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

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Fluorous proline derivatives generated from one-pot, threecomponent [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.

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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, fluo-



Scheme 1. Fluorous synthesis of heterocycles 2-4.

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rous synthesis has been applied to the parallel and mixture synthesis^[8] of small molecules, peptides,^[9] and oligosaccharides.^[10]

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-



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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 (R¹ to R⁴). 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 Et₃N (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 FluoroFlash cartridge. The non-fluorous components such as the unreacted aldehyde, N-alkylmaleimide, and Et₃N salt were eluted out with a fluorophobic solvent (80:20 MeOH/H₂O). 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 singlecrystal 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 CDCl₃) 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 K₂CO₃ 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 *a*-amino acids or *a*-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) Et₃N (3 equiv.), DMF, microwave (130 °C, 20 min), F-SPE.

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1a (R1=Me, R2=pOMe, R3=Et)

2a (R¹=Me, R²=pOMe, R³=Et, R⁴ = H, X = O)

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



Scheme 3. Synthesis of hydantoin-fused tricyclic compounds 2a-d. a) R⁴-PhNCX (5.0 equiv.), DMAP (0.5 equiv.), toluene, microwave (130 °C, 10 min), F-SPE. b) K₂CO₃ (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) ClCH₂COCl (1.5 equiv.), Et₃N (2.5 equiv.), CH₂Cl₂, 25 °C, 30 min, F-SPE. b) R⁴NH₂ (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.

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Scheme 5. Synthesis of benzodiazepinedione-fused tetracyclic compounds **4a**–c. a) 2-nitrobenzoylchloride (3 equiv.), Et₃N (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 \mathbb{R}^1 substitution; only small \mathbb{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.

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