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Fluorous Synthesis of Hydantoin-, Piperazinedione-, and Benzodiazepinedione-Fused Tricyclic and Tetracyclic Ring Systems

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Abstract

Fluorous proline derivatives generated from one-pot, three-component [3+2] cycloaddition of azomethine ylides are employed for different post-condensation reactions to form hydantoin-, piperazinedione-, and benzodiazepinedione-fused tricyclic and tetracyclic ring systems. The high synthetic efficiency is achieved by conducting fast microwave reactions and easy fluorous-solid phase extractions for reaction mixture purifications. Methods developed for these novel drug-like heterocyclic compounds can be applied to diversity-oriented library synthesis.

Keywords

Fluorous synthesis; Microwave reaction; Solid-phase extraction; [3+2] Cycloaddition; Diversity-oriented synthesis

Introduction

Fluorous synthesis employs perfluoroalkyl (Rf) chains as “phase tags”[1] to improve the efficiency of reaction mixture purifications.[2] This technology shares the characteristics of solution-phase synthesis, which has homogenous reaction enviroment,[3] easy intermediate analysis,[4] and good compatibility to other synthetic techniques such as microwave[5] and multicomponent reactions.[6] Compared to its counterpart solid-phase synthesis, fluorous synthesis requires less development time and has the capability to explore new reactions on fluorous support directly.[7] As a “beadless” synthetic technology, fluorous synthesis has been applied to parallel and mixture synthesis[8] of small molecules, peptides,[9] and oligosaccharides.[10]

We have recently developed several methods for synthesis of heterocyclic systems by using an orchestrated sequence of microwave-assisted fluorous multicomponent reaction (F-MCR) and fluorous-solid phase extraction (F-SPE) to speed up reactions and simplify purifications.[6,11] Reported in this paper are approaches to three novel triaza tricyclic and tetracyclic ring systems **2**–**4** (Scheme 1). Proline derivatives **1** generated from one-pot, three-component [3+2] cycloaddition[12] of azomethine ylides are further converted to hydantoin-, piperazinedione-, and benzodiazepinedione-fused compounds **2**–**4,** respectively. Each of these

Supporting Information General experimental procedures and analytical data for representative intermediates and all final products are provided.

three heterocyclic scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R1 to R^4). Compound **2** has a similar ring skeleton as tricyclic thrombin inhibitors.[13] The structure of compound **3** is partially related to diketopiperazine-based inhibitors of human hormone-sensitive lipase.[14,15] Compound **4** contains a privileged benzodiazepine moiety which has a wide range of pharmaceutical utilities.[16]

Results and Discussion

Preparations of fluorous amino esters **5** and one-pot, three-component 1,3-dipolar cycloaddition reactions were conducted by following established procedures.[6a,b] Thus a mixture of 1.0 equiv of a fluorous aminoester, 1.2 equiv of a benzaldehyde, 1.5 equiv of an *N*-alkylmaleimide, and 3 equiv of Et3N in DMF was heated under microwave at 130 °C for 20 min to afford proline derivative **1** (Scheme 2).[17,18] Since the fluorous amino ester **5** was used as the limiting agent, only the desired product **1** was expected to be fluorous. The crude product was loaded on a Fluoro*Flash* cartridge. The non-fluorous components such as unreacted aldehyde, *N*-alkylmaleimide, and Et_3N salt were eluted out with a fluorophobic solvent (80:20 MeOH-H_2O). Fluorous compound **1** was collected by eluting with MeOH, a more fluorophilic solvent. After F-SPE purification, the purity of the product is usually greater than 90% by ^1H NMR analysis (Figure 1). Bicyclic prolins **1** with different R^1–R^3 substitution groups were synthesized in 75–90% yields. The stereochemistry of compound **1a** was established based on the literature information[17c,17g] and confirmed by single-crystal X-ray diffraction (Figure 2, left). No evidence shows the racemization of the amino acid **5** during the cycloaddition.

With the key intermediates **1** in hands, we then performed post-condensation reactions to generate different heterocyclic ring systems. The reaction of **1** with 5 equiv of a phenylisocyanate or a phenylthioisocyanate in the presence of catalytic amount of *N*,*N*-4-dimethylaminopyridine (DMAP) in toluene gave urea or thiourea **6**. After F-SPE purification, compound **6** was mixed with K_2CO_3 and heated under microwave at 100 °C for 5 min. Fluorous tag cleavage and hydantoin ring formation produced tricyclic compound **2** (Scheme 3). Four analogs of **2** were produced in 75–85% yields. After F-SPE followed by HPLC purifications, the products had greater than 95% purities. The stererochemistry of compound **2a** was confirmed by single-crystal X-ray diffraction (Figure 2, right).

In the synthesis of piperazinedione-fused tricyclic compounds **3a** and **3b** (Scheme 4), direct *N*-acylations of **1a** with α-aminoacids or α-aminoacid chlorides were attempted, but reactions gave products in very low yields (10–25%). Acylation of **1a** with chloroacetyl chloride followed by chlorine displacement with $BuNH_2$ or 3,5-dimethylaniline gave compounds **8a** and **8b** in 92% and 90% yields, respectively. The detag/cyclization reactions were promoted by 1,8-diazabicyclo[4.3.0]non-5-ene (DBU) under microwave irradiation at 180 °C for 15 min to give product **3a** in 45% yield. However, under the same conditions, only a very small amount of **3b** (<5%) was detected from the reaction mixture by LCMS.

Synthesis of benzodiazepine-fused tricyclic compounds **4a**–**c** were accomplished by a three-step reaction sequence (Scheme 5). *N*-acylation of **1** with 2-nitrobenzoyl chloride gave acylation product **9**. We have found that the *N*-acylation reaction was sensitive to the R^1 substitution; only small R^1 groups such as H and Me gave products in good yields. Compounds **9** were then reacted with zinc dust in acetic acid under sonication to reduce the nitro group and form **10**. The cyclative tag cleavage of compounds **10** with DBU produced tricyclic compound **4a**–**c** in 45–58% yields.

Conclusion

In summary, we have developed synthetic routes to three triaza tricyclic and tetracyclic rings systems using the common intermediates generated by [3+2] cycloaddition of azomethine ylides. Microwave-assisted fluorous synthesis speeds up reactions and simplifies product purifications. These heterocyclic compounds with ring skeleton, stereochemistry, and substitution variations are good candidates for diversity-oriented synthesis.

Supplementary materials

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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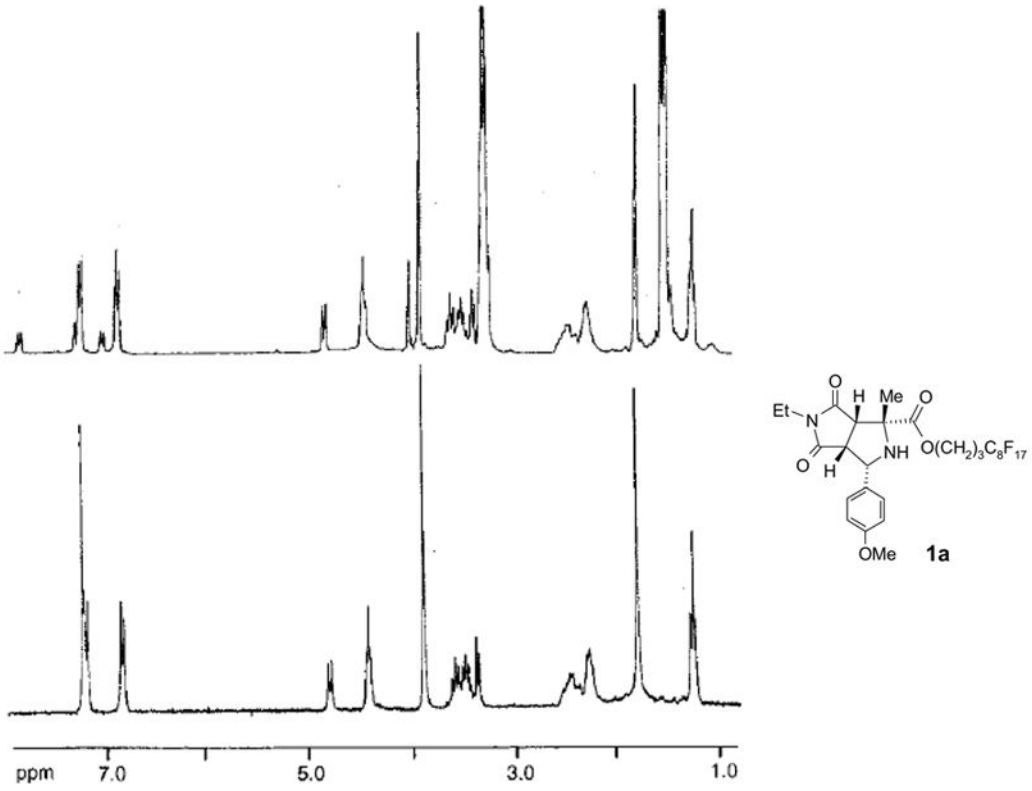


Figure 1.
^{1}H NMR (in $CDCl_3$) analysis of compound **1a,** before (top) and after (bottom) F-SPE.

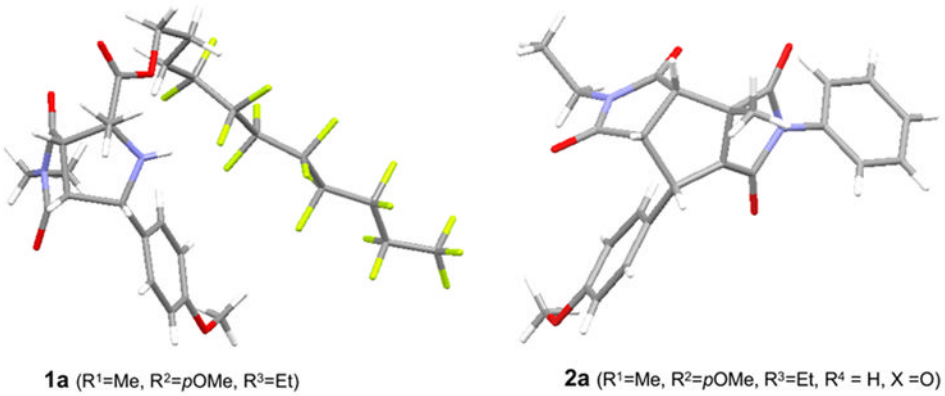
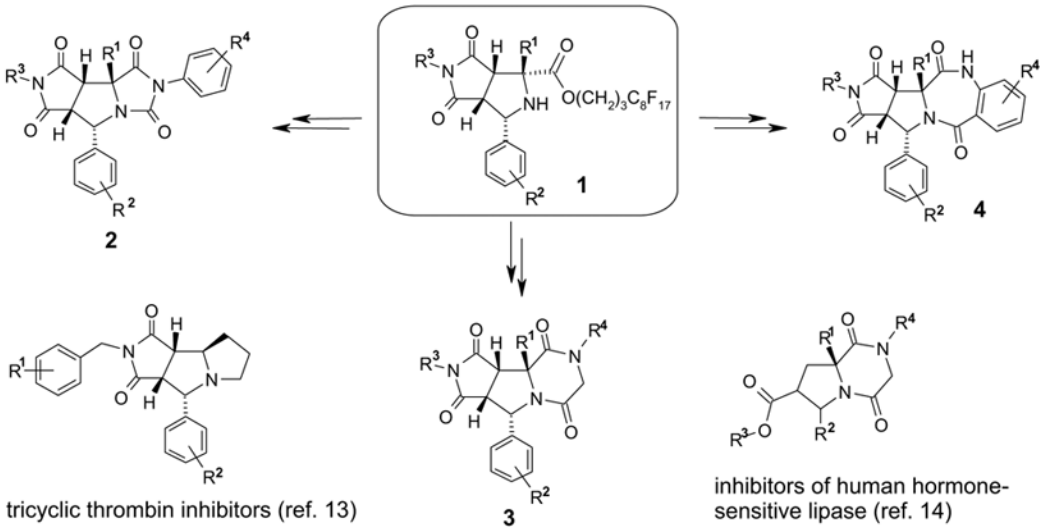
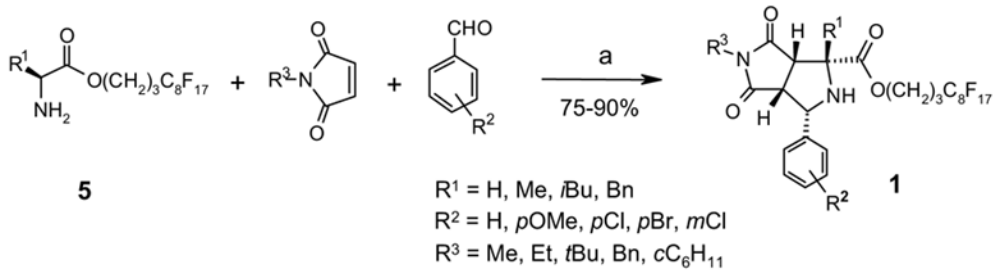


Figure 2.
Single-crystal X-ray structures of compounds **1a** and **2a**

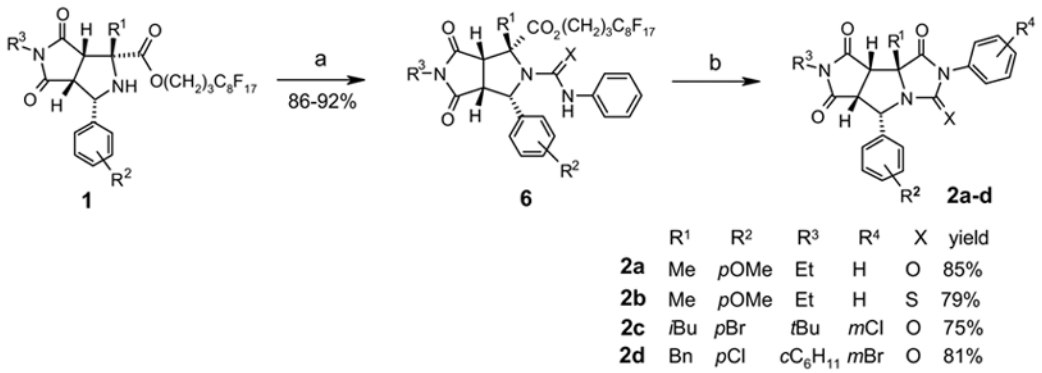


Scheme 1.
Fluorous Synthesis of Heterocyclics **2**–**4**



Scheme 2.

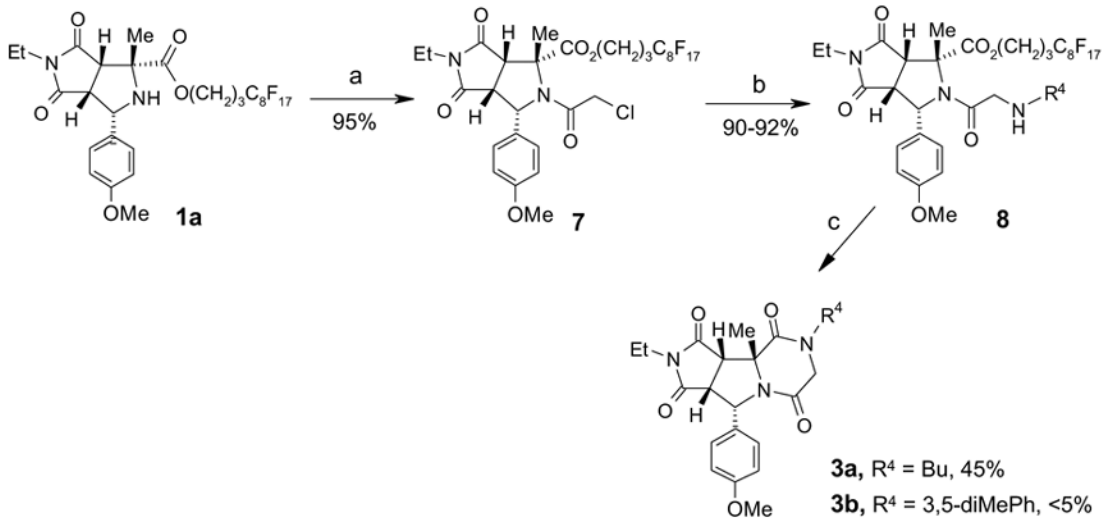
Synthesis of fluorous proline derivatives by one-pot [3+2] cycloaddition of azomethine ylides. a) **5** (1 equiv), aldehyde (1.2 equiv), maleimide (1.5 equiv), Et_3N (3 equiv), DMF, μw (130 ° C, 20 min), F-SPE.



	R¹	R²	R³	R⁴	X	yield
2a	Me	*p*OMe	Et	H	O	85%
2b	Me	*p*OMe	Et	H	S	79%
2c	*i*Bu	*p*Br	*t*Bu	*m*Cl	O	75%
2d	Bn	*p*Cl	cC_6H_{11}	*m*Br	O	81%

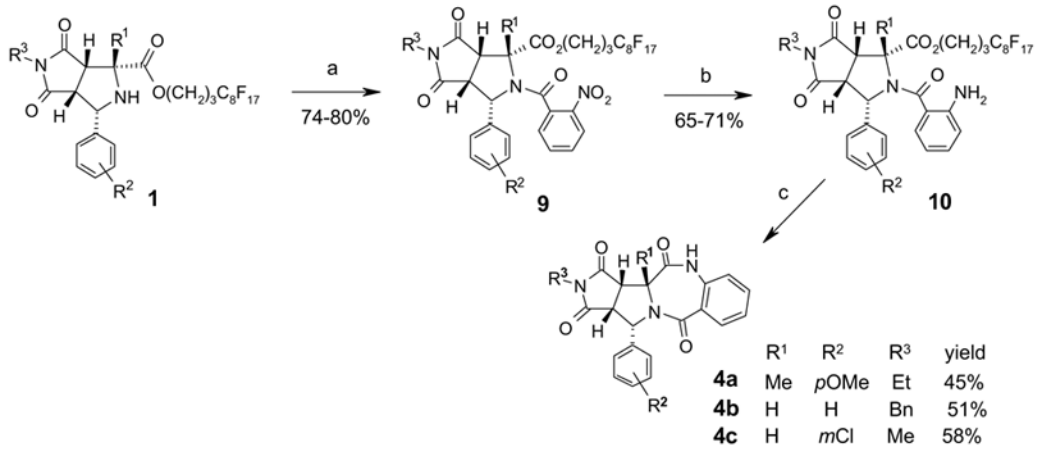
Scheme 3.

Synthesis of hydantoin-fused tricyclic compounds **2a**–**d**. a) R^4-PhNCX (5.0 equiv), DMAP (0.5 equiv), toluene, μw (130 °C, 10 min), F-SPE. b) K_2CO_3 (2 equiv), DMF, μw (100 °C, 5 min), F-SPE, HPLC.



Scheme 4.

Synthesis of piperazinedione-fused tricyclic compounds **3a**–**d.** a) $ClCH_2COCl$ (1.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 25 °C, 30 min, F-SPE. b) R^4NH_2 (2.5 equiv), MeOH, μw (120°C, 10 min), F-SPE. c) DBU (2 equiv), MeOH-DMF, μw (180 °C, 15 min), F-SPE, HPLC.



Scheme 5.

Synthesis of benzodiazepinedione-fused tetracyclic compounds **3a**–**d.**a) 2-nitrobenzoylchloride (3 equiv), Et_3N (2 equiv), DMF, 80 °C, 2 h, F-SPE. b) Zn dust (10 equiv), AcOH, sonication, 25 °C, 2 h, F-SPE, 65–71%. c) DBU (2 equiv), dioxane, μw (130 °C, 5 min), F-SPE, HPLC.