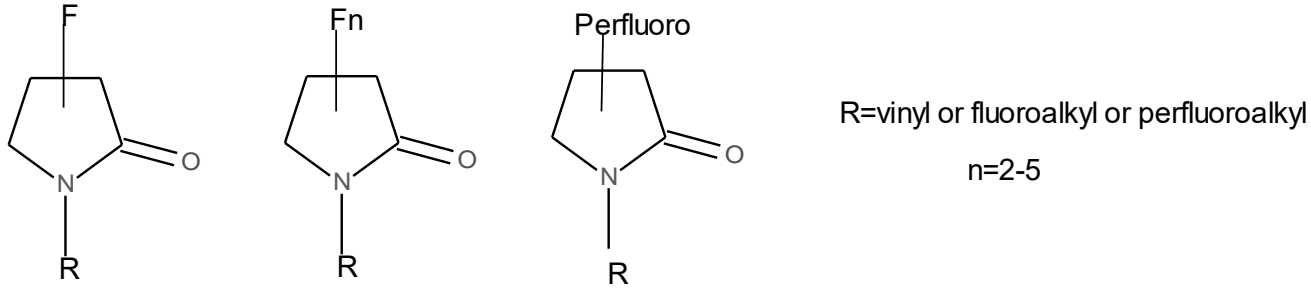
Fluorinated Pyrrolidone Compounds

By Robert B. Login

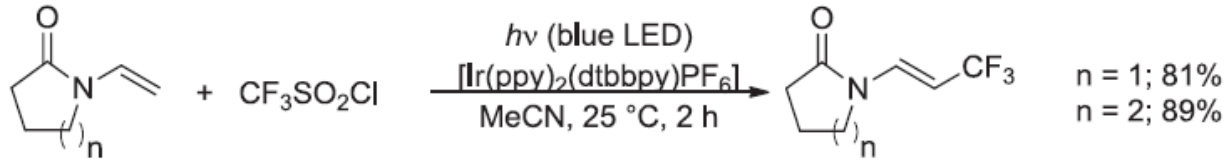
I continue to be interested in pyrrolidone chemistry because of its importance in a wide variety of fields. It is at the heart of numerous patents dealing with drugs for the treatment of problems of the brain such as epilepsy, dementia and cognition. I find few if any references however to fluorinated pyrrolidone derivatives based on these and other medicinal applications. Fluorine is usually substituted for hydrogen in a wide variety of medicinals for many reason one of which is that it renders the compound less susceptible to metabolic deactivation(please look at "Fluorine in medicinal chemistry and chemical biology", Iwao Ojima (editor) 2009 Wiley; for a detailed review of why F is used in medicinals). Fluorine, as various salts, is ubiquitous in the earths crust but appears in few living organism. Hence its ability to prevent deactivation by metabolism by being a sort of proverbial monkey wrench.

This ability is a two edge sword because fluorinated sufactants or their residues are now found in humans and can last in the environment for eons. 3M has stopped producing CF8(perfluorinated octane based surfactants) and has replaced them with CF4 derivatives. Apparently the CF4 chains are eliminated in an acceptable time frame. "C4-perfluorocarbon chain seems not to be very bio accumulative and has a much shorter half-life in humans and other organisms."
(Short-chain Polyfluoroalkyl Substances (PFAS) Environmental project No. 1707, 2015 Danish Protection Agency). Degradation Studies of New Substitutes for Perfluorinated Surfactants in ARCHIVES OF ENVIRONMENTAL CONTAMINATION AND TOXICOLOGY · JULY 2010.

The following chart illustrates the possibilities for fluorinated pyrrolidone derivatives:



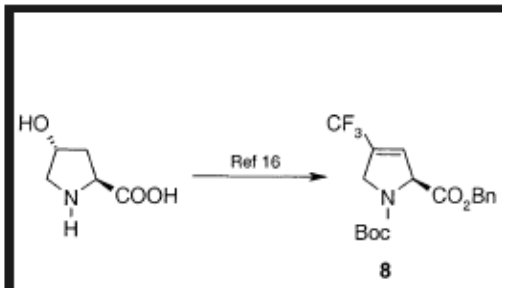
I have found several references to these derivatives, and they can illustrate some of the synthesis methods for fluorinating pyrrolidones.

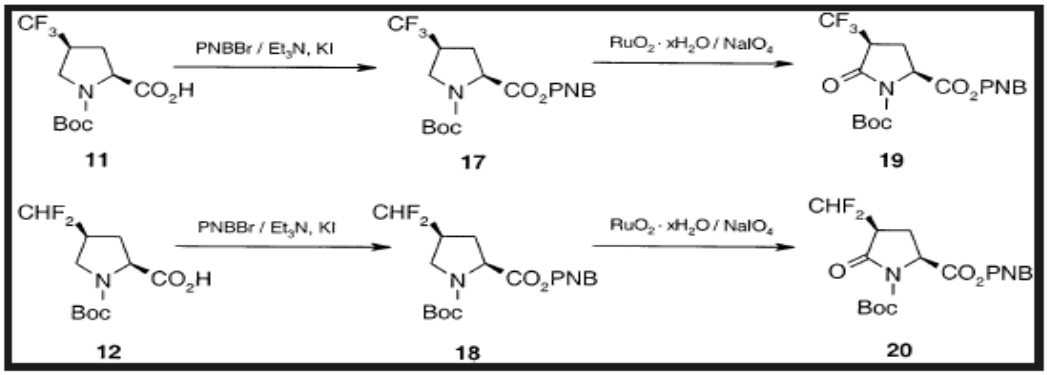


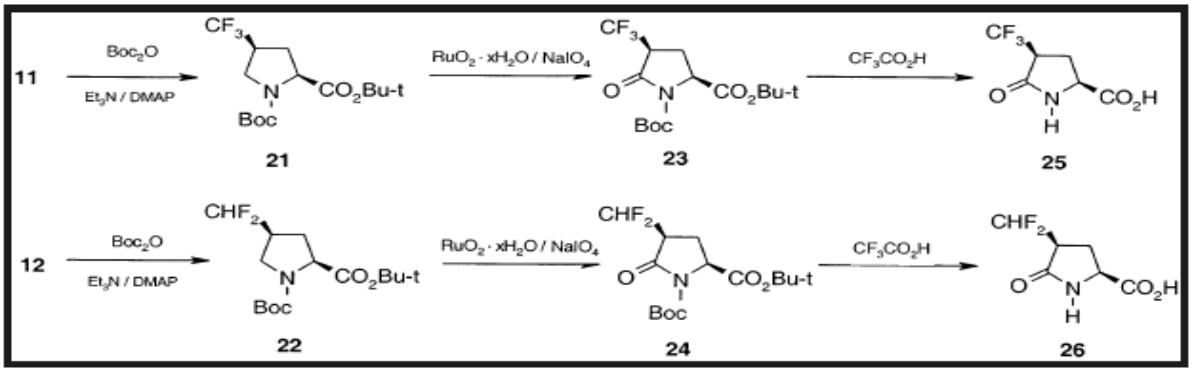
Scheme 71. Photocatalytic trifluoromethylation of enamides [105].

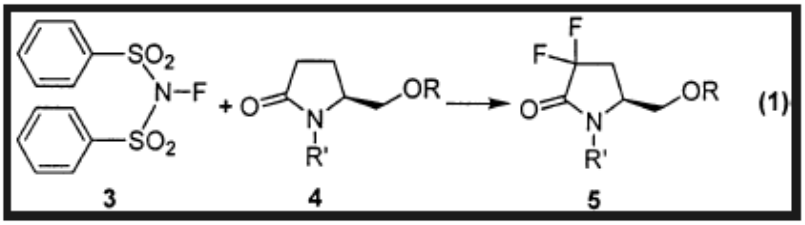
H. Jiang, C. Huang, J. Guo, C. Zeng, Y. Zhang, S. Yu, Chem. Eur. J. 18 (2012) 15158.

16) Qiu, X.-L.; Qing, F.-L. *J. Org. Chem.* **2002**, *67*, 7162.

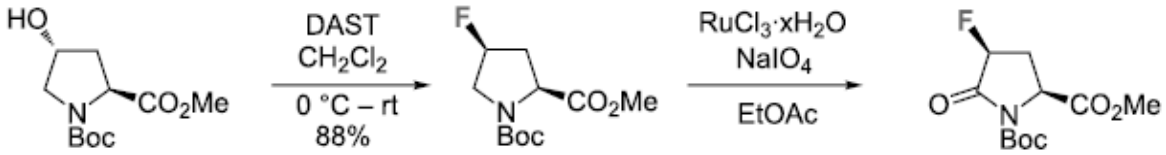



CF3
CO2H
N
Boc
11
PNBBr / Et3N, KI
CO2PNB
17
RuO2 · xH2O / NaIO4
O
19
CHF2
12
18
20

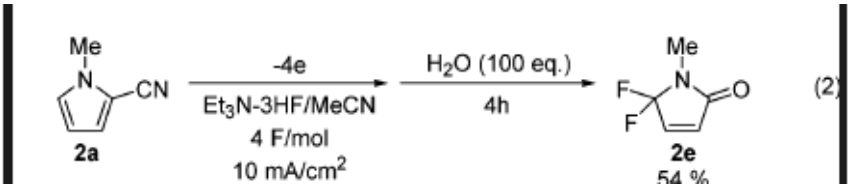

11
Boc2O
Et3N / DMAP
CO2Bu-t
21
RuO2 · xH2O / NaIO4
23
CF3CO2H
25
12
22
24
26


SO2
N–F
SO2
3
+ O
N
R'
OR
4
F
5
(1)

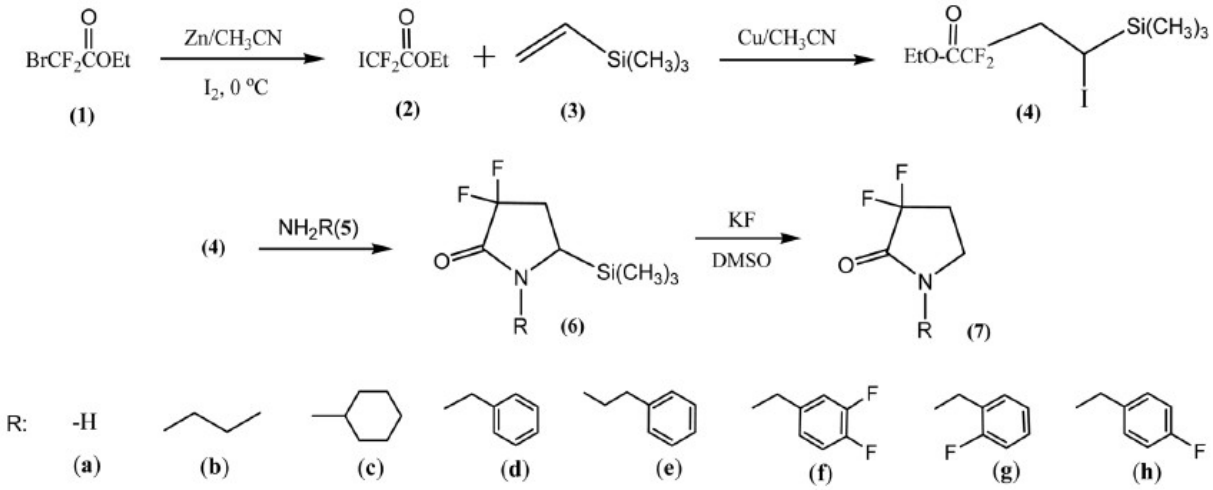

OR'
N
R
1. LDA (1.3eq.)
2. NFSi (1.4eq.)
-78C / THF
F



Beilstein J. Org. Chem. **2013,** *9,* 2812–2820

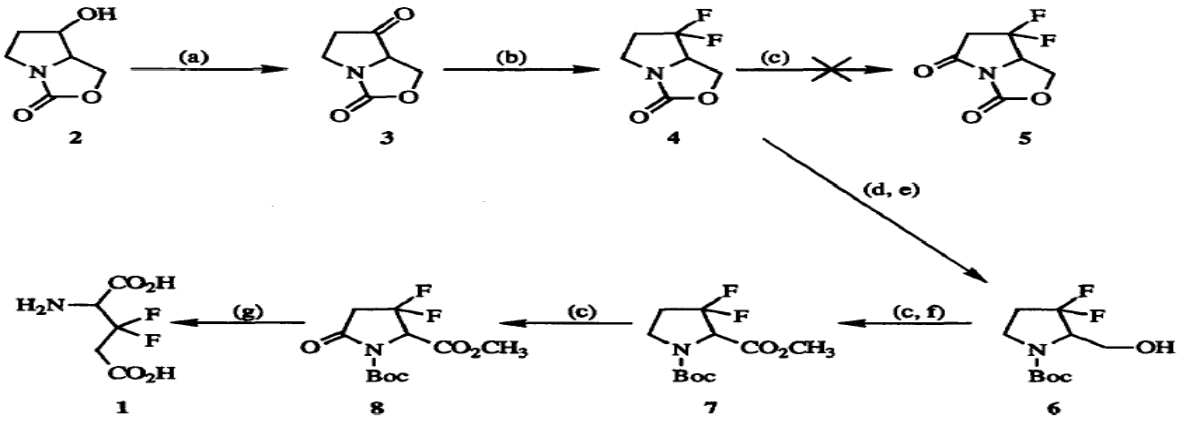


J. Org. Chem., Vol. 71, No. 4, 2006



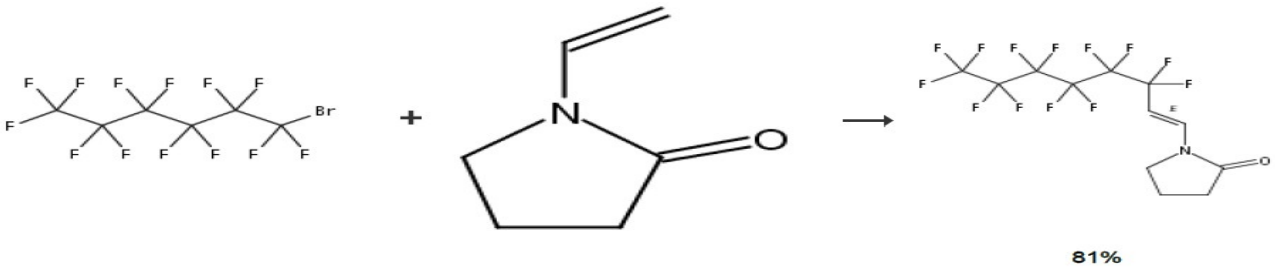
Scheme 1

Bull. Korean Chem. Soc. **2007,** Vol. 28, No. 12



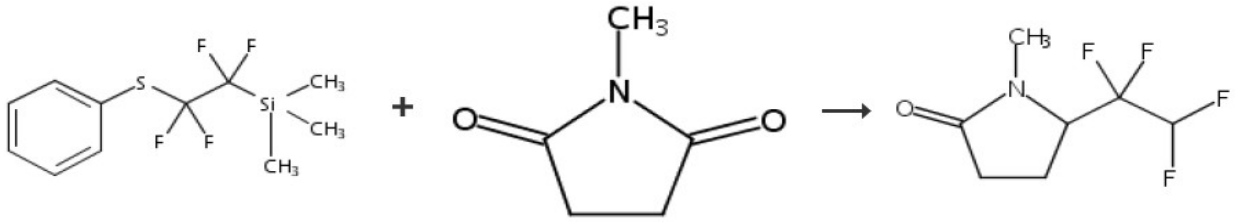
[a]Reagents: (a) $(CF_3C(O))_2O$; DMSO; Et_3N; CH_2Cl_2 (73%); (b) DAST, CH_2Cl_2, -78 °C → RT (64%); (c) $RuO_2 \cdot xH_2O$, 10% $NaIO_4$, EtOAc; (d) 6N HCl, Δ; (e) $(Boc)_2O$, $NaHCO_3CHCl_3$, H_2O (92% from 4); (f) CH_2N_2, Et_2O (93% from 6); (g) Conc. HCl, Δ (7 → 1, 40%).

Tetrahedron Letters, Vol. 34, No. 31, pp. 4917-4920, 1993

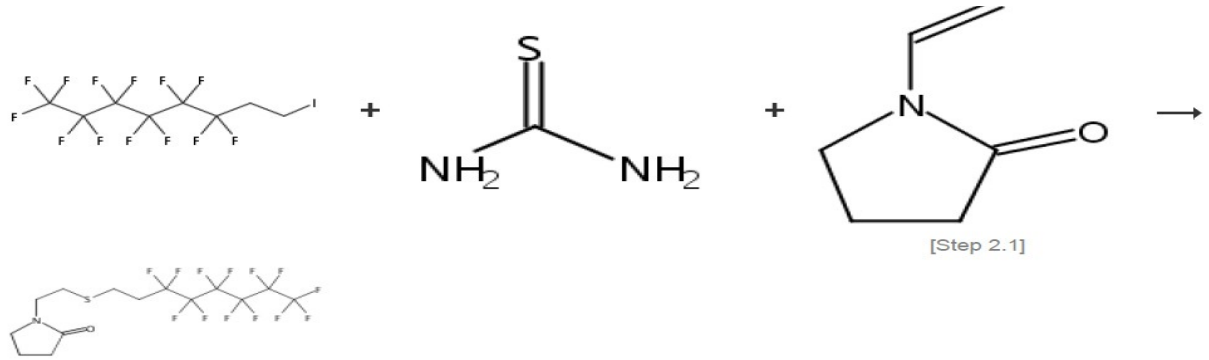


81%

Angewandte Chemie, International
n, 54(4), 1270-1274; 2015

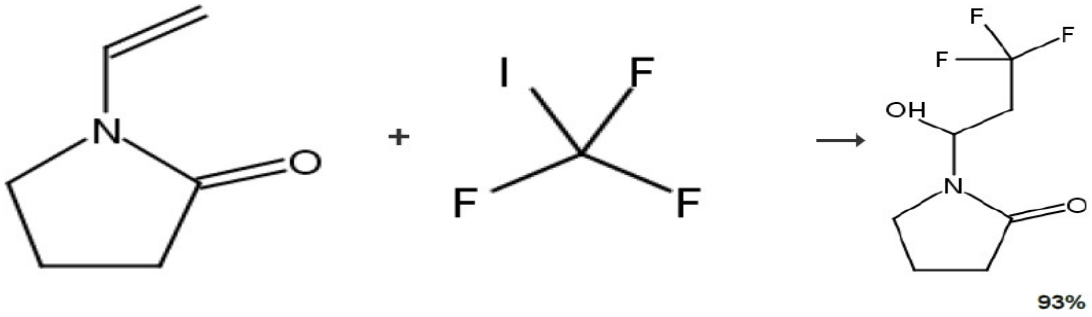


Synlett, 23(8), 1187-1190; 2012

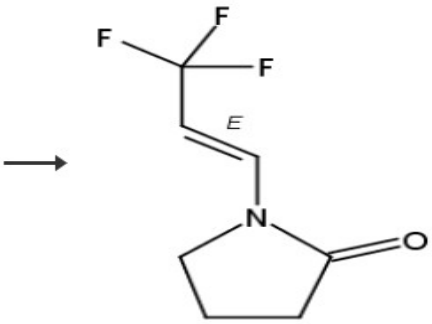


[Step 2.1]

From PCT Int. Appl., 2009073592, 11 Jun 2009

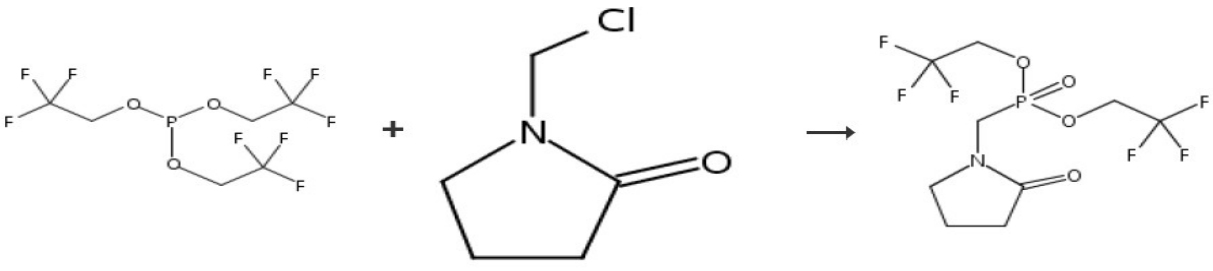


93%



61%

From Jpn. Kokai Tokkyo Koho, 2008231040, 02 Oct 2008



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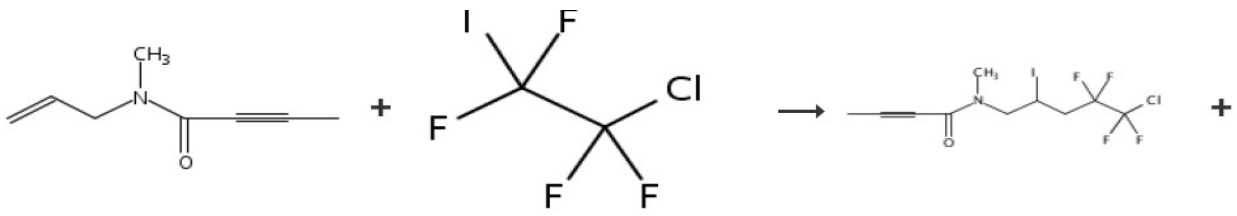
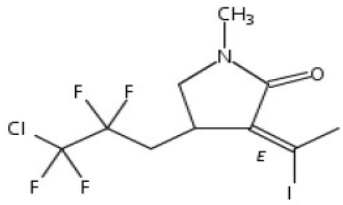
From Russian Journal of General Chemistry (Translation of Zhurnal Obshchei Khimii), 73(2), 317-318; 2003





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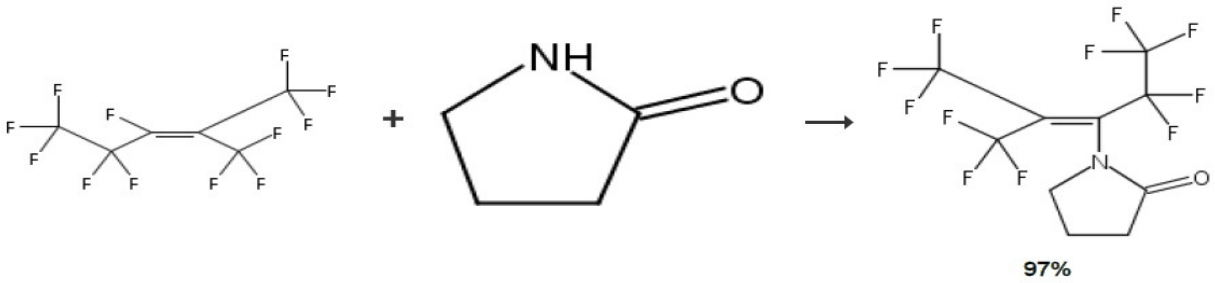
Tetrahedron, 51(9), 2639-58; 1995



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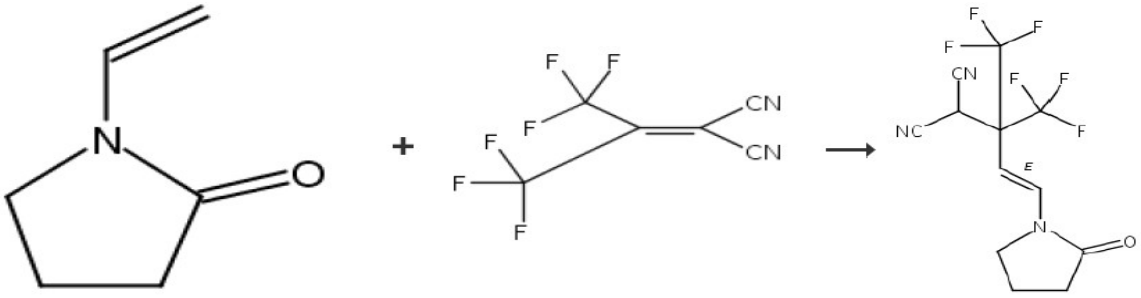
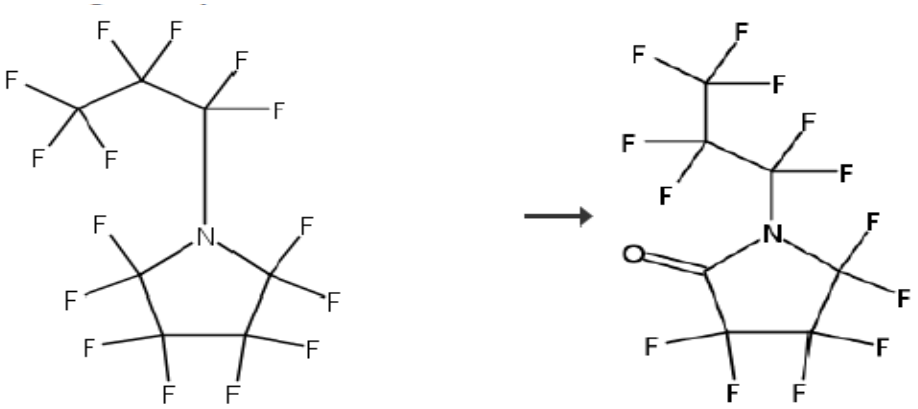
From Zhurnal Prikladnoi Khimii (Sankt-Peterburg), 69(1), 103-111; 1996



72%

From Tetrahedron Letters, 32(16), 1871-4; 1991



The reaction of perfluoro (N-alkyl cyclic amines) with oleum. The formation and characterization of perfluorolactams

By Hayashi, Eiji et al

From Journal of Fluorine Chemistry, 41(2), 213-25; 1988

3,404,147

MONOHALOALKYL AND POLYHALOALKYL LACTAMS

Raymond L. Mayhew, Summit, and Frederick Grosser, Midland Park, N.J., assignors to GAF Corporation, a corporation of Delaware

No Drawing. Continuation-in-part of application Ser. No. 340,799, Jan. 28, 1964. This application Dec. 22, 1965, Ser. No. 515,728

9 Claims. (Cl. 260—239.3)

This patent shows how to fluorinate pyrrolidone using alpha olefins and free-radical initiators.

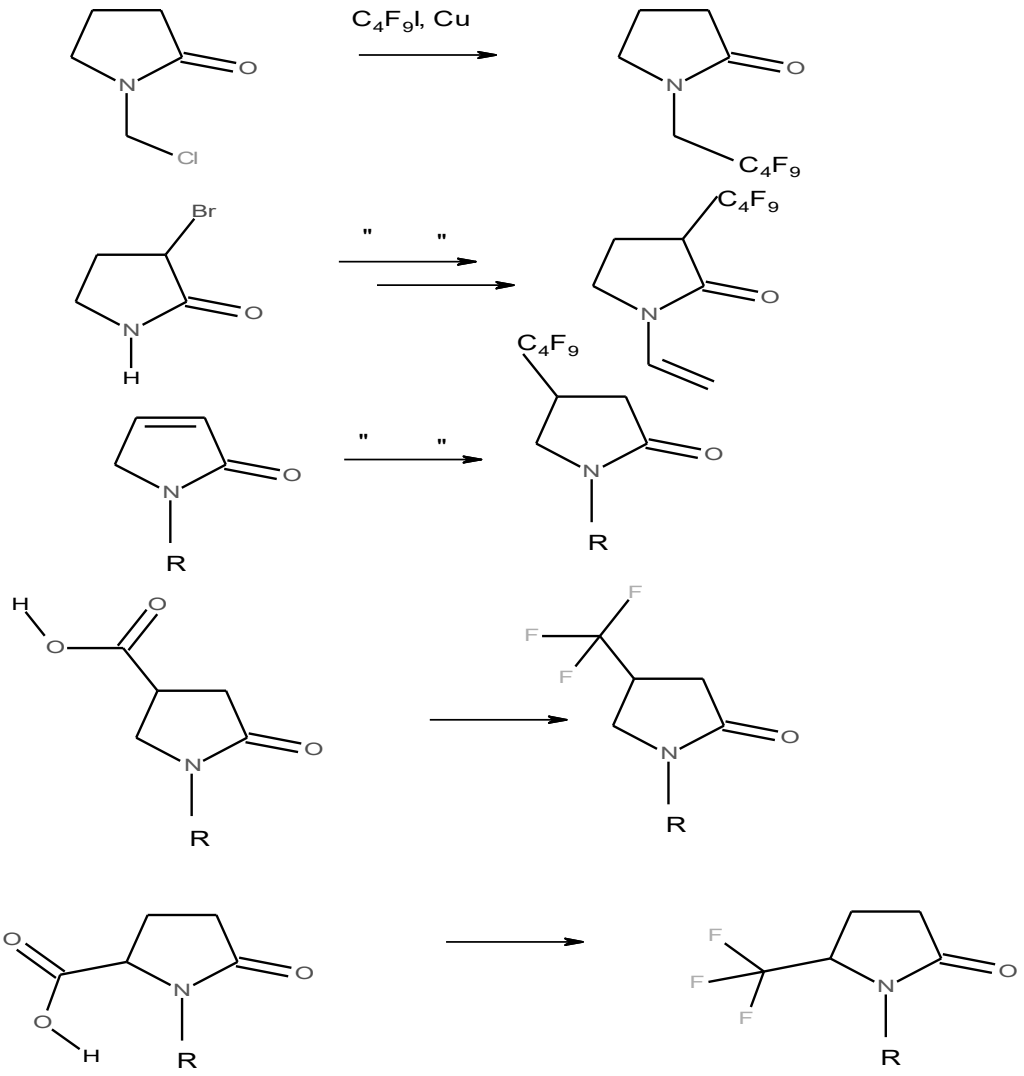


Chart 1

The above chart illustrates some additional possibilities for fluorine derivatives. The problem is the enormous number of fluorinating reagents that are presently being used. Most of the newest reagents were developed because the older ones require special handling and are dangerous. “Modern Fluoroorganic Chemistry” by P. Kirsh, 2013 (Wiley) is a recent accounting and I refer you to it for a more in-depth review of these reagents. Even a newer Chem Review 2015, 115, 756-825 has appeared and I quote from it;

“Thereafter, safer SF4-derived fluorination reagents were discovered and commercialized, including N,N-diethylaminosulfur trifluoride (DAST),21,22 bis(2-methoxyethyl)- aminosulfur trifluoride (Deoxo-Fluor),23 and more recently 4- tert-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),24 (diethylamino)difluorosulfonium tetrafluoroborate (XtalFluorE) and difluoro(morpholino)sulfonium tetrafluoroborate (XtalFluor-M).25 On the other hand, the first sulfur-based fluoroalkylation reagent is probably the perfluoroalkanesulfonyl chloride (Rf SO2Cl), which was used in free radical perfluoroalkylation of alkenes.

During the past decade, a variety of fluorinated sulfones, sulfoxides, sulfides, and sulfoximines have been extensively developed as either nucleophilic or electrophilic fluoroalkylation reagents. In this review, we wish to give an overview of the sulfur-based fluorination and fluoroalkylation reagents and related reactions for organic synthesis in a time frame from 1958 to June 2014.”

Also see USP 3,976,691; 6,207,860 B1; 8,680,332 B2; 2008/0269512 A1.

SF4 is a very toxic gas and DAST is unstable and explosive when heated. So I would of course start with the safest reagents and there are many so it seems to me that one can find a reagent that will do any of the desired fluorinations. Therefore, the real issue with fluorinated pyrrolidone chemistry is the application(s) of such derivatives.

Lets consider fluorinated polyvinylpyrrolidones. From the above examples, its possible to fluorinate the pyrrolidone ring to various extents. Instead of just being blood expanders, such resulting polymers and copolymers could carry oxygen as an expander/blood substitute or as a protective colloid or emulsion stabilizer. This would afford more stable PFCE(perfluorinated carbon emusions) if said F-PVPs are in these

PFCE formulations. In the past PVP has been found to remain in the body and to cause problems; howevere, low MW PVP does not build up in the body and is excreted(Pfirrmann, USP 6,080,397). Fluorinated low MW F- PVP derivatives might also be readily excreted and would be worth investigating as the payoff would be enormous. As I understand, the Pentagon is even supporting attractive candidates.

Water soluble or dispersable polymers with cationic charge would be substantive to hair and textiles, the advantage being that the pyrrolidone moiety can carry oxygen and complexes such as biocides or hydrogen peroxide. In addition, if such polymers would form safe high energy F surfaces that bacteria would have a hard time adhering to, it would be another form of protection. The ability to make oxygen available to damaged skin would be beneficial and a great selling point for such treatments. Application to the hair could protect the treated hair from other treatments and dirt affording the user additional flexibility. See patents;

Patents citing US8343515 B2

Citing Patent	Filing date	Publication date	Applicant	Title
US9132295	Aug 23, 2013	Sep 15, 2015	Indermica, Inc.	Composition having stabilized perfluorocarbons
US20100267842 *		Oct 21, 2010	Richard Kiral	Emulsions of Perfluorocarbons
US20110230566 *		Sep 22, 2011	Maria Isabel Tamargo	Perfluorocarbon eye cream formulations
US20120184898 *	Mar 28, 2012	Jul 19, 2012	Ward Kevin R	Gas based wound and tissue therapeutics
US20130289471 *	May 3, 2013	Oct 31, 2013	Virginia Commonwealth University	Gas based wound and tissue therapeutics

Unlike polymers, small molecules can also have numerous useful applications.

Fluorinated pyrrolidone lactam N-R groups would generate surface activity and like the surfadones, interesting wetting agents. Such fluorinated surfactants might have unique applications such as cleaning agents for fluorinated membranes or as components of flourous solvents, but the most important use would also be in formulating blood substitutes. Surfactants with a pyrrolidone head group and a perfluoroalkane N substituent, would afford a surfactant that has affinity for water, forming micro PFC emulsions. Such a micro PFC emulsion generating amphifilic molecule could solve the emulsion problems with PFC technology and carry oxygen and remove CO2. In addition, in combination with F-PVP steric stabilizers, these N-F pyrrolidone surfactants might form long lasting PFCE's. I quote from Mark T. Friedman et. al. Blood Transfusion in the 21st Century, DISCOVERIES 2014, Jan-Mar, 2(1): e11.

“Yet the promise of blood substitutes, also known as “artificial blood”, which are really oxygen therapeutic agents rather than complete substitutes for blood, has proven to be quite elusive. Development of a therapeutic oxygen carrier, which ideally would be readily available, universally compatible, pathogen free, cost efficient with minimal side effects and a long shelf life, has taken two forms over the years: perfluorocarbon emulsions (PFC’s) and hemoglobin-based oxygen carriers (HBOC’s). PFC’s are chemically-inert, colorless, clear liquids that have the ability to dissolve large volumes of gases, including oxygen and carbon dioxide. However, PFC’s are also water insoluble and must be emulsified for intravenous use, limiting their effectiveness due to low PFC content such that high concentrations of supplemental oxygen must be given in order to achieve a therapeutic effect. Fluosol-DA (Green Cross Corp., Osaka, Japan/Alpha Therapeutic, Los Angeles, CA), a first-generation PFC, received FDA approval in 1989 for use in coronary balloon angioplasty but was withdrawn from the market just 5 years later since it was found to be cumbersome to store (requiring frozen storage) and prepare for therapeutic use as well as the fact that improvements in angioplasty catheter

technology eliminated the need for Fluosol. Second generation PFC's, which have higher PFC content, such as Oxygen (Alliance Pharmaceutical Corp., La Jolla, CA) and Oxyfluor (Hemagen, Inc., St. Louis, MO) were subsequently developed and tested but have not been approved by the FDA."

The need for blood substitutes is acute because typing and storing blood is very expensive and there is the real fear of hidden undetected contamination. Synthetic blood would be free of this concern as it could be readily sterilized. It could be stored easily and made available in large amounts in case of a disaster. This would leave time to get the injured to hospitals. With the advent of terrorism, there is no telling how many people will need blood to survive?

Other Applications

"PFCE's (perfluorinated carbon emusions) could be incorporated into cardioplegic solutions used in open heart surgery. Such an application has the potential to benefit cardiac oxygenation, tissue metabolic status and quicken recovery following the stoppage of the heart. PFCE's could also be used in supplying devascularized organs with oxygen prior to transplantation. Along those same lines, they could be used to perfuse the myocardium or brain tissue in heart attacks and strokes, oxygenating obstructed regions due to blockage and hopefully improving survival and recovery.

Another possible area of application is in cancer therapy. PFCE's could increase the oxygenation of tumors, consequently benefiting radiation and/or chemotherapy in cancer treatment. Chemotherapeutic drugs could beaded to the PFCE and carried along to the site of the cancer. Also, local application of toxic doses of PFCE's (namely PHER-O2) resulted in the necrosis of cancer cells. This is especially promising in the treatment of cancers of the head and neck regions which are currently difficult to treat." Taken from:

http://biomed.brown.edu/Courses/BI108/BI108_2005_Groups/10/webpages/PFClink.htm.

I'm sure progress has been made since 2005 but this gives a good idea of potential applications. It doesn't mention the use of F18 isotope in PET scanning another important use.

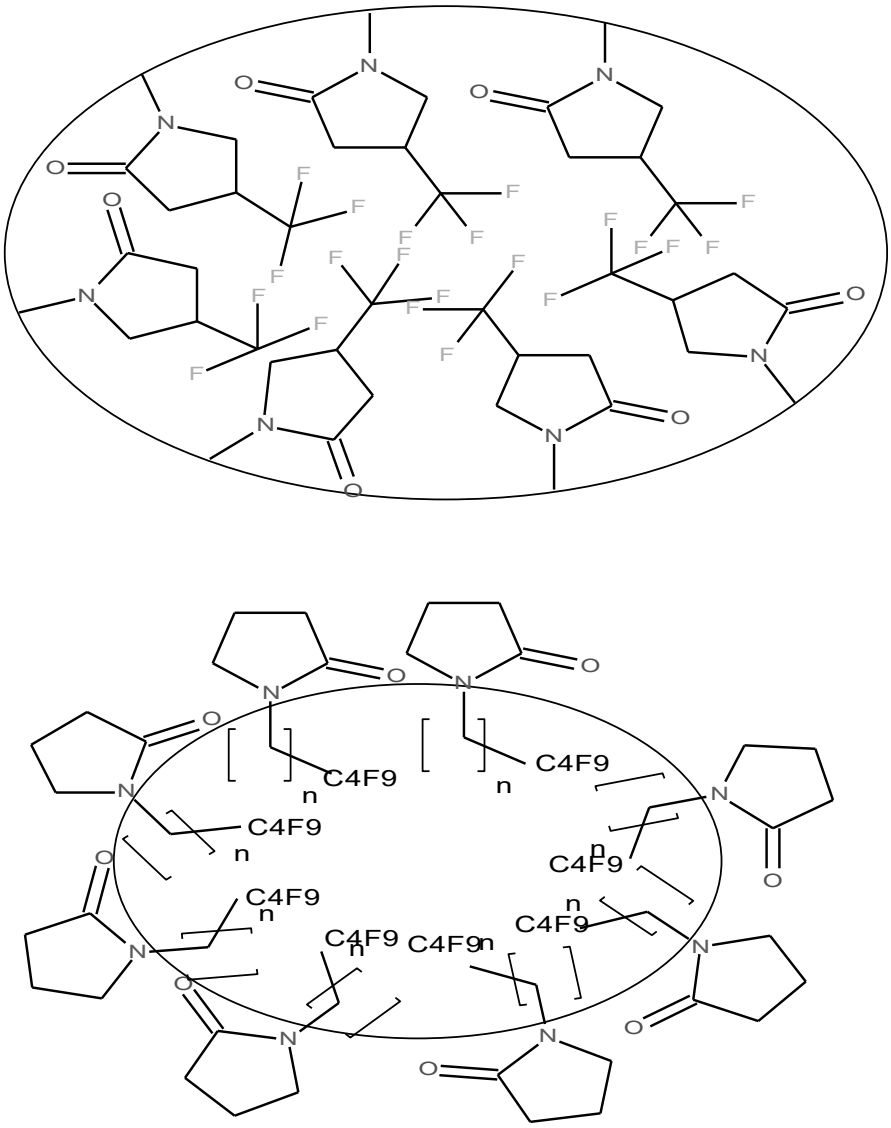


Chart 2

Chart 2 is a summary of the above said ideas. On top it shows a schematic of CF3 substituted PVP indicating the strong ability of organofluorines to reject water and congregate with each other while the pyrrolidones face towards the surrounding aqueous

solution. In the bottom, it shows the fluorinated surfactants also indicating the advoidance of water by organofluorines and now with the pyrrolidone groups in the aqueous phase (these are examples and are not meant to be limiting). Obviously this is guess work as these organofluorine derivatives can also be at the air-water interface and could also form many complicated structures in water and both types of F pyrrolidone derivatives can also be combined but the real question is will PFCE carry oxygen in aqueous microparticle form and aviod the problem of Osward ripening of surfactant stabilized PFC formulations with Fluorinated PVP and/or Fluorinated surfactant pyrrolidones?

I claim:

1. Blood substitutes comprising partially fluorinated low MW polyvinylpyrrolidones stabilized PFCE capable of carrying oxygen to cells and removing carbon dioxide in human beings.
2. The blood substitutes of claim 1 wherein said fluorinated polyvinylpyrrolidones are excreted in urine and do not remain in the human body.
3. Blood substitutes comprising pyrrolidone fluorinated N-alkyl surfactants that stabilize PFCE capable of carrying oxygen to cells and removing carbon dioxide in human beings.
4. The blood substitutes of claim 3 wherein said pyrrolidone fluorinated N-alkyl groups are excreted in urine and do not remain in the human body.
5. The blood substitutes of claim 3 wherein said N-alkyl group is terminated with a C4F9 moiety.
6. The blood substitutes of claim 1 wherein a C4F9 moiety is attached to the pyrrolidone ring.
7. The blood sustitutes of claim 1 wherein a CF3 moiety is attached to the pyrrolidone ring.