-g] After several years, we became interested in IF_5 because it is more reactive than *p*-TolIF_2, even though more hazardous than *p*-TolIF_2. During the studies using IF_5, we found that IF_5 can be used for the introduction of a fluorine atom into the α-position of a sulfur group in sulfides,[2] and desulfurizing difluorination of benzylic sulfides.[3] We also found a unique fluorination reaction of aryl alkyl sulfide with IF_5 where poly-fluorination took place under migration of the arylsulfanyl group.[4] Thus, we showed that IF_5 can be used as a fluorinating reagent, and moreover, a unique new fluorination reaction was developed using IF_5. However, a serious drawback of IF_5 is that it is difficult to obtain. Its instability made its commercial availability difficult. Therefore, we made a new stable fluorinating reagent from IF_5.

2. Development of IF_5-pyridine-HF

To make a stable fluorinating reagent from IF_5, many additives were investigated. When pyridine-HF (1:1 complex) was added to IF_5, a white solid was formed.[5] The white solid is moisture-stable and non-hygroscopic, and therefore, can be handled in air without decomposition. The white solid was poorly soluble in non-polar solvents such as hexane and CH_2Cl_2, and soluble in polar solvents, such as acetonitrile. Next, the white solid was applied to several fluorination reactions, and found to be a suitable fluorinating reagent.

The precise structure of the white solid is unclear, because its X-ray crystal structure analysis is still unsuccessful. However, the weight of the generated white solid is 95% of the total weight of the starting materials used in its synthesis. Therefore, the proposed molecular formula, IF_5-pyridine-HF, should be correct.

3. Fluorination reactions using IF_5-pyridine-HF

3-1. Fluorination of sulfide at α-position

When a sulfide (**1**) was added to a suspension of IF_5-pyridine-HF in CH_2Cl_2, the mixture changed to dark red color and fluorination took place at the α-position of the sulfur group to give a fluorinated product (**2**)[5] (eq. 1). In the reaction of **1** with IF_5, three fluorine atoms were introduced under the same conditions,[4] whereas only one fluorine atom was introduced in the reaction with IF_5-pyridine-HF. Therefore, IF_5-pyridine-HF was found to be less reactive than IF_5 itself.

3-2. Desulfurizing difluorination of benzylic sulfide[5]

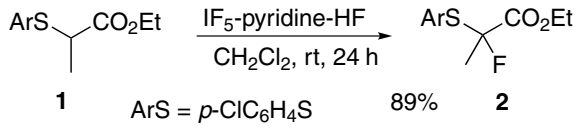
In the reaction of a benzylic sulfide having an electron-withdrawing group (**3**), the fluorination at the α-position of the sulfur group, followed by the substitution of a fluoride with the sulfur group took place to give a *gem*-difluoride (**4**) (eq. 2).

3-3. Synthesis of *gem*-difluoride from aldehyde dithioacetal and ketone dithioketal[5]

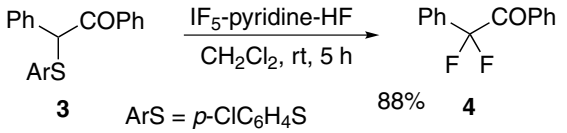
When an aldehyde dithioacetal (**5**) was reacted with IF_5-pyridine-HF, a *gem*-difluoride (**6**) was formed (eq. 3). The dithioacetal or dithioketal of a carbonyl compound without α-hydrogen can be applied to this reaction. When the dithioketal of a ketone has an α-hydrogen, a *poly*-fluorination reaction occurred as shown in section 3-11.

3-4. Introduction of a trifluoromethyl group into an aromatic ring[5]

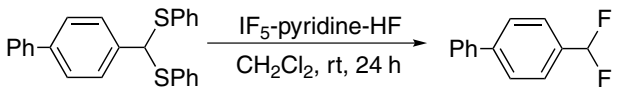
The introduction of a methylsulfanyl group into an aromatic aldehyde dithioacetal (**7**), followed by the reaction with IF_5-pyridine-HF gave a trifluoromethylated aromatic compound (**8**) (eq. 4).



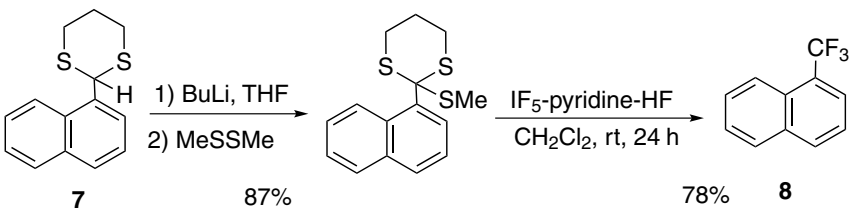
1 ArS = *p*-ClC_6H_4S 89% **2** (1)



3 ArS = *p*-ClC_6H_4S 88% **4** (2)



5 91% **6** (3)



7 87% 78% **8** (4)

3-5. Synthesis of (methylsulfanyl)difluoromethyl ether and trifluoromethyl ether from alcohol and phenol dithiocarbonates[6]

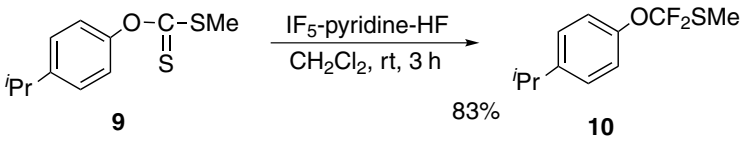
When a dithiocarbonate (**9**) was reacted with IF_5-pyridine-HF, the corresponding (methylsulfanyl)difluoromethyl ether (**10**) was selectively formed. On the other hand, when the reaction was carried out in the presence of Et_3N-6HF, the corresponding trifluoromethyl ether (**11**) was selectively formed (eq. 5).

This reaction can be applied to the dithiocarbonate of aliphatic alcohols, and a liquid crystal material having a trifluoromethoxy group (**12**) was synthesized (eq. 6).

3-6. Fluoromethyl ether synthesis[7]

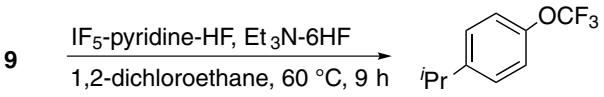
(Methylsulfanyl)methyl ether is known as a protecting group of hydroxy groups. A (methylsulfanyl)methyl ether of phenol (**13**) was converted to the corresponding fluoromethyl ether (**14**) by the reaction with IF_5-pyridine-HF (eq 7). This reaction can be applied to the (methylsulfanyl)methyl ether of phenols and aliphatic alcohols.

A fluoromethyl ether of an amino acid derivative (**15**), a potential PET tracer, was prepared by the reaction with IF_5-pyridine-HF (eq. 8).

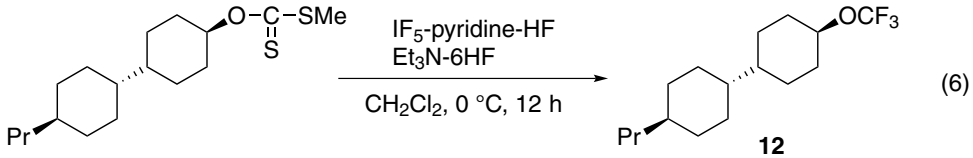


9 83% **10**

(5)

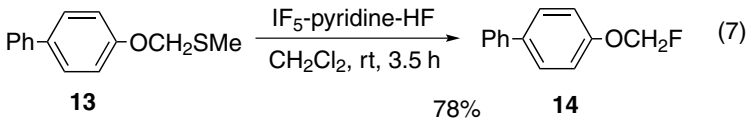


74% **11**



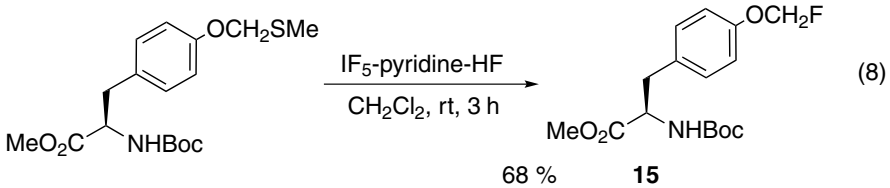
65% **12**

(6)



13 78% **14**

(7)



68 % **15**

(8)

3-7. Glycosyl fluoride synthesis[8]

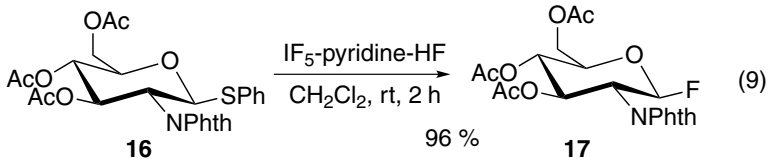
Glycosyl fluoride is used as a key intermediate for *poly*-saccharide synthesis, and has been prepared from the corresponding (phenylsulfanyl)glycoside by the reaction with a fluorinating reagent and an oxidant. On the other hand, the application of IF_5-pyridine-HF alone was sufficient to convert (phenylsulfanyl)glycoside (**16**) to the corresponding glycosyl fluoride (**17**) (eq. 9). This reaction can be used for the synthesis of furanose, pyranose, and disaccharide derivatives.

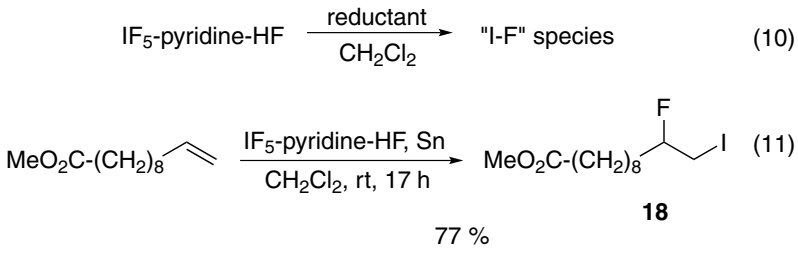
3-8. Generation of "IF" species and its application to the iodofluoroalkane synthesis[9]

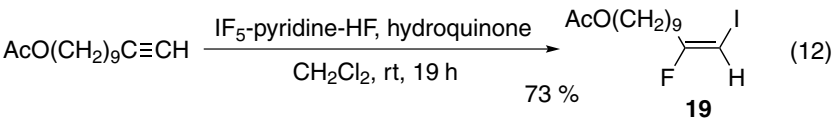
The "IF" species has been conveniently generated by several methods, such as by the reaction of I_2 with F_2, and used for the addition reaction to alkenes without isolation.[10] When IF_5-pyridine-HF was reduced with a reductant such as I_2, KI, and Sn, the "IF" species was generated (eq. 10). When the reaction was carried out in the presence of an alkene, the corresponding iodofluorination product (**18**) was formed. The reaction proceeded regioselectively (eq. 11).

3-9. Generation of "IF" species part 2, and its application to iodofluoroalkene synthesis[11]

When the "IF" species was generated in the presence of an alkyne, the corresponding iodofluoroalkene was formed. In the conventional method, the expected iodofluoroalkene was obtained from an internal alkyne, however, in the reaction with a terminal alkyne, the corresponding iodofluoroalkene was formed in poor yield, and the formation of a by-product was observed.[12] On the other hand, in the reaction with IF_5-pyridine-HF, the iodofluoroalkene was formed regio- and stereoselectively from the terminal alkyne as well as from the internal alkyne by using *p*-hydroquinone as the reductant (eq. 12).







3-10. Iodoazidation of alkene[13]

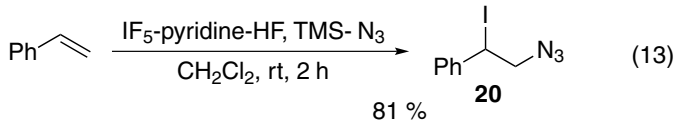
When IF_5-pyridine-HF was reacted with Me_3SiN_3, and then an alkene was added, the iodoazidation of the alkene took place. In the reaction with a terminal alkene, the *anti*-Markovnikov type adduct (**20**) was formed selectively (eq. 13). The reaction with cyclohexene gave a mixture of *cis*- and *trans*-adducts. These results indicated that the reaction proceeded through a radical mechanism, and IF_5-pyridine-HF acted as an oxidant.

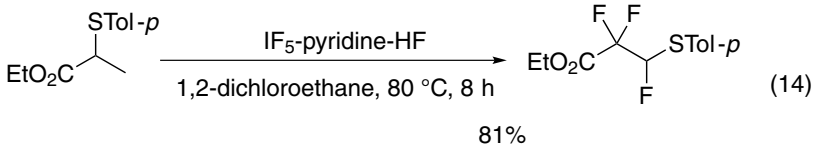
3-11. Poly-fluorination of sulfide[14]

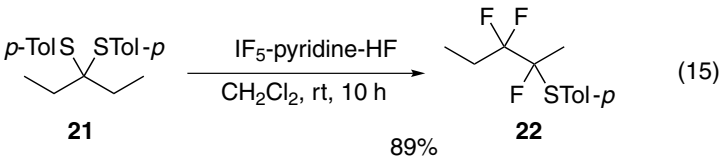
When an alkyl aryl sulfide was reacted with IF_5, *poly*-fluorination took place under migration of the ArS group to give the corresponding *poly*-fluorinated product.[4] On the other hand, in the reaction with IF_5-pyridine-HF, only the *mono*-fluorinaton of the aryl alkyl sulfide took place under the same conditions (section 3-1). However, the introduction of an electron-donating group into the aryl group and by carrying out the reaction at a higher temperature, the *poly*-fluorination of the sulfide could be achieved even by the reaction with IF_5-pyridine-HF (eq. 14).

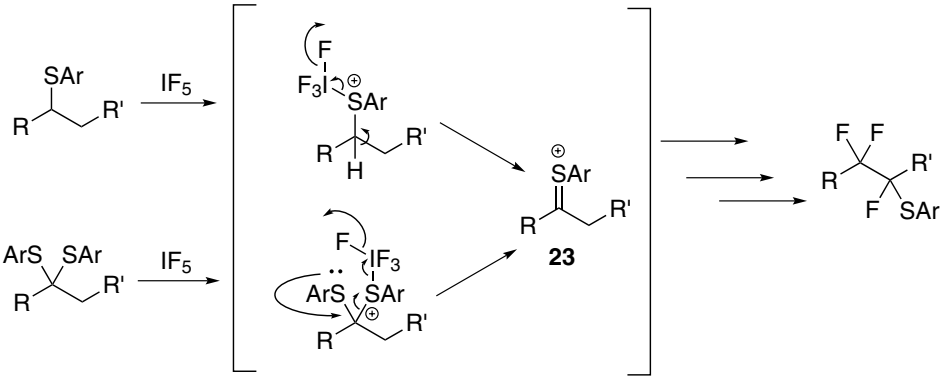
In the reaction of IF_5-pyridine-HF with the dithioketal of a ketone with an α-hydrogen (**21**), the corresponding *poly*-fluorinated product (**22**) was also formed (eq. 15).

In both the reactions, the same intermediate (**23**) should be formed (**Scheme 1**).









Scheme 1.

4. Conclusion

We prepared a new fluorinating reagent, IF_5-pyridine-HF, which has advantages of unusual stability and ease of use. We also developed several reactions using IF_5-pyridine-HF. We hope that IF_5-pyridine-HF will be used by many chemists.

Acknowledgment

We are grateful to DAIKIN INDUSTRIES, LTD. for their donation of IF_5, and the Society of Iodine Science for their financial support.

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Introduction of the author:

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Graduate School of Engineering, Hokkaido University

[Education]
1974-1976: Master of Engineering at Kyoto University
1984: PhD of Engineering at Hokkaido University (Professor Akira Suzuki, mentor)
1984-1985: Postdoctoral Fellow at Wisconsin University (Prof. E. Vedejs)
[Academic career]
1976-1994: Assistant Professor at Faculty of Engineering, Hokkaido University
1994-2001: Associate Professor at Faculty of Engineering, Hokkaido University
2001-2014: Professor at Faculty of Engineering, Hokkaido University
2014-2016: Specially Appointed Professor at Faculty of Engineering, Hokkaido University
[Honor]
1989: Incentive Award in Synthetic Organic Chemistry, Japan
[Research interests]
New fluorination reactions, Synthesis of organofluorine compounds

TCI Related Products

P2140	IF_5-Pyridine-HF	1g	5g	25g
D0714	Dimethyl Disulfide (= MeSSMe)	25g	100g	500g
T0801	Trimethylsilyl Azide (= TMS-N_3)	5g	25g	100g

Chemistry Chat -Focusing on the Elements-

New Allotropes of Main Group Elements

Kentaro Sato

When I was a high schooler, I was taught that there were only three allotropes of carbon: diamond, graphite, and amorphous carbon. But after the 80's, textbooks were rewritten drastically with the addition of buckyball fullerene C_{60}, cylindrical carbon nanotube, and single-layered graphene. It should need no explanation now as to how much these new carbon allotropes have contributed to the advancement of diverse fields including materials science, organic chemistry, and condensed matter physics.

If carbon offers such interesting variations of substances, it should be natural for us to wonder, what about other elements? In fact, new allotropes of other elements, with structures ranging from spherical to planar to three-dimensional networks, have been reported one after another in recent years to push the envelope of science. In this article, let us go through some of the new allotropes of main group elements.

Boron

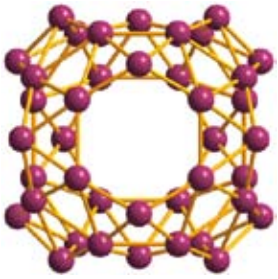
Boron is positioned on the left side of carbon in the periodic table and known to take some unique cluster structures because of its electron deficiency and the property to form three-center two-electron bonds. A number of boron clusters of the $B_nH_n^{2-}$ type that take deltahedral structures (polyhedral structures consisting of equilateral triangular sides), are known. Dodecahydrododecaborate ion ($B_{12}H_{12}^{2-}$), for example, has a beautiful icosahedral structure.

Many of the allotropes of boron form larger network assemblies consisting of this B_{12} icosahedral cluster. For example, α-rhombohedral boron has a nanostructure in which the icosahedral clusters are packed in a similar way to the arrangement called "cubic close packing." In addition, other structural variations are known such as amorphous boron and "face-centered cubic" metal form of boron (which exists only under high pressure conditions).

Then, is it possible for boron to form spherical caged structures like fullerene? Although the exact boron analogue of C_{60} may be too difficult, B_{80}, which has boron atoms added to the center of each hexagonal side, was considered stable enough to exist and computational studies have been done.

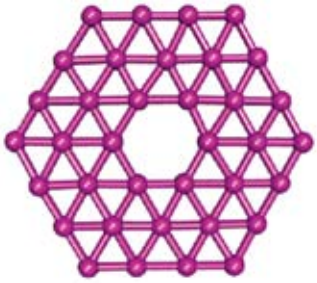
More recently, however, the B_{40} cluster was discovered (*Nat. Chem.* **2014**, *6*, 727.). The formation of this all-boron fullerene was confirmed by Lai-Sheng Wang's group at Brown University, who treated boron with laser irradiation and cooled with helium gas.

Named "borospherene", this molecule consists of 48 triangles, 2 six-membered rings, and 4 seven-membered rings, all based on boron atoms. As shown in the figure below, it belongs to the D_{2d} point group. It is somewhat hard to picture and really makes you wonder why this shape is so stable. It is possible that other borospherenes with different number of boron atoms and structure will be discovered in near future.



Borospherene (extracted from Wikipedia)

Separately from borospherene, the Wang group has considered a boron-based sheet-like structure and named it "borophene" from its relation to graphene. The structure of borophene contains a planar six-membered ring surrounded by a network of triangles. The Wang group has shown evidence for the formation of this B_{36} cluster, which is considered as a basic unit (*Nat. Commun.* **2013**, *5*, 3113.). The science of boron, like carbon did, could develop further to expand the fascinating world of "nano-borons."



Borophene (B_{36})

Nitrogen

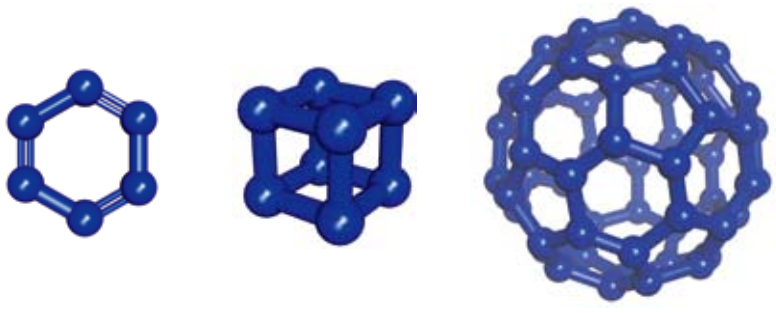
Let us move on to nitrogen, the other neighbor of carbon. Neutral allotropes of nitrogen had long been unknown other than normal N_2 gas, but the existence of tetranitrogen (N_4) was confirmed in 2002 (*Science* **2002**, *295*, 480.). However, its lifetime was only microseconds long and it was too unstable to be isolated. The fragmentation pattern suggested that the structure of tetranitrogen was linear and formed by the weak interaction of two N_2 molecules.

Besides that, the nitrogen analogues of benzene (hexazine, N_6), cubane (N_8), and fullerene (N_{60}) have been investigated theoretically even though they have not been synthesized actually. These compounds, if they can be prepared, are expected to release high energies upon decomposition and thus have a potential application as explosive materials.

In 2004, Max Planck Institute for Chemistry in Germany reported the synthesis of "polynitrogen" (*Nat. Mater.* **2004**, *3*, 558.). In this work, it was found that nitrogen atoms form a single-bonded polymeric network when compressed under the conditions of 110 GPa and 2000 K.

This polynitrogen is thought to possess five times or even higher energy capacity than the most powerful nonnuclear explosives known today. Explosives of this kind have appeared in science fictions in the past, but they are becoming a reality. Of course, this polymeric allotrope of nitrogen can be neither prepared practically nor stored, so it has no prospect of being used as a weapon.

As for solely nitrogen-based ions, azide ion (N_3^-) is known for a long time. Its handling requires caution because of its explosive property, but it has a wide application including preservative and detonating agent. In organic synthesis, it is a useful regent used traditionally as a source of nitrogen.



Theoretically considered nitrogen allotropes

There is also an ion called pentazolyl anion (N_5^-), which is an all-nitrogen pentagonal ion isoelectric to cyclopentadienyl anion. It was obtained by [3+2] cycloaddition of *p*-methoxybenzenediazonium cation and azide that formed the pentazole skeleton, followed by oxidative deprotection using cerium ammonium nitrate (*Chem. Comm.* **2003**, 1016.). Even though the anion is stabilized to an extent by the aromaticity, the repulsions between the nitrogen atoms cause it to decompose with the half-life of 2.2 days.

As another example, there is a species called pentazenium cation (N_5^+) (*J. Am. Chem. Soc.* **2001**, *123*, 6308.). This substance was discovered by the High Energy Density Matter program run by the U.S. Air Force.

Pentazenium was prepared by reacting fluorodiazonium (N_2F^+) and azide. The SbF_6^- salt of pentazenium was stable enough for isolation and X-ray crystallographic analysis, and the cation was found to have a V-shaped bent structure.

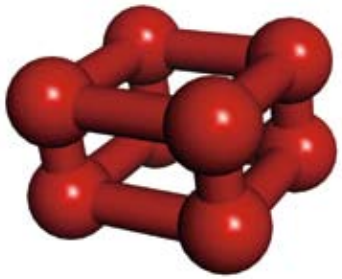
In theory, this pentazenium cation and azide or pentazolyl anion would form a salt composed of only nitrogen atoms. But who would dare to try to synthesize it, considering its easily predictable explosive nature? Well, it turns out that similar experiments have been done and salts like $N_5^+[B(N_3)_4]^-$ and $N_5^+[P(N_3)_6]^-$ have been actually synthesized (*Angew. Chem. Int. Ed.* **2004**, *43*, 4919.)! This paper has a picture of an exploded Teflon tube and the experimental section is filled with cautionary remarks, describing an extreme case of chemical research.

Oxygen

A well-known allotrope of oxygen is ozone (O_3). It is a pale blue toxic gas and its strong oxidizing property is second only to fluorine. Ozone is produced by ultraviolet irradiation or silent discharge of oxygen, and in synthetic laboratories, it is used to oxidatively cleave carbon-carbon double bonds in the reaction known as ozonolysis. In some areas, it is used for disinfection of tap water.

The presence of tetraoxygen, the quartet of oxygen atoms, was predicted in 1924 by Gilbert Lewis, who is famous for formulating the definition of acids and bases. The experimental demonstration, however, proved difficult and had been elusive until 2001, when the group at University of Rome finally detected it by mass spectrometry. The structure of tetraoxygen was neither four-membered ring nor Y-shaped as anticipated, but turned out to be a complex of two oxygen molecules, one in ground state and the other in excited state.

There is one more allotrope of oxygen. When oxygen is compressed with gradually increased pressure at room temperature, the volume decreases steeply after 10 GPa and the color changes from blue to red. The identity of this so-called "red oxygen" had long been a mystery, but it was elucidated in 2006 to be the O_8 cluster composed of four oxygen molecules based on the powder X-ray diffraction patterns (*Phys. Rev. Lett.* **2006**, *97*, 085503.). The discovery came as a major surprise as this "octaoxygen" structure had not been predicted even theoretically.



Unit structure of ε-oxygen ("red oxygen")

The examples we just covered suggest that the chemistry of allotropes has more unexplored possibilities. Next time, let us cover allotropes of the period 3 elements and more.

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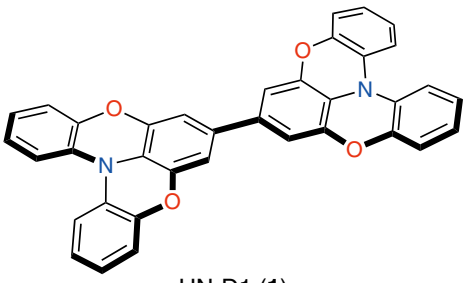
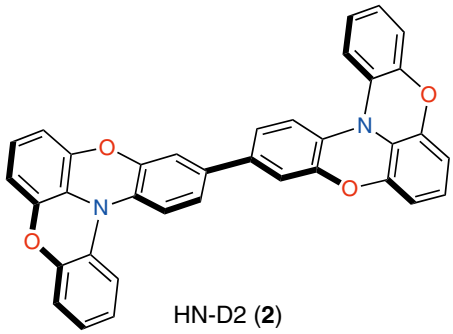
[Specialty] Organic chemistry
[Website] The Museum of Organic Chemistry <http://www.org-chem.org/yuuki/MOC.html>

Pseudoplanar Hole Conductor: HN-D

B4908	7,7'-Bi[1,4]benzoxazino[2,3,4-*kl*]phenoxazine (= HN-D1) (**1**)	200mg 1g
B4907	3,3'-Bi[1,4]benzoxazino[2,3,4-*kl*]phenoxazine (= HN-D2) (**2**)	200mg 1g



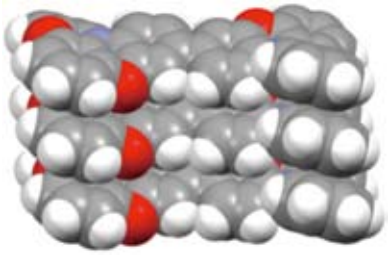
HN-D1 (**1**)

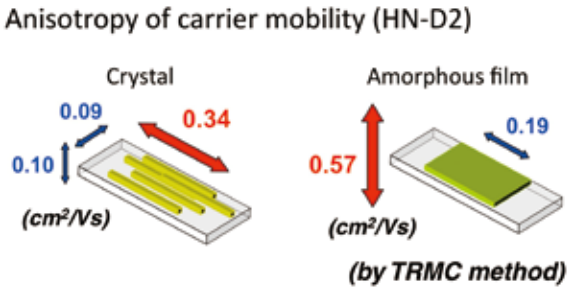


HN-D2 (**2**)

The direction of carrier transport in an organic electronics device differs with the structure of the device. Although development of high mobility organic semiconductors is promising, control of molecular arrangement in the solid state is also important to increase carrier mobility toward a target direction. A conventional organic electronics material involves crystalline molecules with a rigid and planar structure. For amorphous materials, one has developed organic molecules with a twisted propeller structure.

Wakamiya *et al*. developed pseudoplanar materials (**1**, **2**) in which those structures are intermediate between planar and propeller types.[1,2] They partially introduced an ether-bridged structure into a conventional propeller-type molecule, *N,N,N′,N′*-tetraphenylbenzidine derivative. The pseudoplanar structure provides one-dimensionally-arranged on-top π-stacking in the crystal. These materials show relatively high mobility along the molecular stacking direction in the crystal, and also demonstrate large anisotropy of carrier mobility in the amorphous film. It was considered that the pseudoplanar materials (**1**, **2**) maintain a molecular stacking along the perpendicular direction with respect to a device substrate in the amorphous film. Accordingly, they are expected to be useful for organic solar cell and organic light-emitting diode devices, because these devices require high carrier mobility in the perpendicular direction toward a device substrate.





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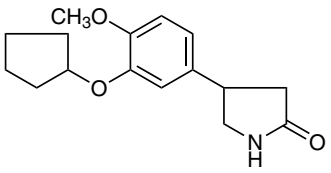
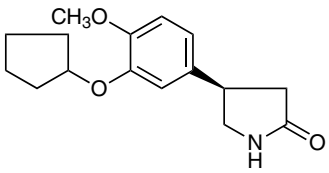
A PDE4s Inhibitor and its Enantiomers

R0110	Rolipram (1)	50mg	250mg
R0182	(*R*)-(–)-Rolipram (2)	10mg	50mg
R0183	(*S*)-(+)-Rolipram (3)	10mg	50mg



Rolipram (**1**)



(*R*)-(-)-Rolipram (**2**)
(Active enantiomer)

Rolipram (**1**) is a selective inhibitor of phosphodiesterases 4 (PDE4s). PDE4s are responsible for hydrolysis of the cyclic nucleotides cAMP and cGMP to 5'-AMP and 5'-GMP, respectively, particularly in nerve and immune cells. The inhibition of PDE4s by **1** induces the elevation of intracellular cAMP concentration. Consequences **1**-induced elevation of cAMP suppress expression of proinflammatory cytokines and other mediators of inflammation.[1] **1** has been reported as a drug for the treatment of autoimmune diseases, Alzheimer's disease, cognitive enhancement, and respiratory diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD).

(*R*)-(–)-Rolipram (**2**) is the active enantiomer of **1**, and has been reported that **2** is approximately 3 times more potent than (*S*)-(+)-rolipram (**3**) against PDE4s.[2] In 2015, Kobayashi *et al.* have been reported a new multistep continuous-flow synthesis of **2** and **3** using only columns packed with a chiral heterogeneous catalyst, respectively.[3] The reactions proceed smoothly without the isolation of any intermediates and without the separation of any catalysts, co-products, by-products, and excess reagents.

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1) The antidepressant and anti-inflammatory effects of rolipram in the central nervous system
J. Zhu, E. Mix, B. Winblad, *CNS Drug Rev.* **2001**, *7*, 387.
2) Stereospecificity of rolipram actions on PDE4
J. E. Souness, L. C. Scott, *Biochem. J.* **1993**, *291*, 389.
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a) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329.
b) S. Kobayashi, *Chem. Asian. J.* **2016**, *11*, 425-436.

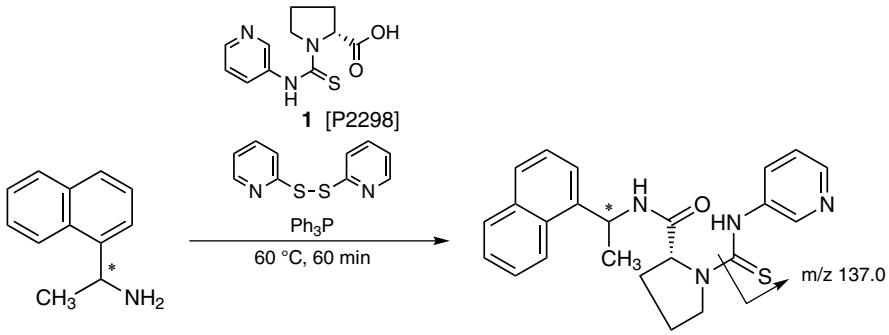
Related Products

A2381	3',5'-cAMP Hydrate		1g	5g
A0158	5'-AMP	1g	5g	25g
G0172	5'-GMP 2Na Hydrate		25g	100g

Chiral Derivatization Reagent Possessing a Pyridylthiourea Structure

P2298 (*R*)-1-(3-Pyridylthiocarbamoyl)pyrrolidine-2-carboxylic Acid [= (*R*)-PyT-C] (1) 100mg

(*R*)-PyT-C (**1**), which was developed by Toyo'oka *et al.*, is a useful chiral derivatization reagent possessing a pyridylthiourea structure for the enantiomeric separation and the quantitative determination of chiral amines in LC-ESI-MS/MS. In the presence of 2,2'-dipyridyl disulfide and triphenylphosphine as activation reagents, amines are labeled with **1** to afford the corresponding labeled amines. When enantiomeric mixtures of amines are employed, the diastereomeric labeled amines are given. The formed diastereomers are clearly separated by reversed-phase chromatography using an ODS column. Furthermore, the resulting derivatives show a characteristic product-ion (m/z 137.0) derived from **1**, and highly sensitive detection and quantitation are performed from the SRM (selected reaction monitoring) chromatograms. This procedure is also applied to the simultaneous separation and detection of chiral amines. Thus, this analytical procedure is expected to open up a wide range of possibilities for application in the field of metabolomics.



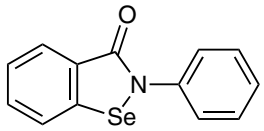
Typical Procedure:
A 10 mM **1** in acetonitrile (20 μL) is reacted at 60 °C for 60 min with chiral amines (10 μM) in the presence of 10 mM triphenylphosphine in acetonitrile (20 μL) and 10 mM 2,2'-dipyridyl disulfide in acetonitrile (20 μL). After removal of the solvent under a gentle nitrogen stream, the residues are re-dissolved in the initial mobile phase, and then an aliquot (2 μL) is subjected to UHPLC-ESI-MS/MS. The separations of the pair of diastereomers for chiral amines are performed by isocratic elution using water/acetonitrile containing 0.1% formic acid. The SRM chromatograms of each pair of diastereomers are obtained from the monitoring ion of m/z 137.0, derived from the MS transition of corresponding protonated-molecular ion, $[M+H]^+$.

Reference

1) R. Nagao, H. Tsutsui, T. Mochizuki, T. Takayama, T. Kuwabara, J. Z. Min, K. Inoue, K. Todoroki, T. Toyo'oka, *J. Chromatogr. A* **2013**, *1296*, 111.

Selenium-containing Antioxidant

E0946 Ebselen (1) 25mg 100mg



1

Glutathione peroxidase (EC1.11.1.9, GPx) is an enzyme related with anti-oxidation in mammal bodies.[1] The enzyme consists of four sub-units and contains a selenium atom per subunit.[2] The selenium atom exists in the enzyme as selenocysteine residue (Sec45*) and it is proposed that the residue forms the active center of the enzyme.[3] The selenocysteine residue forms a catalytic triad with two other amino acid residues, Gln79* and Trp153*.[3] Based on the knowledge, small organic molecules containing selenium have been designed as a mimic of the enzyme.[3] Ebselen (**1**) is one of such seleno-molecules and possesses GPx like activity.[4,5] Therefore, **1** works as an anti-oxidant.[6]

As shown in Table, **1** possesses interesting biological activities including anti-inflammatory activity, immuno-modulation, neuroprotective activity, *etc.* **1** also inhibits several enzymes such as NADPH oxidase, nitric oxide synthases, and 5- and 15-LOXs.

*The residue numbers are according to the sequence alignment of human enzyme (Human pGSHPx) reported by Ren *et al.*[7]

Table. Biological Activities of Ebselen

Activities	References
Anti-inflammatory	*Biochem. Pharmacol.* **1989**, *38*, 649. *Agents Actions* **1988**, *24*, 313. *Immunopharmacol.* **1993**, *25*, 239.
Immuno-modulation	*Biomed. Environ. Sci*. **1997**, *10*, 253
Neuroprotective	*Br. J. Pharmacol*. **1997**, *122*, 1251. *Stroke* **1998**, *29*, 12.
Interaction with nitric oxide and peroxynitrite	*Adv. Pharmacol*. **1997**, *38*, 229. *J. Biol. Chem.* **1997**, *272*, 27812.
Inhibition of enzymes: NADPH oxidase nitric oxide syntheses 5- and 15- LOXs	 *Biochem. Pharmacol.* **1989**, *38*, 649. *Eur. J. Pharmacol*. **1994**, *267*, R1. *Biochem. Pharmacol.* **1994**, *48*, 65.

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M. J. Parnham, H. Sies, *Biochem. Pharmacol.* **2013**, *86*, 1248.
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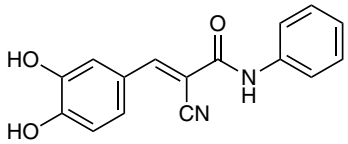
B. Ren, W. Huang, B. Åkesson, R. Landenstein, *J. Mol. Biol.* **1997**, *268*, 869.

Tyrosine Kinase Inhibitor

A2704 Tyrphostin AG 494 (1) 20mg 100mg



1

Tyrphostins are a series of the small molecules which are designed to bind to the subsite of the protein tyrosine kinase (PTK) domain.[1] Tyrphostin AG494 (**1**) inhibits tyrosine kinases shown in the table.[2-4] **1** also blocks cyclin-dependent kinase 2 (cdk2) activation.[5]

Table. Inhibition of selected protein kinases by AG494[2-4]

	Protein kinase	IC_{50} (μM)
Study I[2]	PolyGAT phosphorylation	0.7
	HER1/EGFR	1.25
	ErbB2/neu (HER1-2)	42
	EGF-dependent proliferation	15 (>50)
Study II[3]	HER1/EGFR	1.1 ± 0.24
	ErbB2/neu (HER1-2)	45 ± 4.3
	Her2/neu	39 ± 13
	PDGF-R	6.0 ± 2.4
	Insulin-R	>100
	c-abl	50-100
Study III[4]	HER1/EGFR	0.7
	Her2/neu	42
	PDGF-R	6
	Insulin-R	>100
	p210 Bcr-Abl	75

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