ELSEVIER

Journal of Fluorine Chemistry 100 (1999) 157–161

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Industrial scale production of Selectfluor™ fluorination agent: from initial concept to full scale commercial production in a 5 year period

James J. Hart, Robert G. Syvret*

Fluorine Technology Center, Air Products and Chemicals, Allentown, PA 18195, USA

Received 4 May 1999; received in revised form 30 June 1999; accepted 22 July 1999

Abstract

The Selectfluor™ electrophilic fluorination agent **1** is now produced in multi-ton per year quantities and is one of only a few fluorine-containing fine chemicals that are produced by direct fluorination with F_2 on an industrial scale. From the initial concept of the ''ideal fluorination agent'' to the present day industrial scale production of Selectfluor™, the route to the successful commercialization included a series of critical steps. A chronological account of the road to commercialization of Selectfluor™, noting the important product development factors, is provided herein. © 1999 Elsevier Science S.A. All rights reserved.

Keywords: Selectfluor™ fluorination agent; Electrophilic fluorination; Commercial fluorination processes

1. Introduction

Although the Selectfluor™ electrophilic fluorination agent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane *bis*(tetrafluoroborate), CM–TEDA–F(BF_4^-)$_2$ **1**, has been known for less than a decade [1], it has already become the electrophilic fluorination agent of choice for a wide variety of applications [2–4]. The diversity in applications is illustrated in part by some of the most interesting examples which include the fluorination of alkenyl borates [5], boranes [6–8], ascorbic acid derivatives [9], and pyrimidine bases [10], the synthesis of fluoro-carbohydrates [11] and important aromatic substrates [12], as well as for the production of commercial steroids [13].

The discovery and subsequent development of the Selectfluor™ fluorination agent family culminated from a joint effort between researchers at UMIST and Air Products and Chemicals, and was the subject of the very first report on Selectfluor™ which appeared in 1992 [1]. The impetus to begin development of a commercial fluorination agent began initially at Air Products in the late 1980s when the charter to ''obtain more value from fluorine'' was passed from Andrew Woytek, Director of Research for Specialty Gases to Dr. Guido Pez of the Corporate Science and Technology Center who at the time was responsible for fundamental research in fluorine chemistry. It was this initial directive, coupled with the vision and insight of Guido Pez which led to the formation of an alliance with professor Eric Banks and his team at UMIST, the formation of a research and development team at Air Products, and ultimately to the successful commercialization of the Selectfluor™ fluorination agent.

The time frame spanning the initial discovery and commercial production (multi-tons per year) of Selectfluor™ fluorination agent **1** was approximately 5 years. There were a number of key and important factors along the road to development which proved to be vital to the successful commercialization of Selectfluor™. While an overview of the Selectfluor™ fluorination agent from the discovery perspective was recently published by Eric Banks [14], it is the purpose of the present report to describe the chronology of the Selectfluor™ fluorination agent's development, beginning with the initial concept and ending in its commercial production, and to describe the important factors along the way which contributed significantly to its rapid and successful commercialization.

2. The chronology of the development of Selectfluor™

The story of the development of Selectfluor™ will be presented chronologically by addressing a number of key issues and questions which include:

1. What inspired the development of a new electrophilic fluorination agent in the first place? What was the

*Corresponding author. Tel.: +1-610-481-3536; fax: +1-610-481-6517.
E-mail address: syvretrg@apci.com (R.G. Syvret)

0022-1139/99/$ – see front matter
PII: S0022-1139(99)00199-2

rationale behind the development and what was the need in the marketplace?
2. Once the decision was made to develop a commercial electrophilic fluorination agent, how then was the target molecule defined, including what were the properties that the ''ideal'' fluorination agent should have?
3. Then, with a clear understanding of the type of fluorination agent that the market really needed, the discovery ''phase'' began which led, ultimately, to the discovery of the Selectfluor^{TM} agent family. As will be described, the discovery phase was an iterative process whereby all of the desired properties of the fluorination agent were incorporated.
4. Leading out of the discovery phase was the product development phase, wherein the three most critical aspects of the whole process took place more or less concurrently, that is the process development and scale up functions, product applications and commercial development efforts, and a comprehensive battery of safety testing coupled with good product stewardship.

3. Why develop a new fluorination agent?

As previously mentioned the initial directive from upper management to ''get more value from fluorine'' was quickly translated in practical terms into ''what was the need in the marketplace for selective fluorination technology?'' In fact, the impetus to get into this area came from repeated customer requests for a replacement for perchlorylfluoride, $FClO_3$, which, at the time that we began our effort in this area, was being used exclusively for the 6-position fluorination of most, if not all commercial cortical steroids. The leading steroid manufacturers were demanding a replacement for perchlorylfluoride primarily because of its bad reputation as a safety hazard [15–17] but also because of the considerable uncertainty that existed with respect to its continued supply. As was quickly learned, not only were the potential customers demanding a suitable replacement for $FClO_3$, moreover, they had a very clear and well-defined set of criteria that the ideal fluorination agent would have to meet.

According to the potential customers, the ideal fluorination agent would meet the following criteria:

1. It would have fluorination performance at least equivalent to, and preferably better than that of $FClO_3$ in terms of steroid 6-position fluorinations.
2. It would have to offer significant safety advantages in terms of its handling and use and would also have to be scaleable in their processes in order to provide commercial volumes of fluoro-steroids.
3. It would have to be competitively priced with $FClO_3$ in terms of the steroid fluorination step, with all associated handling and processing costs taken into account.

In addition to the potential customer's criteria for the ideal fluorination agent, we developed a set of our own:

1. It had to be safe for us to produce, handle and ship.
2. The method of its preparation had to be scaleable from the laboratory to commercial volumes.
3. The commercial process had to be economical to practice.
4. Preferably, the new fluorination agent would be a proprietary composition.

With the above criteria firmly in mind, the discovery phase of this development project began with the goal of finding the ''ideal'' fluorination agent.

4. Discovery of the Selectfluor^{TM} family of electrophilic fluorination agents

Apart from the normal influences of serendipity and good luck, there were three key elements of the discovery process that contributed significantly to the timely discovery of the Selectfluor^{TM} fluorination agents.

First, a number of existing electrophilic fluorination agents were evaluated against the criteria that had been established for the ideal agent, and, in every case, several inadequacies were identified. For instance, in the specific cases of xenon difluoride and the *N*-fluoro-quinuclidines, there were serious concerns relating to the cost of producing these reagents at commercial volumes, primarily due to the cost of the xenon and quinuclidine precursors. In addition to the cost, the limited availability of either precursor meant that some sort of spent reagent recovery and recycle process would ultimately be necessary to make the reagents economically viable. Furthermore, there was also some question as to whether the known processes for making these fluorination agents were scaleable, or whether the technology could be protected in a proprietary sense.

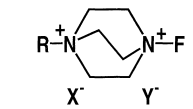
Secondly, a conscious decision was made to focus on Air Products' core competencies, not only in elemental fluorine chemistry, but also in amine chemicals.

Thirdly, a strong and very active technical alliance had been established between the research team in the corporate science and technology center (CSTC) at Air Products and Eric Banks and his coworkers at the University of Manchester Institute of Science and Technology (UMIST), thus providing to the project a world-class resource in academic fluorine chemistry.

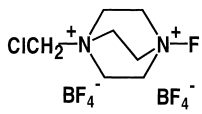
In retrospect, it was a perfect mixture of the three key factors noted above, which, not only suggested an entirely new composition was needed, but also that focused the search on the triethylenediamine (TEDA) moiety as the base molecule. These were the key factors which ultimately led to the discovery of the Selectfluor^{TM} family of fluorination agents.

5. The Selectfluor™ fluorination agent family

The Selectfluor™ family of compositions were actually discovered about 7 years ago by Eric Banks and his co-workers at UMIST who were working under a contract sponsored by the CSTC group at Air Products. It was this discovery that formed the basis of the US composition of matter patent which is assigned to Air Products [18]. In the generic structure of Selectfluor™, below, one can see that the reagent is indeed based on the TEDA moiety which is produced by Air Products' chemicals group as a polyurethane foam catalyst. Furthermore, as the structure is depicted it represents the family of power-variable fluorination agents where the electrophilicity of the N–F bond can be modulated by simply increasing or decreasing the electron withdrawing strength of the R group [1]. In addition, a variety of anion combinations can be selected which impart to these molecules very different solubility characteristics.



Generic structure of Selectfluor™

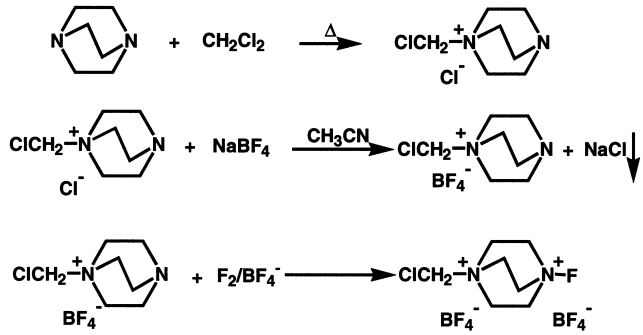


Commercial Selectfluor **1**

Although the Selectfluor™ family represents a variety of compositions, there is currently only one available in commercial quantities. The commercial compound, CM–TEDA–F $(BF_4^-)_2$ **1**, is a white, free-flowing crystalline solid which can be handled safely in ambient air. It incorporates the chloromethyl group as the quaternizing functionality as well as two tetrafluoroborate anions for charge neutrality, and it is the combination of these two properties which impart to this molecule the ideal balance between the N–F bond electrophilicity ("F^+" strength) and overall thermal stability of the molecule. In fact, this compound is second only to the well-known DesMarteau [19] compound, $(CF_3SO_2)_2NF$, in terms of its fluorinating strength and is thermally stable up to about 195°C. Finally, the ease of incorporating both the chloromethyl group and the BF_4 anions made this a good choice as the compound to scale up and commercialize.

6. The commercial process for the production of Selectfluor™

The commercial process for preparing Selectfluor™ **1** is depicted in Scheme 1. The process chemistry has been fully described in detail in other reports [18,20,21]. It is a basic three step process wherein the first reaction involves the chloromethylation of TEDA in refluxing methylene chloride. The second reaction is an anion metathesis reaction



Scheme 1

designed to get the BF_4 anion incorporated. The third and final step of the process is the low-temperature direct fluorination reaction between the monoquaternary precursor salt and fluorine, in the presence of a BF_4 anion source, which leads to the commercial Selectfluor™ compound **1** in excellent yield and with high purity.

What has been summarized to this point is some of the rationale that was used and some of the background behind the discovery of Selectfluor™. What occurred from this point in time onwards was the product development phase of the project, where Selectfluor™ evolved from the laboratory into a viable commercial product.

7. The product development phase

The product development phase for Selectfluor™ had three key components to it which occurred more or less concurrently. Moreover, each of these key components were absolutely critical to the successful commercialization of the fluorination agent, and if any one of the key components had not been successfully accomplished, it is certain that the development of Selectfluor™ would have proceeded no further.

8. The first key component — process development and scale up

The first of the key components was the process development and scale up function. This was a key step in moving the fluorination agent from the laboratory to the pilot plant scale where multi-kilogram test quantities could be generated for applications and safety testing and involved a tremendous amount of effort in terms of developing a chemical process which was suited to a pilot plant environment. Furthermore, the very nature of this process, being an exothermic direct fluorination process, presented numerous process design challenges to overcome in the course of development.

The commercial Selectfluor™ process involves three distinct unit operations which include a low-temperature fluorination conducted in a continuous stirred tank reactor

(CSTR), a slurry separation method, and a product drying step. In terms of scaling up these unit operations there were three primary considerations that had to be addressed.

First, since the process involves the highly exothermic reaction between F_2 and the precursor, there were significant heat transfer challenges to overcome. For instance, fluorine dilution was necessary to achieve an even distribution of fluorine over the entire cross section of the reactor, which aided in controlling the heat of reaction and in preventing localized ''hot spots'' where undesirable side reactions can occur. Achieving the proper fluorine dispersion was also critical to achieve good heat transfer and this was accomplished by careful choice of the type, location, and number of spargers employed. Of course, cooling is of paramount importance as well, and is typically accomplished using a jacketed vessel containing one or more internal cooling coils. The Selectfluor™ cooling system was carefully designed to achieve and maintain a uniform temperature profile and included the careful selection of a heat transfer fluid that not only met the reactor design specifications but also was environmentally safe.

Secondly, because the reaction mixture is heterogeneous, there were significant mass transfer considerations to address, dealing primarily with the mechanism of agitation. Understanding the various aspects of agitation is required to achieve good gas/liquid mass transfer, and becomes even more complicated when solids are being formed in the reactor which must be kept suspended. Combinations of various types of impellers were evaluated in order to achieve the intended results throughout the entire reactor operation. During scale up, particular attention was paid to process optimization with focus on the power per unit volume, the impeller tip speed, and ensuring the proper impeller interactions. Furthermore, because of the dangers associated with fluorine leaks, magnetic drive agitation systems are generally the agitation systems of choice as they are inherently safer to use with no moving seals that can fail.

Thirdly, all process development and scale up activities had to be accomplished with safety being the primary concern. Extensive safety reviews were conducted on the commercial process, and a number of automatic shutdowns were incorporated into the system to guard against any unwanted or unexpected temperature, pressure, or level excursions. After properly sizing rupture discs based on worst case scenarios (runaway reactions or a thermal decomposition), a redundant rupture disc was fitted to the reactor for an additional margin of safety.

9. The second key component — applications and commercial development

The activities of product applications and commercial development effort played crucial roles in keeping the Selectfluor™ product development effort moving in a positive direction. At Air Products, Dr. Sankar Lal led the applications effort and was able to demonstrate that Selectfluor™ not only perform well with a variety of customer specific steroid applications, but also demonstrated its broad general applicability [2]. Keeping pace with the applications development was the commercial development effort led by Gary Saba and his team, which provided the crucial liaison between the customer's requirements and the Air Products development efforts. The customers were involved throughout all aspects of the development process, and their constructive feedback was one of the underlying reasons why the commercial development effort was successful.

In addition, continuous applications support was provided to the customers in terms of working closely with them as their processes were modified and adapted to utilize the new Selectfluor™ fluorination technology.

10. The third key component — safety testing and product stewardship

The third key component of the product development effort involved the extensive safety testing of Selectfluor™ for all conceivable hazards that one could possibly imagine. Some of these tests are used routinely to assess the thermal stability of various compounds on the milligram scale, for instance thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) [22]. However, when a compound is being evaluated for commercial production, the full gamut of thermal testing must be done, which includes evaluations at the multigram scale utilizing accelerating rate calorimetry (ARC) [23,24], the Radex-Solo thermal screening system, and the Phi-Tec [25] method. Perhaps the ultimate test of a compound's thermal stability is the SADT, self accelerating decomposition temperature test, required in some cases for shipping purposes by the United States Department of Transportation. The SADT test involves a 55 (US) gallon drum filled with the test material, which is heated to and held at a temperature of 56°C for a period of 7 days. During this time, the internal temperature of the drum is monitored for temperature excursions from 56°C, which cannot exceed ±5° if the material is to ''pass'' the test. In addition to thermal stability, the material must also be assessed for its shock sensitivity, for instance using the BAM Institutes Fallhammer Test, for explosivity using the card-gap test, and in the case of compounds like Selectfluor™, which is a free-flowing solid, even the dust must be tested for its explosivity using the Fenwal Dust Explosivity Protocol.

As is the case for most new chemical products, a variety of toxicological properties of Selectfluor™ had to be fully understood before it was released for commercial sale. Included here was an evaluation of Selectfluor™ for its oral LD_{50}, 640 mg kg^{-1} (male rat oral), its acute lethal dermal dose, >2.0 g kg^{-1} (rat), its eye and skin irritancy, which is mild in either case (rabbit and guinea-pig), and

even an assessment of the material as a potential carcinogen or mutagen, both negative in the case of Selectfluor™. An important issue to address, and in particular if the material is to be imported into Europe, is an assessment of its environmental impact in the event that it accidentally ends up in some natural body of water. Included here are tests evaluating the effect of the material on the inhibition of algal growth, on activated sewage sludge respiration, and on acute toxicity to rainbow trout, *Oncorhynchus mykiss*, and *Daphnia Magna*.

Finally, proper stewardship of the new material is an important issue to assure continued commercial viability. For instance, in the specific case of Selectfluor™, a tremendous amount of effort was put into the development of new analytical methods in order to meet the rigorous purity standards set by the customers for this new product. And good product stewardship is not limited only to an understanding of the product purity, but extends also to a complete understanding of the impurity profile as well, and the effect of each of the impurities on the thermal stability and fluorination performance of the compound. Lastly, good product stewardship means that a thorough understanding of the bulk properties of the material are required, for instance in terms of materials compatibility, transportation issues, storage conditions, and shelf-life limitations.

11. Summary

The development of Selectfluor™ began in response to what was identified as a real market need for an improved selective fluorination agent, specifically to replace perchloryl fluoride. Although the Selectfluor™ family is a collection of compositions, it was the single composition **1** that was chosen for commercial development since it gave the optimum combination of good thermal stability and fluorination performance. It was this focused effort that permitted commercialization to occur in a 5 year time period. Finally, product stewardship has been done proactively and with the intention of learning and understanding every single aspect of the Selectfluor™ product, beginning with its production and ending with its final use.

Acknowledgements

We are greatly indebted to Professor Eric Banks and his many colleagues for their valued insight and wisdom over the years and, in particular, for the discovery of the Selectfluor™ fluorination agents. We appreciate the vision and leadership provided to the Air Products team by Dr. Guido Pez and Mr. Andy Woytek. Many Air Products colleagues have contributed greatly to the Selectfluor™ success, most notably Dr. Sankar Lal for applications efforts and Mr. Gary Saba and Dr. Reiner Taege for commercial development efforts. Finally, a tremendous crew of dedicated pilot plant operators, analytical technicians, and other support staff at Air Products have each made significant individual contributions which have led to the success of Selectfluor™.

References

[1] R.E. Banks, S.N. Mohialdin-Khaffaf, G.S. Lal, I. Sharif, R.G. Syvret, J. Chem. Soc., Chem. Commun. (1992) 595.
[2] G.S. Lal, J. Org. Chem. 58 (1993) 2791.
[3] R.E. Banks, V. Murtagh, 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane *Bis*(tetrafluoroborate), in: L.A Paquette et al. (Eds.), Encyclopedia of Reagents for Organic Synthesis, vol. 2, Wiley, New York, 1995, pp. 1150–1153.
[4] G.S. Lal, G.P. Pez, R.G. Syvret, Chem. Rev. 96 (1996) 1737.
[5] N.A. Petasis, A.K. Yudin, I.A. Zavialov, G.K.S. Prakash, G.A. Olah, Synlett (1997) 606.
[6] S.V. Ivanov, S.M. Ivanova, S.M. Miller, O.P. Anderson, K.A. Solntsev, S.H. Strauss, Inorg. Chem. 35 (1996) 6914.
[7] H. Thomsen, O. Kaeckel, U. Krause, W. Pretz, Z. Anorg. Allg. Chem. 622 (1996) 2061.
[8] S.V. Ivanov, A.J. Lupinetti, K.A. Solntsev, S.H. Strauss, J. Fluorine Chem. 89 (1998) 65.
[9] P. Ge, K.L. Kirk, J. Org. Chem. 62 (1997) 3340.
[10] G.S. Lal, W. Pastore, R.J. Pesaresi, J. Org. Chem. 60 (1995) 7340.
[11] M.D. Burkart, Z. Zhang, S.-C. Hung, C.-H. Wong, J. Am. Chem. Soc. 119 (1997) 11743.
[12] J.-J. Yang, D. Su, A. Vij, T.L. Hubler, R.L. Kirchmeier, J.M. Shreeve, Heteroatom Chem. 9 (1998) 229.
[13] V. Reydellet-Casey, D.J. Knoechel, P.M. Herrinton, Org. Proc. Res. Dev. 1 (1997) 217.
[14] R.E. Banks, J. Fluorine Chem. 87 (1998) 1.
[15] J.F. Gall, in: E.A. Parolla (Ed.), Kirk-Othmer Encyclopedia of Chemical Technology, vol. 9, 2nd ed., Wiley, New York, 1966, pp. 598–610.
[16] R.G. Syvret, Perchloryl Fluoride, in: L.A. Paquette et al. (Eds.), Encyclopedia of Reagents for Organic Synthesis, vol. 6, Wiley, New York, 1995, pp. 3939–3942.
[17] C.M. Sharts, W.A. Sheppard, Organic Reactions, 21 (1974) 225; and references therein.
[18] R.E. Banks, US Patent 5 086 178, 1992.
[19] S. Singh, D.D. DesMarteau, S.S. Zuberi, M. Witz, H.-N. Huang, J. Am. Chem. Soc. 109 (1987) 7194.
[20] R.E. Banks, M.K. Besheesh, S.N. Mohialdin-Khaffaf, I. Sharif, J. Fluorine Chem. 78 (1996) 43.
[21] R.E. Banks, M.K. Besheesh, S.N. Mohialdin-Khaffaf, I. Sharif, J. Chem. Soc. Perkin Trans. 1 (1996) 2069.
[22] W.W. Wendlandt, Thermal Analysis, chs. 5 and 6, 3rd ed., Wiley, New York, 1986.
[23] D.I. Townsend, J.C. Tou, Thermochim. Acta 37 (1980) 1.
[24] D.W. Smith, M.C. Taylor, R. Young, T. Stephens, American Laboratory, June 1980.
[25] J. Singh, International Symposium on Runaway Reactions, AIChE, NY, 1989, pp 313–330.