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Fluorous-Enhanced Multicomponent Reactions for Making Drug-Like Library Scaffolds

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Abstract

Multicomponent reactions (MCRs) generate multiple bonds in a single reaction process, which is highly efficient to construct relatively complex molecules. Conducting post-MCR modification reactions further increases the molecular complexity and diversity. MCR has become a powerful approach to make drug-like molecules in lead generation chemistry. In fluorous MCR (F-MCR), one of the starting materials is attached to a fluorous tag and used as the limiting agent. After the MCR, the fluorous component is fished out from the reaction mixture and used for post-MCR modifications. The fluorous tag can be finally removed in traceless fashion by displacement or cyclization reactions. Unique fluorous technology such as fluorous solid-phase extraction (F-SPE) facilitates the separation process. Other techniques such as microwave irradiation and plate-to-plate SPE can also be used to make the F-MCR even more efficient. Syntheses of unique heterocyclic and natural product-like library scaffolds using Ugi/de-Boc/cyclization, MCR/Suzuki coupling, and [3+2] cycloaddition/de-tag/cyclization protocols are described in this paper.

Keywords

diversity-oriented synthesis; drug-like molecules; fluorous synthesis; library scaffolds; microwave reactions; multicomponent reactions; solid-phase extraction

INTRODUCTION

Since the late 1980's, a significant amount of effort on lead generation chemistry has been spent on solid-phase organic synthesis (SPOS) of compound libraries [1,2]. SPOS has advantages of simple product separation and production of large number of libraries. However, the inherent disadvantages such as heterogeneous reaction environment, long method development times, and difficulty to analyze attached intermediates have limited the further development of SPOS [3,4]. In last years, many pharmaceutical and biotechnology companies have redirected the lead generation chemistry to parallel solution-phase synthesis and emphasized production of smaller libraries with high molecular diversity, bigger quantity, and higher purity [4]. Fluorous technology combines the characteristics of a solution-phase reaction with solid-phase separation techniques. It has high combinatorial potency like the adoption of existing reaction conditions, less dependent on specialized instruments, easy analysis of attached intermediates, and quickly produces pure compounds [5–10]. As such it emerges as a new broad-based technology platform for organic synthesis and drug discovery chemistry.

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FLUOROUS MULTICOMPONENT REACTION AND PURIFICATION

Multicomponent reactions (MCRs) have high efficiency for rapid assembly of complex molecules [11–16]. However, the number of known MCRs is limited. In order to produce novel library scaffolds, it usually requires performing post-MCR modifications to increase the molecular complexity and also the molecular diversity. In fluorous MCRs (F-MCRs) (Fig. 1), one of the starting materials containing a fluorous tag is used as the limiting agent. After the condensation reaction, the fluorous component is separated from the reaction mixture containing many non-fluorous components by fluorous tag-based separation [17]. The fluorous component is then subjected to post-MCR modifications and the fluorous tag is finally removed in traceless fashion by conducting displacement or cyclization reactions. The purification of intermediates and final products can be achieved by simple fluorous solid-phase extraction (F-SPE) (Fig. 2) [18–20]. The fluorous silica gel with $-\text{Si}(\text{Me})_2\text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$ as a stationary phase selectively retains the fluorous molecules when the mixture is eluted with a fluorophobic solvent such as 80:20 MeOH- H_2O . The fluorous molecule is released from the SPE cartridge when washing with a fluorophilic solvent such as 100% MeOH. For parallel synthesis of compound libraries, the F-SPE can be performed in 24-, 48-, or 96-well plate-to-plate formats [21] to increase the throughput (Fig. 3, left picture). Automated F-SPE has also been developed using the RapidTrace SPE workstation [22]. The large scale intermediate purifications can be accomplished on flash chromatography systems available from Biotage or Isco and equipped with fluorous cartridges (Fig. 3, right picture). Other techniques such as microwave irradiation can be used to reduce the reaction time and to make F-MCRs even more efficient [23–27].

Amines, benzaldehydes, and carboxylic acids are popular reagents for MCRs. Similar reagents attached to fluorous protecting groups [28,29] have been employed for F-MCRs. Syntheses of structurally diverse library scaffolds using Ugi/de-Boc/cyclization, MCR/Suzuki coupling, and [3+2] cycloaddition/de-tag/cyclization approaches are described in this paper (Fig. 4).

UGI/DE-BOC/CYCLIZATION PROTOCOL

The Ugi/de-Boc/cyclization approach to synthesize quinoxalinones **1** and benzimidazoles **2** was originally developed by the Hulme group (Fig. 5) [30,31]. The Ugi reactions were conducted at room temperature and required 36–48 h for completion. The condensation products **3** and **4** were purified by double scavenging with polymer-supported tosylhydrazine and diisopropylethylamine to remove excess aldehydes and unreacted acids, respectively. Final products produced by de-Boc/cyclization were purified by flash chromatography. A microwave-assisted fluorous approach has been developed to reduce the reaction time and simplify the purification (Fig. 5) [32]. The Ugi reactions were finished in 20 min under microwave irradiation using F-Boc-protected diamine as the limiting agent. The original double scavenging step was replaced by a simple F-SPE. The de-Boc/cyclization step was also conducted under microwave heating and products **1** and **2** were purified by F-SPE. We have noticed that the F-Boc group is slightly more stable towards TFA deprotection. A higher concentration of TFA-THF (1:1) was used for Boc cleavage under the microwave heating conditions.

The benzodiazepine-quinazolinone ring skeleton **9** can be found in many natural alkaloids such as circumdatins [33], benzolmalvin [34,35], asperlicin [36], and sclerotigenin [37,38]. This scaffold has been synthesized by the Ugi/de-Boc/cyclization protocol (Fig. 6) [39]. The regular Boc group was used to protect the anthranilic acid, and fluorous benzyl amine (F-Bn) was used as the limiting agent to generate Ugi condensation product **5**. TFA-THF (1:1) was used for selective de-Boc/cyclization to form benzodiazepinedione **6**. A small amount of de-Bn compound was also detected. The compound **6** was acylated with 2-nitrobenzoyl chloride. The nitro group of **7** was then reduced with zinc dust in acetic acid under sonication. The resulted

amino group spontaneously cyclized to form benzodiazepine-quinazolinone ring system **8**. The F-Bn was removed by treatment with 90:5:5 TFA-H₂O-dimethylsulfide to give final product **9**.

MCR/SUZUKI COUPLING PROTOCOL

Perfluorosulfonyl-attached benzaldehydes **10** are a valuable synthon for F-MCRs (Fig. 7). They can be easily prepared by reaction of readily available perfluorooctanesulfonylfluoride with hydroxybenzaldehydes under a general reaction condition [40]. In a multistep synthesis, the perfluorooctanesulfonyl tag has three functions: 1) protection of the hydroxyl group; 2) introduction of fluorine tag for F-SPE; and 3) activation of the hydroxyl group for Suzuki-type coupling reactions. In addition to the Suzuki coupling reactions, other Pd-catalyzed coupling reactions can also be used for tag cleavage [41–43]. Aryl perfluorooctanesulfonyl group is a good aryl iodide and aryl bromide alternative.

In a three-component MCR, a fluorine benzaldehyde was reacted with isonitrile and 2-aminopyridine or 2-aminopyrazine to form imidazo[1,2-*a*]pyridine or imidazo[1,2-*a*]pyrazine ring systems **11** [44]. The condensation products were then employed for Suzuki-type reactions with boronic acids or thiols to form compounds **12**. A library prepared by parallel synthesis using four sets of building blocks is shown in Fig. 8.

Fluorine benzaldehydes have been used for one-pot, three-component 1,3-dipolar cycloaddition of azomethine ylides to form proline-fused heterocyclic systems **13** (Fig. 9) [45]. The cycloaddition products were subjected to the Suzuki coupling reactions to displace the tag and introduce an additional functional group. Four sets of building blocks were used for a two-step parallel synthesis of diaryl-substituted proline derivatives **14** which have four points of diversity.

The spirooxindole ring exists in several natural products which have desirable biological activities [46]. The ring skeleton can be easily assembled by a three-component reaction involving fluorine α,β -unsaturated ketone **15**, amino acid, and *N*-phenyl isatin [47]. The fluorine tag attached to **16** was removed by the Suzuki coupling reaction for post-MCR modification to further decorate the scaffold (Fig. 10).

[3+2] CYCLOADDITION/DE-TAG/CYCLIZATION PROTOCOL

Another important synthon for F-MCRs are fluorine aminoesters **18**. They have been used in [3+2] cycloaddition/de-tag/cyclization protocol for making library scaffolds (Fig. 11). A fluorine aminoester as the limiting agent can react with aldehydes and alkenes for one-pot, three-component cycloaddition through azomethine ylides. This reaction can be conducted under conventional or microwave heating. The cycloaddition was highly stereoselective and generated bicyclic pyrrolidines **19** [48]. The X-ray crystal structure analysis of compound **19** is shown in Fig. 12. The [3+2] cycloaddition product can be easily separated from the reaction mixture containing unreacted non-fluorine starting materials by F-SPE. The ¹H NMR spectra of compound **19** before and after F-SPE are shown in Fig. 13.

Proline derivatives generated from the [3+2] cycloaddition have been used for diversity-oriented synthesis (DOS) of hydantoin-, piperazinedione-, and benzodiazepine-fused heterocyclic scaffolds **21**, **23**, and **25** (Fig. 14) [48]. Each of these three scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R¹ to R⁴). The structure of compound **21** is similar to tricyclic thrombin inhibitors [49], the structure of compound **23** is similar to diketopiperazine-based inhibitors of human hormone-sensitive lipase [50], while compound **25** contains a privileged benzodiazepine moiety which has a wide range of pharmaceutical utilities.

Synthesis of scaffold **21** was accomplished by reaction of **19** with 5 equiv. of phenylisocyanate in the presence of catalytic amount of *N,N*-4-dimethylaminopyridine (DMAP) to give urea **20**. Compound **20** was mixed with K_2CO_3 and heated under microwave for fluorine tag cleavage and formation of hydantoin-fused product **21**. Piperazinedione-fused tricyclic scaffold **23** was synthesized by acylation of **19** with chloroacetyl chloride followed by chlorine displacement with $BuNH_2$ to form **22**. The detag/cyclization reaction was promoted by 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) under microwave heating to give **23**. Synthesis of benzodiazepine-fused scaffold **25** was accomplished by a three-step post-MCR modification. *N*-acylation of **19** with 2-nitrobenzoyl chloride followed by zinc-acetic acid reduction under sonication gave compound **24**. The fluorine tag cleavage promoted by DBU produced benzodiazepinedione-fused scaffold **25**. The chemistry developed for scaffolds **21** and **25** has been applied to fluorine mixture synthesis of libraries [51].

In the synthesis of a bridged-tricyclic ring system **28** (Fig. 15) [52], fluorine aminoester reacted with a slightly excess amount of *N*-alkylmaleimide and *N*-phthalimidoacetaldehyde to form **26**. After the cycloaddition product **26** was acylated to form **27**, it underwent hydrazinolysis to give the desired product **28**. This three step synthesis produced a unique heterocyclic compound with three points of diversity [53].

In the development of [3+2] cycloaddition reactions using fluorine aminoesters as the starting material, we discovered an unprecedented reaction sequence which produced a novel hexacyclic ring system **29** (Fig. 16) [54]. One-pot, double intramolecular 1,3-dipolar cycloaddition reaction using 4 equiv. of an *O*-allyl salicylaldehyde and one equiv. of a fluorine aminoester under microwave heating generated the polycyclic ring in stereoselective fashion. The structure of the major diastereomer has been confirmed by X-ray crystal structure analysis. This is a highly efficient reaction which generates four new rings, six bonds, and seven diastereocenters in an one-pot reaction.

CONCLUSION AND OUTLOOK

Although the landscape of drug discovery chemistry had significant changes recently, new synthetic techniques which reduce reaction time, increase yield and selectivity, simplify product purification, and that can be easily automated are well appreciated by organic and medicinal chemists. The development of solution phase-based fluorine technology is targeted to meet those demands. As a newcomer to the family of combinatorial chemistry, fluorine technology has demonstrated a good “combinatorial capability” for embracing other high-throughput synthesis and purification techniques. F-MCR protocols for synthesis of drug-like molecules described in this paper exemplify the integration of MCR, microwave reaction, and F-SPE technique to improve the efficiency of existing chemistry and to explore new chemistry as well. The broad fluorine technology platform generates more and more impacts on synthesis, purification, immobilization, microarray, and screening of small molecules and biomolecules for life science applications [28,55].

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Fig. 1.
Conceptual figure of fluorine MCR and post-MCR modification

Fig. 2.
Cartoon of fluororous solid-phase extraction

Fig. 3.
Pate-to-plate and flash column F-SPE systems

Fig. 4.
Fluorous multicomponent synthesis of diverse library scaffolds

Fig. 5.
Syntheses of quinoxalinones **1** and benzimidazoles **2**

Fig. 6.
Synthesis of benzodiazepine-quinazolinones **9**

Fig. 7.
Fluorous benzaldehydes **10** for F-MCRs

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Fig. 9.
Synthesis of diaryl-substituted proline derivatives **14**

Fig. 10.
Synthesis of a spiroheterocyclic system **17**

Fig. 11.
Diversified library scaffolds produced from fluorous aminoesters **18**

Fig. 12.
Synthesis of compound **19** and its X-ray crystal structure

Fig. 13.
¹H NMR spectra of compound **19** before (top) and after (bottom) F-SPE

Fig. 14.
[3+2] cycloaddition/de-tag/cyclization protocol for DOS

Fig. 15.
Synthesis of bridged-heterocycle scaffold **28**

Fig. 16.

One-pot synthesis of a novel hexacyclic ring system **29** and proposed mechanism