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

Wei Zhang,*[a] Yimin Lu,[a] Christine Hiu-Tung Chen,[a] Dennis P. Curran,[b] and Steven Geib[b]

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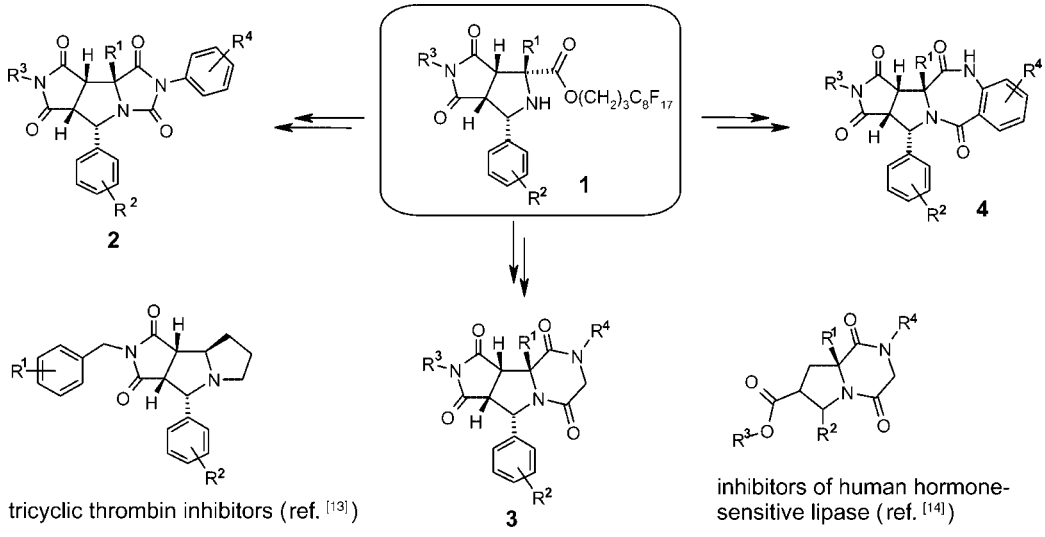
Fluorous proline derivatives generated from one-pot, three-component [3+2] cycloaddition of azomethine ylides are employed in different post-condensation reactions to form hydantoin-, piperazinedione-, and benzodiazepinedione-fused tricyclic and tetracyclic ring systems. High synthetic efficiency is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

Introduction

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



Scheme 1. Fluorous synthesis of heterocycles **2**–**4**.

We have recently developed several methods for the synthesis of heterocyclic systems by using an orchestrated sequence of a microwave-assisted, fluorous multicomponent reaction (F-MCR) and fluorous solid-phase extraction (F-

[a] Fluorous Technologies, Inc. University of Pittsburgh Applied Research Center,
970 William Pitt Way, Pittsburgh, Pennsylvania 15238, USA
Fax: +1-412-628-3053
E-Mail: w.zhang@fluorous.com
[b] Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA
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SPE) to speed up reactions and simplify purification.[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 three heterocyclic scaffolds has four stereocenters on the central pyrrolidine ring and up to four points of diversity (R^1 to R^4). Compound **2** has ring skeleton similar to those of 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,6b] Thus a mixture of a fluorous amino ester (1.0 equiv.), a benzaldehyde (1.2 equiv.), an *N*-alkylmaleimide (1.5 equiv.), and Et_3N (3 equiv.) in DMF was heated under microwave irradiation 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 onto a Fluoro*Flash* cartridge. The non-fluorous components such as the 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 methanol, a more fluorophilic solvent. After F-SPE purification, the purity of the product was usually >90% as determined by ^1H NMR spectroscopic analysis (Figure 1). Bicyclic prolines **1** with different R^1–R^3 substitution groups were synthesized in 75–90% yields. The stereochemistry of compound **1a** was established on the basis of literature information[17c,17g] and was confirmed by single-crystal X-ray diffraction (Figure 2, left). There is no evidence for the racemization of amino acid **5** during the cycloaddition.

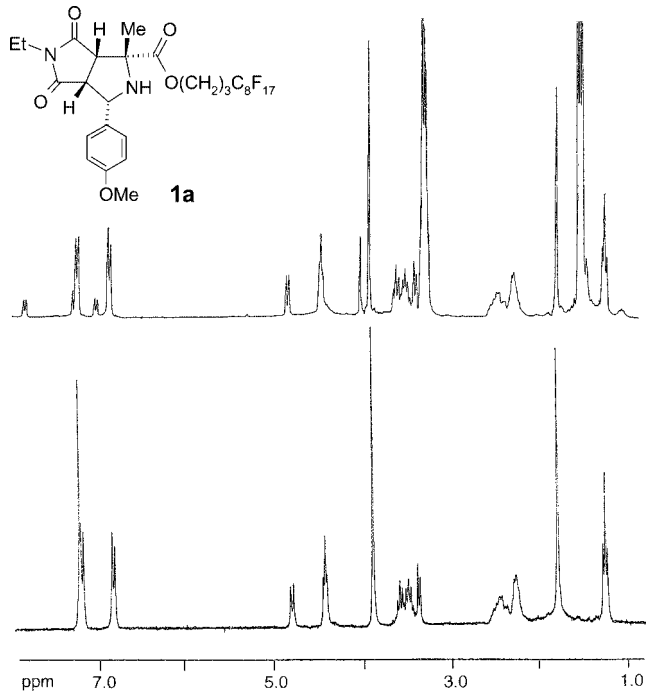
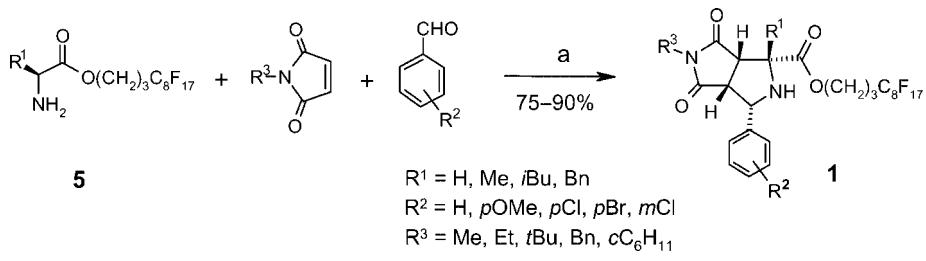


Figure 1. ^1H NMR spectroscopic analysis (in $CDCl_3$) of compound **1a**, before (top spectrum) and after (bottom spectrum) F-SPE.

With the key intermediates **1** in hand, we then performed post-condensation reactions to generate different heterocyclic ring systems. The reaction of **1** with a phenylisocyanate or a phenylthioisocyanate (5 equiv.) in the presence of a 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 irradiation at 100 °C for 5 min. Fluorous tag cleavage and hydantoin ring formation led to tricyclic compound **2** (Scheme 3). Four analogs of **2** were produced in 75–85% yields. After F-SPE and HPLC purification, the purities of the products were >95%. The stereochemistry 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*-acylation of **1a** with α-amino acids or α-amino acid chlorides were attempted, but the reactions gave products in very low yields (10–25%). Acylation of **1a** with chloroacetyl chloride followed by chlo-



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

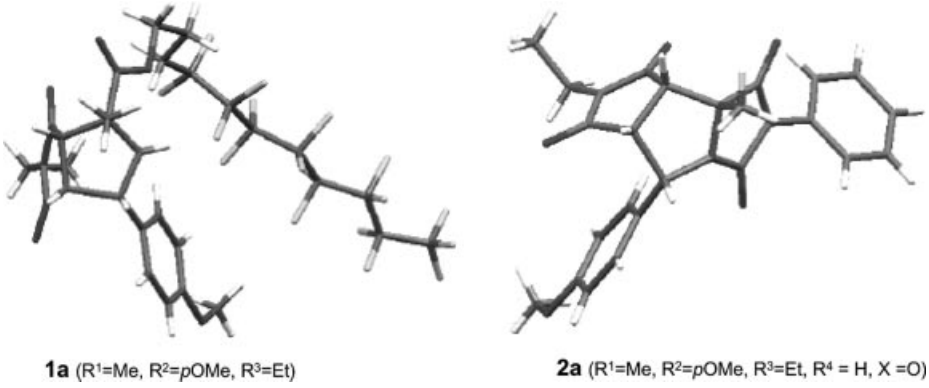
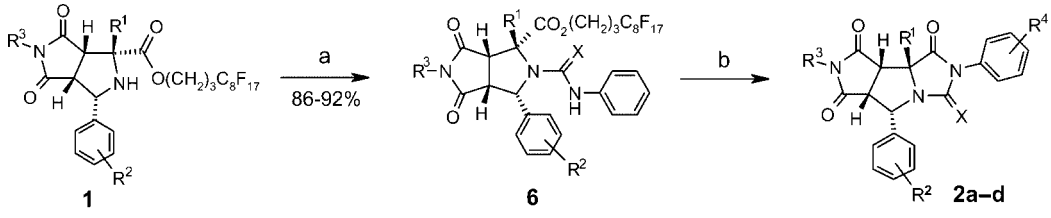


Figure 2. Single-crystal X-ray structures of compounds **1a** and **2a**.

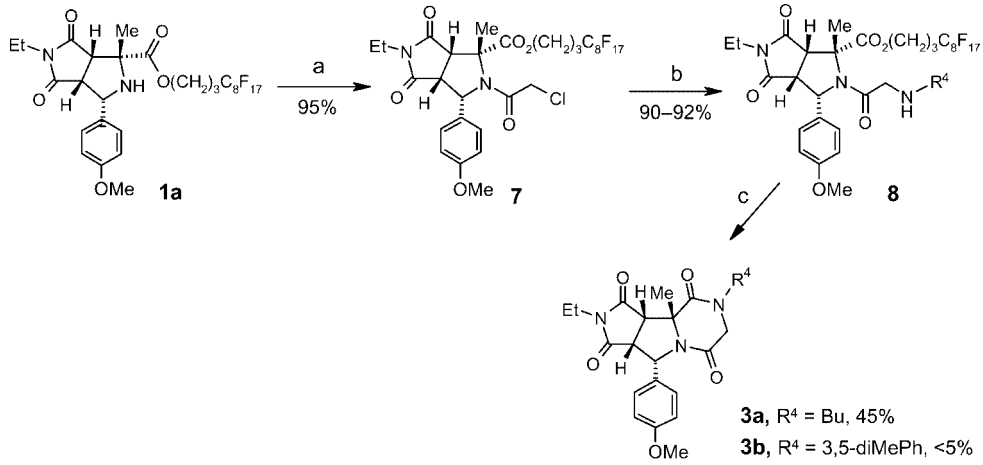


	R¹	R²	R³	R⁴	X	yield
2a	Me	*p*OMe	Et	H	O	85%
2b	Me	*p*OMe	Et	H	S	79%
2c	*i*Bu	*p*Br	*t*Bu	*m*Cl	O	75%
2d	Bn	*p*Cl	cC_6H_{11}	*m*Br	O	81%

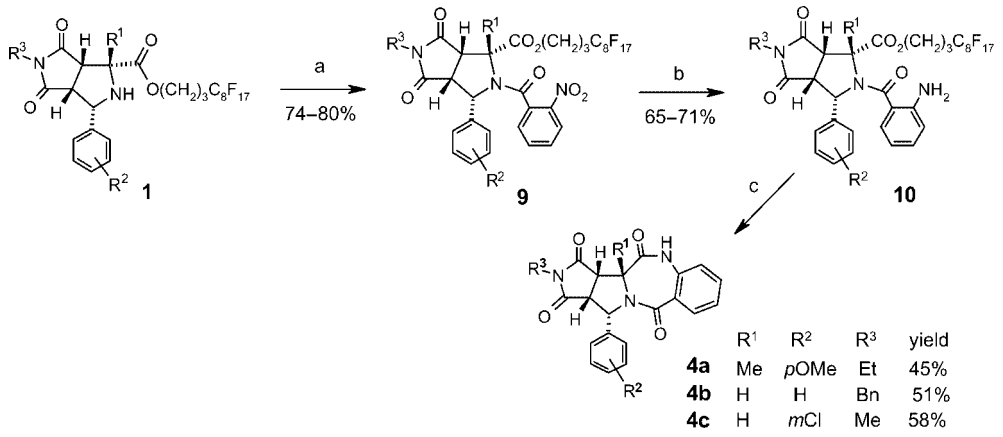
Scheme 3. Synthesis of hydantoin-fused tricyclic compounds **2a**–**d**. a) R^4-PhNCX (5.0 equiv.), DMAP (0.5 equiv.), toluene, microwave (130 °C, 10 min), F-SPE. b) K_2CO_3 (2 equiv.), DMF, microwave (100 °C, 5 min), F-SPE, HPLC.

rine 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.

The syntheses 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 the acylation product **9**. We have found that



Scheme 4. Synthesis of piperazinedione-fused tricyclic compounds **3a**–**b**. 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, microwave (120 °C, 10 min), F-SPE. c) DBU (2 equiv.), MeOH-DMF, microwave (180 °C, 15 min), F-SPE, HPLC.



Scheme 5. Synthesis of benzodiazepinedione-fused tetracyclic compounds **4a**–**c**. 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, microwave (130 °C, 5 min), F-SPE, HPLC.

the *N*-acylation reaction was sensitive to R^1 substitution; only small R^1 groups such as H and Me gave products in good yields. Compounds **9** were then treated 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 compounds **4a**–**c** in 45–58% yields.

Conclusion

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

Supporting Information (see footnote on the first page of this article): General experimental procedures and analytical data for representative intermediates and all final products are provided.

Acknowledgments

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