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Microwave-Enhanced High-Speed Fluorous Synthesis

Wei Zhang

Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, USA

Abstract

Increasing reaction speed and simplifying product purification are two major ways to improve the efficiency of organic synthesis. A new technology for high-speed solution-phase synthesis has been developed by combination of microwave heating and fluorous purification. This review describes different techniques for microwave-enhanced fluorous synthesis and their applications in Pd-catalyzed cross-coupling reactions, free-radical reactions, multicomponent reactions, and compound library synthesis.

Keywords

Fluorous chemistry; Microwave synthesis; Solid-phase extraction; High-throughput synthesis; Multicomponent reaction

1 Introduction

Over the last decade, a significant amount of effort in high-throughput synthesis (HTS) has been dedicated to the development of solid-phase organic synthesis (SPOS) and production of compound libraries [1,2]. SPOS simplifies the purification process and has the capability to synthesize small quantities of very large libraries by the “split and pool” protocol. However, SPOS has several well recognized limitations [3,4] such as slow reaction kinetics caused by heterogeneous reactions, long method development times, and limitations of reaction scope and scale. Furthermore, the large libraries generated by SPOS usually lack molecular diversity, and compound purities can be inadequate.

In many pharmaceutical and biotechnology companies, the current effort on HTS has been redirected to solution-phase and diversity-oriented syntheses [4]. Compound libraries with high molecular diversity are given more consideration for discovery programs. Small targeted (focused) libraries (roughly 50–200 compounds) are increasingly popular for lead optimization projects. Quantities for testing or deposition in compound collections are increasing to the 10–50 mg range, and requirements for purity have stiffened (> 90% is now common). New synthetic methods are currently needed which are better integrated with medicinal chemistry, less dependent on specialized instruments, easy to combine with existing reaction and separation methods, applicable for both small and large library synthesis, and capable of quickly producing pure compounds. Fluorous chemistry has been developed as a broad-based technology platform that addresses many challenges in the modern drug discovery environment [5].

¹ w.zhang@fluorous.com.

2 Fluorous Technologies

2.1 Fluorous Tagging Strategy

The development of fluororous technologies provides an opportunity to combine solution-phase reactions with phase tag-based separations [6–11]. Per-fluorinated (fluorous) chains such as C_6F_{13} and C_8F_{17} are employed as phase tags to facilitate the separation process. The fluororous chain is usually attached to the parent molecule through a $(CH_2)_m$ segment to insulate the reactive site from the electron withdrawing fluorines. A fluororous chain $C_nF_{2n+1}(CH_2)_m$ can be abbreviated to Rf_nh_m when it is presented in the reaction equation. In principle, any synthetic method developed in conventional solution-phase or in polymer-bound chemistry can be adapted to fluororous synthesis. Fluorous groups can be used to tag reagents (including scavengers and catalysts) (Scheme 1A) or to tag substrates (Scheme 1B) [12]. Fluorous reagents are commonly used for single or short-step parallel synthesis, while fluororous-tagged substrates are more suitable for multistep parallel synthesis [9].

2.2 Fluorous Separation

Fluorous separations rely on the strong and selective affinity interaction between fluororous molecules and fluororous separation media. The separation medium can be fluororous solvents which are immiscible with common organic solvents at room temperature and thus can be used for liquid–liquid extractions. A “heavy fluororous” tag (60% or more fluorine by molecular weight) is required to drive the fluororous molecule to a fluororous phase from a nonfluorous phase. Perfluorinated alkanes such as FC-72 (perfluorohexanes) and highly fluorinated ethers such as HFC-7100 ($C_4F_9OCH_3$) are good solvents for F-LLE. FluoroFlash silica, a commercial product from FTL, with a $-SiMe_2CH_2CH_2C_8F_{17}$ stationary phase is another kind of fluororous separation media which can be used for F-SPE or chromatography [13,14]. Fluorous silica gel separates “light fluororous” molecules which have relatively low fluorine content from compounds with no or different fluorine content. F-SPE is a binary technique that divides mixtures into two fractions based on the presence or absence of a fluororous tag. Fluorophobic solvents such as 80 : 20 MeOH – H_2O is used to elute non-fluorous components, the fluororous component retains on the SPE cartridge until it is eluted with a more fluorophilic solvent such as MeOH. The F-SPE technique can also be used in “plate-to-plate” format [15] for parallel separations. Fluorous-HPLC can be used for analysis and separation of fluororous molecules. Common solvent systems used for reverse-phase HPLC such as MeOH – H_2O and MeCN – H_2O are commonly used for F-HPLC.

2.3 Features of Fluorous Synthesis

Fluorous synthesis integrates the characters of solution-phase reactions and solid-phase-type separations [12]. It has good “combinatorial” capabilities and offers the following advantages: 1) Fluorous reactions can be easily followed by common analytical methods such as TLC, HPLC, IR and NMR; 2) Fluorous components can be separated by fluororous methods as well as conventional methods such as distillation, recrystallization, and chromatography; 3) Compounds with fluororous tags (such as C_8F_{17}) have good solubility in a range of organic solvents, no fluororous solvents are needed for reactions and separations; 4) More than one fluororous reagent can be used in a single reaction; 5) Fluorous methods can easily be adaptation from non-fluorous procedures from the literature; 6) Fluorous synthesis can be combined with other methods such as microwave technology, multi-component reactions, and solid-phase synthesis; 7) Fluorous materials can be recovered after fluororous separation.

The most important characteristics that make fluororous synthesis superior to solid-supported synthesis is the favorable reaction kinetics associated with the solution-phase reactions. Comparison reactions using fluororous vs. solid-supported thiols to scavenge a bromide are shown in Fig. 1 [16]. Using 1.5 equiv of F-thiol **1**, more than 95% bromide was quenched in

less than 40 min (top line). Under the same conditions and using 1.5 equiv PS-thiol **2**, only 50% of the halide was quenched after 80 min (bottom line). By doubling the amount of PS-thiol to 3.0 equiv, the conversion was improved to 95% after 60 min (middle line). The comparison experiment clearly shows that the fluorous reagent reacts much faster than the solid-supported reagent. Fluorous reagents are real molecules, they can be used in a stoichiometric manner and can be analyzed by standard methods such as LCMS and NMR. Solid-supported reagents are functionalized by the user, their chemical and physical properties vary from batch to batch and are difficult to analyze by the user. It is not uncommon that a large excess (3.0 equiv or even more) of solid-supported reagents is used to “over kill” the reactions. This kind of practice results in high costs of reagents as well as high volume of solvent used for the reaction and the resin washes after the reaction. These issues can be avoided in fluorous synthesis.

3 Microwave-Assisted Fluorous Synthesis

3.1 Integrated Reaction and Separation System

Microwave irradiation as a powerful and controlled heating source has been widely employed in organic synthesis to reduce the reaction time, improve yield or selectivity, and reduce the amount of solvent used for reactions [17–21]. The blending of microwave heating and polymer-supported reactions to simplify purification is a logical consequence to address the separation issue. Significant progress has been made in this area [22–25]; however, there are still limitations related to the physical and chemical stability of polymer support under microwave heating and to the heterogeneous nature of solid-phase reactions. The C–F bond of perfluorinated molecules has excellent chemical stability (Teflon is a fluorous polymer), which makes fluorous molecules well suited for microwave reactions at high temperature. Microwave-assisted fluorous synthesis as a new HTS technology could improve both the reaction and purification efficiency [26,27]. An integrated system shown in Fig. 2 is constituted by an automated microwave reactor, a “plate to plate” SPE unit for parallel separations, and a centrifuge system for concentration of products in a plate format [15].

3.2 Metal-Catalyzed Reactions

3.2.1 Fluorous Substrates—One of the most important applications of microwave reactions is for transition-metal-catalyzed transformations [28]. The Curran and Hallberg groups first introduced microwave heating to fluorous Stille reactions (Scheme 2) [29]. The reactions employed $(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_3$ attached tin reagents **3** as substrates, $\text{PdCl}_2(\text{PPh}_3)_2$ as a catalyst, and DMF as a solvent. A slight excess of tin reagent (1.2 equiv) was used to ensure the consumption of the halides or triflates (1.0 equiv). Reactions reached completion under microwave heating in less than 2 min. The reaction mixtures were subjected to a three-phase extraction with FC-84 (perfluoroheptanes), dichloromethane, and water. Fluorous tin derivatives and unreacted tin reagent were distributed to the bottom-phase of the solvent FC-84, the product and the catalyst to the middle-phase of dichloromethane, and LiCl salt to the water phase on top. The product isolated from the fluorous layer was further purified by flash chromatography. To improve the efficiency of fluorous liquid–liquid extraction, a tin reagent with heavier fluorous tags $(\text{C}_{10}\text{F}_{21}\text{CH}_2\text{CH}_2)_3$ has been developed for the Stille reactions [30].

As the longer-chain analogs of triflates and nonaflates, perfluorooctanesulfonates **4** are also highly reactive, stable for room temperature storage, and resistant towards hydrolysis. They can be easily prepared by reaction of various phenols with perfluorooctanesulfonyl fluoride using K_2CO_3 or Cs_2CO_3 as a base. Perfluorooctanesulfonates have been used in Pd-catalyzed transformations including Suzuki–Miyaura, Heck, and Buchwald–Hartwig type reactions to form aryl carbon–carbon, carbon–hydrogen, and carbon–heteroatom bonds (Scheme 3). Using

perfluorooctanesulfonates for multicomponent reactions compound libraries synthesis are described in Sects. 3.3 and 3.4.

A general method for fluororous Suzuki reaction of perfluorooctanesulfonates has been developed using $[\text{Pd}(\text{dppf})\text{Cl}_2]$ ($\text{dppf} = 1,1'$ -bis(diphenylphosphano)ferrocene) as a catalyst, K_2CO_3 as a base, and 4 : 4 : 1 toluene/acetone/ H_2O as a solvent system (Scheme 4) [31]. Reactions were conducted under microwave heating at 100–130 °C for 10 min and the reaction mixtures were directly loaded onto a FluoroFlash cartridge for F-SPE. The biaryl product was collected in the fraction of 80 : 20 MeOH/ H_2O , while the cleaved fluororous tag remained on the cartridge until it was washed out with MeOH.

Using conditions similar to those developed for fluororous Suzuki reactions, aryl sulfides were synthesized by reaction of fluororous sulfonates with thioles (Scheme 5) [32]. The reaction mixtures were in this case also purified by F-SPE.

Fluororous Buchwald–Hartwig type amination reactions using $\text{Pd}(\text{OAc})_2$ and BINAP as a catalyst, Cs_2CO_3 as a base, and toluene as a solvent were examined under microwave and oil-bath heating conditions (Scheme 6) [33]. Under microwave irradiation at 120–150 °C for up to 30 min, reactions did not reach completion. Formation of a dark-brown precipitate suggested that the incomplete reactions could be caused by rapid decomposition of the catalyst under the microwave heating. Under oil-bath heating at 80–90 °C for 48 h, the coupling reactions proceeded smoothly.

Fluororous arylsulfonates have also been employed for deoxygenation reactions with formic acid with $\text{Pd}(\text{dppf})\text{Cl}_2$ as a catalyst, K_2CO_3 as a base, and 4 : 4 : 1 MePhH/ Me_2CO / H_2O as a solvent system (Scheme 7) [34]. The reactions were performed under microwave irradiation at 100 °C for 20 min followed by F-SPE separations to provide purified final products.

3.2.2 Fluororous Catalysts—In last decade, significant progress has been made in fluororous catalysis reactions and recovery of the catalysts by fluororous biphasic separations [14]. The Larhed and Curran groups employed bidentate fluororous-tagged 1,3-bis(diphenylphosphino) propane ligand (F-dppp) for the Heck vinylation reactions. Reactions with fluororous and non-fluororous dppps were examined under microwave and conventional heating conditions (Scheme 8) [35]. Results generated from different reactions are comparable in regioselectivity and yields. The microwave-assisted reaction with F-dppp has advantages of reaction speed, purification, and catalyst recovery; the reaction finished in 15 min and the reaction mixture was directly loaded onto the SPE cartridge for purification, while the reaction with normal dppp and under conventional heating finished in 18 h and was purified by extraction with diethyl ether from the basic aqueous layer.

Larhed and coworkers employed fluororous triphenylphosphine as a ligand and $\text{Mo}(\text{CO})_6$ as a CO source for palladium-catalyzed hydrazidocarbonylations of aryl iodides and bromides (Scheme 9) [36]. The fluororous ligand was recovered by extraction with fluororous solvent FC-84.

Fluororous distanoxane **7** and tin oxide **8** have been evaluated in catalytic transesterification reactions by the Panek and Porco groups for the purpose of easy removal of tin catalysts by F-SPE from the reaction mixture (Scheme 10) [37]. For homodimerization of a monomer under microwave irradiation, it was found that the fluororous tin oxide **8** gave the best yield (80%), while distanoxane **7** enhanced catalytic activity (78% yield) as compared to non-fluororous distanoxanes **5a–c** (42–60% yields) and tin oxide **6** (27% yield).

In addition to fluororous catalysis, the preparation of fluororous catalyst itself can benefit from microwave-assisted synthesis. The Wood group reported the preparation of rhodium

perfluorobutyramide ($\text{Rh}_2(\text{pfm})_4$), a catalyst for olefin aziridinations, under microwave heating (Scheme 11) [38]. The product was isolated from the reaction mixture by FC-72 extraction.

3.3 Free Radical Reactions

Organotin hydrides are popular reagents for free radical reactions. However, the removal of their derivatives from the reaction mixture is not always an easy task. Potential tin residues left in the final product limit the application of tin reagents in medicinal chemistry. One way to address this issue is to use fluoros tin reagents. The Curran and Hallberg groups developed a heavy fluoros tin hydride **9** and used it under continuous microwave heating conditions for halide reduction and cyclization reactions (Scheme 12). Reactions were conducted in benzonitrile (BTF) to increase the solubility of the tin reagent [30]. Reaction mixtures were worked up by a three-phase extraction with FC-84, dichloromethane, and water. The products were further purified by circular chromatography.

3.4 Multicomponent Reactions

Multicomponent reactions (MCRs) have high efficiency in the construction of complex molecules [39,40]. In general practice, more than one reagent is used in excess to push the reaction to go to completion. The unreacted components left in the reaction mixture may complicate the product purification. The employment of a fluoros component as the limiting agent for the MCRs is a good way to simplify the purification.

The Ugi reaction involves components of aldehyde, acid, amine, and isocyanide. Scheme 13 shows an Ugi reaction using fluoros benzyl-attached aniline as the limiting component [41]. The condensed product **10** was fished out from the reaction mixture by F-SPE and use for further derivatization to construct the benzodiazepinedione ring system.

The synthesis of proline-fused heterocyclic systems by 1,3-dipolar cycloaddition has been well-established in solution-phase synthesis (Scheme 14) [42]. It is usually performed as a one-pot, three-component reaction of a dipolarophile with an in situ prepared azomethine ylide. Perfluoroalkanesulfonyl protected hydroxybenzaldehydes [43] or fluoros alcohol protected amino esters [44] have been developed as two different fluoros components for the synthesis of proline derivatives **11** and **12**.

A one-pot, double intramolecular 1,3-dipolar cycloaddition reaction of azomethine ylides was developed by reaction of 4 equiv of an *O*-allyl salicylaldehyde with a fluoros amino ester under microwave heating to generate a novel hexacyclic ring system **13** that contains seven stereocenters (Scheme 15) [45].

3.5 Compound Library Synthesis

Compound library synthesis relies heavily on integrated technologies to address both reaction and separation issues. The good “combinatorial” capability of the fluoros technology has demonstrated its great potential in this area [9].

Perfluorosulfonates have been demonstrated as a valuable fluoros synthon. In multistep synthesis, the perfluorooctanesulfonyl tag plays three roles: 1) as a protecting agent for the hydroxyl group; 2) as a fluoros tag to facilitate intermediate purification; and 3) as an activating group to promote the coupling reaction.

Scheme 16 shows parallel syntheses of cyclic and acyclic amide compounds. Fluoros benzaldehydes were first subjected to reductive amination reactions. The resulting amines were then reacted with isocyanates to form substituted hydantoin rings **14** or with benzoyl chlorides

to form amides **15**. Purified F-sulfonates were used for palladium-catalyzed cross-coupling reactions to form corresponding biaryl **16** [31] and arylsulfide **17** [32] products, respectively.

Scheme 17 illustrates another fluorosulfonate-based synthesis of library scaffolds. The tagged substrates were taken through aldol condensation and cycloaddition reactions to form the pyrimidine ring **18**. The intermediates were then reacted with boronic acids for Suzuki reactions to form biaryl compounds **19** [31], reacted with HCO₂H to give traceless detagged products **20** [34], or reacted with amine to form products **21** [33].

Perfluoroalkanesulfonyl protected hydroxybenzaldehydes have been used together with isonitriles and 2-aminopyridines or 2-aminopyrazines for 3-component condensation reactions to form imidazo[1,2-*a*]pyridine or imidazo[1,2-*a*]pyrazine ring systems **22** (Scheme 18) [46]. The condensed products were employed for Pd-catalyzed cross-coupling reactions with boronic acids or thiols to produce compounds **23** or **24**, respectively.

Zhang and Tempest optimized the Ugi/de-Boc/cyclization synthesis for quinoxalinones **27** and benzimidazoles **28** developed by Humles (Scheme 19) [47]. The original thermal reactions required 36–48 h for the Ugi reaction and the condensation products **25** and **26** were purified by double scavenging with an immobilized tosylhydrazine and diisopropylethylamine to remove excess aldehydes and unreacted acids [48]. Boc-protected diamines were used in the fluorosulfonate approach. The Ugi reactions were finished in 20 min under microwave irradiation and the double scavenging step was replaced by a simple F-SPE. The de-Boc/cyclization step was also conducted under microwave heating and products **27** and **28** were purified by F-SPE.

Parallel synthesis of a bicyclic proline library **29** has been developed by a two-step synthesis involving 1,3-dipolar cycloaddition of fluorosulfonate benzaldehydes followed by Pd-catalyzed Suzuki coupling reactions with boronic acids (Scheme 20) [43]. Both reactions were conducted under microwave irradiation and the reaction mixtures were purified by F-SPE without the need of performing a following chromatography step.

Fluorosulfonate aminoesters have been employed in 3-component 1,3-dipolar cycloaddition reactions and post-condensation modifications in the synthesis of a bridged-tricyclic ring system **30** (Scheme 21) [49].

Fluorosulfonate aminoesters have also been used in DOS of three unique triaza tricyclic and tetracyclic ring systems (Scheme 22) [44]. Bicyclic pyrrolidines **12** generated from one-pot, three-component 1,3-dipolar cycloaddition of azomethine ylides were further converted to hydantoin-, piperazinedione-, and benzodiazepine-fused compounds **31–33**, respectively. Each of these three heterocyclic scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R¹ to R⁴). The structure of compound **31** is similar to tricyclic thrombin inhibitors [50]. The structure of compound **32** is similar to diketopiperazine-based inhibitors of human hormone-sensitive lipase [51]. Compound **33** contains a privileged benzodiazepine moiety which has a wide range of pharmaceutical utilities [52].

The synthesis of N-alkylated dihydropteridinones **34** started with a displacement reaction of 4,6-dichloro-5-nitropyrimidine with a fluorosulfonate amino-ester (Scheme 23) [53]. The compounds formed **35** were then reacted with secondary amines to yield **36**. The reduction of the nitro group of **36** was conducted by hydrogenation using Pd on charcoal as a catalyst. The cyclization reactions of **37** were promoted by microwave irradiation. The N-alkylation reaction of the cyclized products **38** with benzyl halides gave monobenzylated products **34** in high selectivity. All the intermediate and final products were purified by F-SPE or crystallization.

In the synthesis of a compound library of allosteric Akt kinase inhibitors **39**, Lindsley and coworkers employed different HTS techniques (Scheme 24) [54]. A polymer-supported base

and a fluorous thiol scavenger were used in the alkylation reaction of **40**. F-SPE purified intermediate was then used for microwave-assisted cycloaddition of **41**. Similar intermediates have been used for generation of an unnatural canthine alkaloid library **42** by performing cycloaddition reactions with an indo-tethered acyl hydrazide [55].

Ladlow and coworkers recently developed an acid-labile fluorous benzaldehyde protecting group **43** to facilitate the parallel synthesis of sulfonamides **44** (Scheme 25) [56]. The Suzuki coupling step was conducted under microwave irradiation. All the intermediates and the final products were purified by F-SPE.

4 Summary and Outlooks

The integration of microwave heating and fluorous technologies has generated a powerful solution to address both the reaction and separation issues in parallel and combinatorial synthesis. With the further development of multimode microwave reactors for plate reactions and F-SPE for plate-to-plate separations, microwave-assisted fluorous synthesis will play an even more important role in compound library synthesis.

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Abbreviations

μw	microwave
HTS	high-throughput synthesis

SPOS	solid-phase organic synthesis
FTI	Fluorous Technologies, Inc
Rf_n h_m	$C_nF_{2n+1}(CH_2)_m$
F-LLE	fluorous liquid–liquid extractions
F-SPE	fluorous solid-phase extraction
HPLC	high-performance liquid chromatography
TLC	thin-layer chromatography
IR	infrared spectroscopy
NMR	nuclear magnetic resonance
LCMS	liquid chromatography and mass spectrometry
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BTF	benzotrifluoride
MCR	multicomponent reaction
DOS	diversity-oriented synthesis

Fig. 1.
Comparison of fluoros and PS-scavenging reactions

Fig. 2.

A microwave-assisted fluororous synthesis system, microwave reactor (*left*), plate-to-plate SPE (*middle*), and a plate centrifuge unit (*right*)

A) Reagent Tagging **B) Substrate Tagging**

Scheme 1.
Fluorous tagging strategies

Scheme 2.
Stille reactions with fluorinated substrates

Scheme 3.
Fluorous arylsulfonate-based coupling reactions

Scheme 4.
Fluorous Suzuki reactions

Scheme 5.
Formation of aryl sulfides

Scheme 6.
Amination reactions of fluorosulfonyl aryl ketones

Scheme 7.
Deoxygenation of fluorosulfonates

Scheme 8.
Fluorous catalyst for Heck reactions

Scheme 9.

Fluorous catalyst for hydrazidocarbonylation reactions

Scheme 11.
Synthesis of fluorous catalyst

$(\text{C}_{10}\text{F}_{21}\text{CH}_2\text{CH}_2)_3\text{SnH}$ **9**

Scheme 12.
Fluorous tin-promoted free radical reactions

Scheme 13.
Fluorous Ugi reaction

Scheme 14.
Fluorous 1,3-dipolar cycloaddition reactions

Scheme 15.
Double 1,3-dipolar cycloaddition reaction

Scheme 16. Synthesis of diversified cyclic and acyclic amide compounds **16** and **17**

Scheme 17.
Multi-step synthesis of substituted pyrimidines **19–21**

Scheme 18.
MCRs for synthesis of heterocyclic libraries **23** and **24**

Scheme 19.
Synthesis of quinoxalinones **27** and benzimidazoles **28**

Scheme 20.
Synthesis of biaryl substituted prolines **29**

Scheme 21.
Synthesis of bridged-tricyclic ring system **30**

Scheme 22.
Fluorous synthesis of diversified heterocyclic ring systems

Scheme 23. Fluorous synthesis of N-alkylated dihydropteridinones **34**

Scheme 24.
Synthesis of libraries **39** and **42**

Scheme 25.
Synthesis of sulfonamides **44**