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Solid-Phase Synthesis of 1,7-Disubstituted-1,3,5-triazepane-2,4-diones

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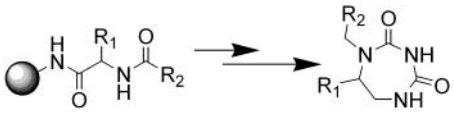
ABSTRACT

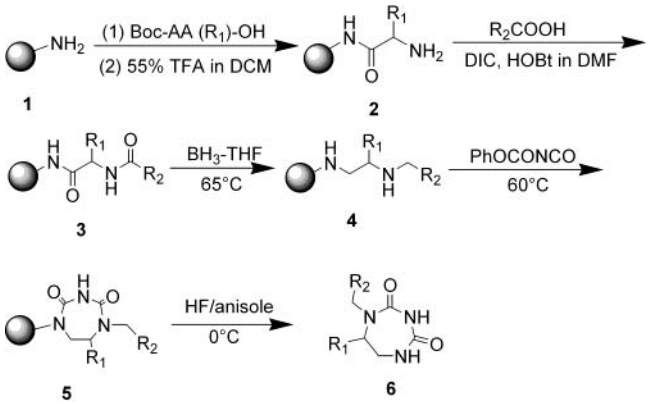


The solid-phase synthesis of 1,7-disubstituted-1,3,5-triazepane-2,4-diones from resin-bound amino acids is described. The exhaustive reduction of solid-support bound amides with borane afforded the requisite secondary amines, which following treatment with phenyl isocyanatoformate and cleavage, provided the corresponding triazepane-2,4-diones.

The rapid synthesis of large organic compound collections by combinatorial methods using solid-phase approaches is a promising strategy for the discovery of new pharmaceutical lead compounds.[1] The focus of this field of research, which initially involved the synthesis of peptides and oligonucleotides, is now on the synthesis of small organic molecules on the solid phase.[2] Heterocycles, such as benzodiazepines,[3] hydantoins,[4] pyrrolidines,[5] and bicyclic guanidines,[6] have received special attention in combinatorial synthesis as a result of their interesting biological properties.[7] This strategy has permitted the synthesis of large numbers of heterocycles in a short time frame, enabling their use in high-throughput screening.[8] Triazepines are found in many biologically active compounds and are known to be useful for the treatment of HIV disease,[9] as potential antifungals,[10] and as enhancers for anticancer agents.[11] As part of our ongoing efforts directed toward the solid-phase synthesis of small molecule and heterocyclic compounds by using amino acids and peptides as starting materials,[12] we report here an efficient strategy for the synthesis of 1,7-disubstituted-1,3,5-triazepane-2,4-diones from resin-bound acylated amino acids.

The parallel solid-phase synthesis of 1,7-disubstituted-1,3,5-triazepane-2,4-diones was carried out on the solid phase by using the "tea-bag" methodology.[1b] The reaction sequence is illustrated in Scheme 1. Starting from *p*-methylbenzhydryl-

Scheme 1. Solid-Phase Synthesis of 1,7-Disubstituted-1,3,5-triazepane-2,4-diones



(1) (a) Geysen, H. M.; Meloen, R. H.; Barteling, S. *J. Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3998. (b) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131. (c) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *345*, 8486.

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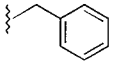
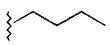
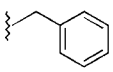
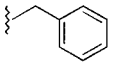
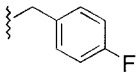
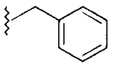
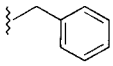
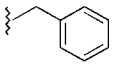
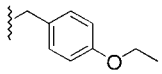
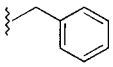
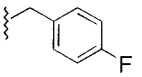
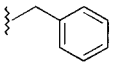
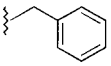
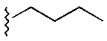
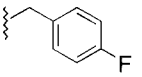
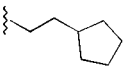
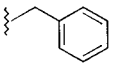
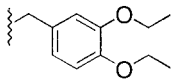
Table 1. Individual 1,7-Disubstituted-1,3,5-triazepane-2,4-diones

entry	R_1	R_2	yield[a]	purity[b]	MW(found)[c]
6a			75	68	290.7([M + H]$^+$)
6b			79	79	290.7([M + H]$^+$)
6c			82	71	309.8([M + H]$^+$)
6d			81	58	342.1([M + H]$^+$)
6e			78	70	247.3([M + H]$^+$)
6f			82	55	368.4([M + H]$^+$)
6g			65	71	342.8([M + H]$^+$)
6h			75	65	324.7([M + H]$^+$)
6i			79	78	308.9([M + H]$^+$)
6j			84	74	297.0([M + H]$^+$)
6k			92	42	398.3([M + H]$^+$)

[a] Yields (in %) are based on the weight of crude material and are relative to the initial loading of the resin. [b] The purity of the crude material was estimated on the basis of analytical traces at $\lambda = 214$ nm. [c] Confirmed by mass spectra (ESI).

amine (MBHA) resin, a Boc-amino acid (Boc-AA(R_1)-OH) was coupled to the resin. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resulting primary amine was acylated with a wide range of commercially available carboxylic acids to provide the resin-bound acylated amino acid **3**. The resin-bound diamide was treated with borane in THF, resulting in the exhaustive reductive of the amides to yield resin-bound diamine **4**. Resin-bound diamine **4** was then treated with phenyl isocyanatoformate in dimethylformamide to give the corresponding resin-bound 1,7-disubstituted-1,3,5-triazepane-2,4-dione **5**. The desired product was readily obtained following cleavage from the resin by using HF/anisole (95/5) for 1.5 h at 0 °C in reasonable yield and purity (Table 1).[13] The product was characterized by electrospray LC-MS and ^{1}H and ^{13}C NMR.

We have optimized the reaction conditions of this synthetic route by the parallel synthesis of 1,7-disubstituted-1,3,5-triazepane-2,4-diones. Compounds representing more than 20 amino acids for the first position of diversity (R_1) and 15 carboxylic acids for the second position of diversity (R_2) were synthesized. Amino acids that generated a reactive functionality after reduction (e.g., asparagine and glutamine) were not included in the R_1 position. Also, those amino acids having an extra amine functionality, such as lysine, were not used for position R_1. We observed that *N*-benzyl derivatives at the second position of diversity (R_2), resulting from reduced substituted benzoic acids, are partially removed during the HF cleavage. In most cases, substituted phenylacetic acid derivatives and nonaromatic acids gave satisfactory results. If *N*-(chlorocarbonyl)isocyanate was used as the cyclization reagent, the purities of the products were found to be low. The purities of the products were improved by using phenyl isocyanatoformate, which has a better leaving group, as the cyclization reagent. Following a number

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(10) Mona, A. M.; Ola, A. E.; Hesham, T. Y. F.; Fawzia, A. A. *Alexandria J. Pharm. Sci.* **1996**, *10*, 133.
(11) Sawanishi, H.; Wakusawa, S.; Murakami, R.; Muramatsu, H.; Suzuki, H.; Takashima, A.; Aizawa, T.; Miyamoto, K. I. *J. Med. Chem.* **1995**, *38*, 5066.
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of attempts using different concentrations of phenyl isocyanatoformate, we observed that working at low concentration and using a small excess of the reagents led to the desired compound having high purity. High concentration and/or large excesses of the reagent increase the probability that two different secondary amines will react with phenyl isocyanatoformate and thus prevent cyclization. The best results were obtained by two treatments of diamine **4** with 5 equiv of phenyl isocyanatoformate in dimethylformamide (0.04 M) at 60 °C for 24 h.

In summary, this approach is a continuation of our efforts directed toward the synthesis of acyclic and heterocyclic compounds from amino acids and short peptides.[8] Using the concept of "libraries from libraries",[14] we were thus able to generate 1,7-disubstituted-1,3,5-triazepane-2,4-diones from the polyamines resulting from the exhaustive reduction of resin-bound acylated amino acids.

Acknowledgment. This work was supported by National Cancer Institute grant CA78040 (Houghten).

Supporting Information Available: Copies of LC-MS of compounds **6a**, **6c**, **6i**, **6j** and ^{1}H and ^{13}C NMR spectra of compounds **6i, 6k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **Typical procedure** for the synthesis of a 1,7-disubstituted-1,3,5-triazepane-2,4-dione (**6**): 100 mg of MBHA resin was contained in a polypropylene mesh packet.[1b] Following neutralization with 5% DIEA in DCM, the resin was washed with DCM. The first Boc amino acid (6 equiv, 0.1 M) was coupled using hydroxybenzotriazole (HOBt, 6 equiv, 0.1 M) and diisopropylcarbodiimide (DICI, 6 equiv, 0.1 M) for 90 min. Upon removal of the Boc group with 55% TFA in DCM (30 min), the packet was washed and neutralized with a solution of 5% DIEA in DCM. The resin-bound amine was acylated with a carboxylic acid (10 equiv, 0.1 M) in DMF by using DICI and HOBt as coupling reagent overnight. The exhaustive reduction of the resin-bound amides was carried out in a 50 mL glass conical tube under nitrogen. To each tube was added the resin packet and boric acid (12 equiv). Trimethyl borate (12 equiv) was added, followed by the slow addition of borane−THF complex (40 equiv). After cessation of hydrogen evolution, the capped tubes were heated at 65 °C for 72 h in a heating block followed by decantation of the reaction solution and quenching with MeOH. The resin packet was then washed with DMF and MeOH. The resin was treated with piperidine at 65 °C for 20 h to disproportionate the borane complex. Following decantation of the piperidine−borane solution, the resin packet was washed with DMF, DCM, and MeOH and dried. The cyclization reaction was performed under nitrogen. The resin-bound polyamine was reacted with phenyl isocyanatoformate in dimethylformamide (5 equiv, 0.04 M) at 60 °C for 24 h. After the resin packet was washed with DMF, DCM, and MeOH and dried, the cyclization reaction was performed again. Following cleavage of the resin with HF/anisole (95/5) for 90 min at 0 °C, the desired product was extracted with acetic acid/water (95/5) and lyophilized. The product was characterized by electrospray LC-MS under ESI conditions and ^{1}H and ^{13}C NMR. Compound **6i**: MS(ESI) *m*/*z* 308.9(M + H^{+}); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.1), 1.18−1.32 (4H, m), 1.60−1.66 (2H, m), 2.87−2.93 (2H, m), 3.03−3.23 (4H, m), 4.05 (1H, m), 6.15 (1H, brs), 0.6.97−7.02 (2H, M), 7.17−7.20 (2H, m), 7.61 (1H, brs); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.10, 22.68, 28.56, 29.84, 33.64, 43.73, 53.83, 59.33, 130.48, 130.54, 134.60, 151.45, 154.55, 160.96, 162.91.

(14) Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dorner, B.; Weber, P.A.; Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138.