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Solid phase synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones

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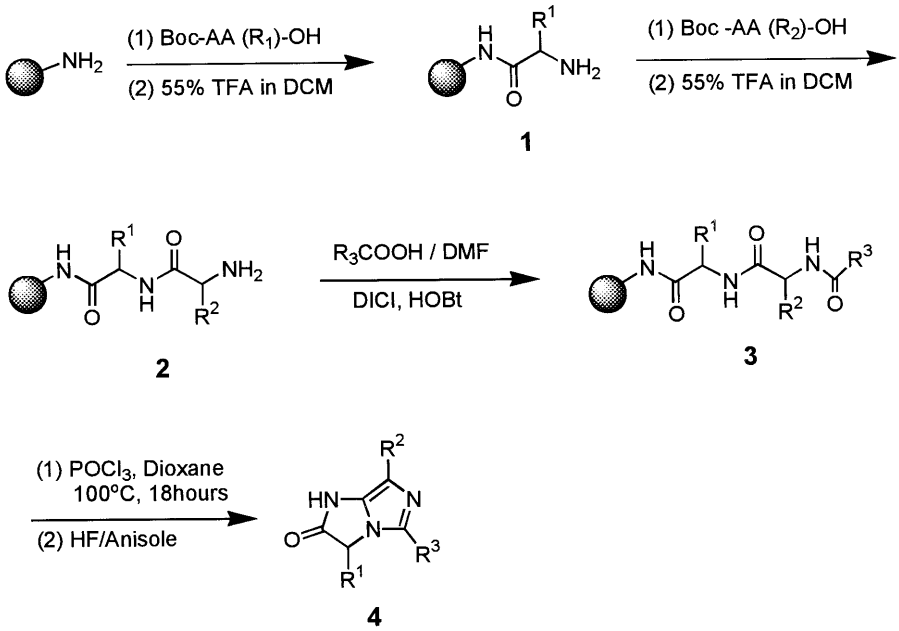
Abstract—The solid phase synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones from acylated dipeptides via cyclization using Bischler–Napieralski conditions is described.

The rapid synthesis of large organic compound collections by combinatorial methods on the solid phase is a promising strategy for the discovery of new pharmaceutical lead compounds.[1] Recently, the focus of this field of research, in addition to the synthesis of peptides and oligonucleotides, has been on the synthesis of small organic molecules on the solid phase.[2] Heterocycles have received special attention in combinatorial synthesis due to their biologically interesting properties.[3]

Imidazole-containing moieties are found in many biologically active compounds and are known to have useful therapeutic implications. Such compounds, which are conformationally constrained scaffolds, are quite common in nature and many imidazole-containing natural products have been isolated encompassing a wide range of biological activies.[4] As part of our ongoing efforts directed toward the solid phase synthesis of small molecule and heterocyclic compounds and the



1 **2** **3** **4**

Scheme 1. Synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones.

Keywords: solid phase synthesis; [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones; cyclization.

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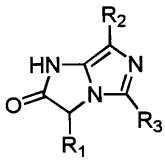
Table 1. Individual [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones



Entry	R_1	R_2	R_3	Yield[a]	MW (expected)	MW (found)
4a	$-CH(CH_3)_2$	$-CH_2Ph$	$-CH_2Ph$	42.3	345.4	346.2 (M+H)
4b	$-CH(CH_3)_2$	$-CH_2Ph$	$-CH_3$	53.5	269.3	270.0 $(M+H)^+$
4c	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	42.1	311.4	312.2 $(M+H)^+$
4d	$-CH(CH_3)_2$	$-CH_2CH(CH_3)_2$	$-CH_3$	62.5	235.3	236.1 $(M+H)^+$
4e	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	$-CH_2Ph$	36.2	359.5	360.3 $(M+H)^+$
4f	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	$-CH_3$	52.6	283.4	284.2 $(M+H)^+$
4g	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	$-CH_2Ph$	35.4	311.4	312.2 $(M+H)^+$
4h	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$	$-CH_3$	49.3	235.6	236.2 $(M+H)^+$
4i	$-CH_2Ph$	$-CH(CH_3)_2$	$-CH_3$	41.6	269.3	270.1 $(M+H)^+$
4j	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	$-CH_2Ph$	44.5	359.5	360.3 $(M+H)^+$

[a] Yield of crude product based on resin substitution.

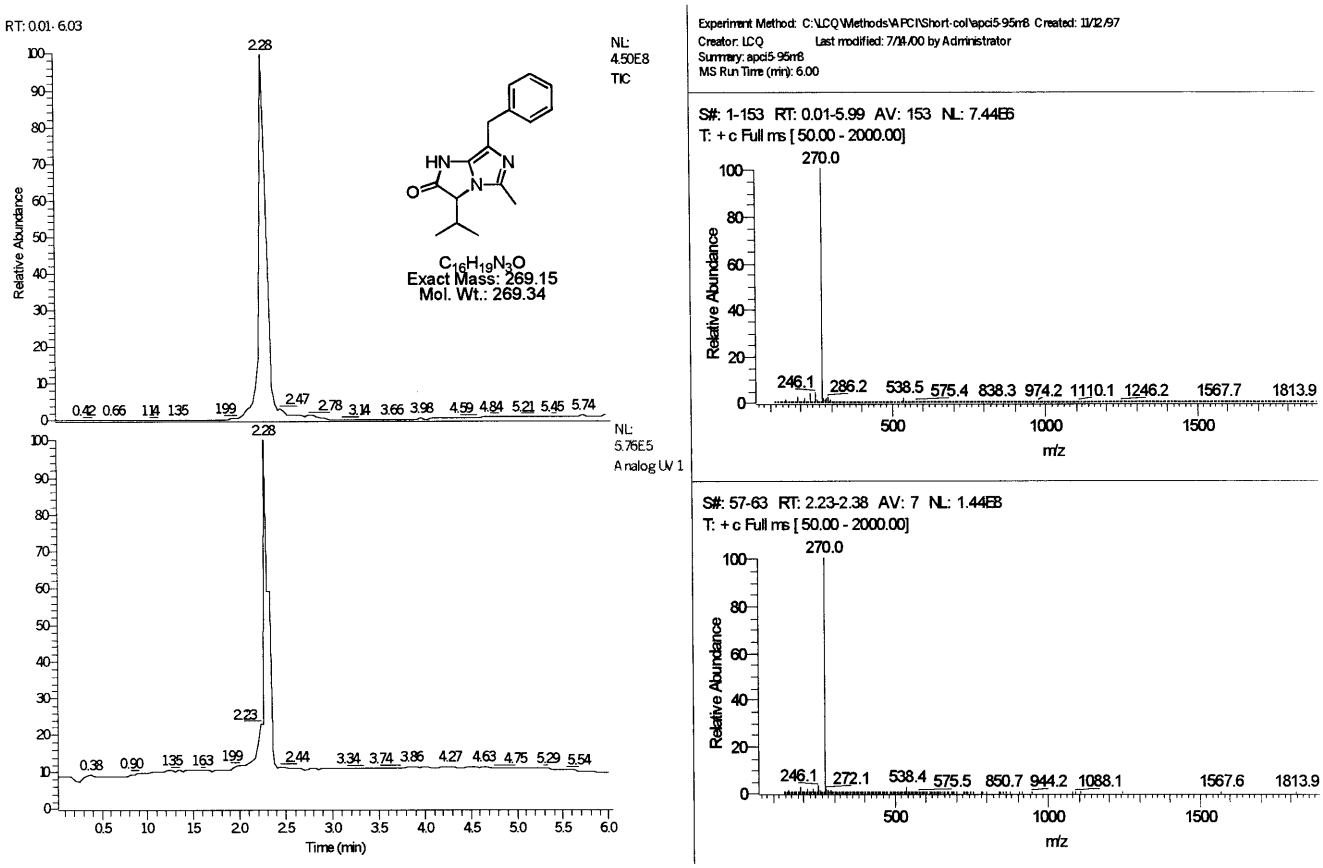


Figure 1. LC-MS of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-one **4b**.

generation of combinatorial libraries of organic compounds using amino acids and peptides as starting materials,[5] we report here an efficient method for the synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones from resin-bound acylated dipeptides.

The parallel synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*] imidazol-2(3*H*)-ones was carried out on the solid phase using the 'tea-bag' methodology.[1b] The reaction sequence is illustrated in Scheme 1. Starting from *p*-methylbenzhydrylamine (MBHA) resin-bound *N-tert*-butyloxycarbonyl (Boc) amino acid (Boc-AA(R^1) -OH) **1**, the Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resulting primary amine was coupled with a second Boc-protected amino acid (Boc-AA(R^2)-OH) to provide the resin-bound dipeptide **2**. Following removal of the Boc

protecting group using 55% TFA in DCM, the resulting free amine was *N*-acylated with a carboxylic acid (R^3CO_2H) in DMF using diisopropylcarbodiimide (DICI) and hydroxybenzotriazole (HOBT) as coupling reagents to give acylated dipeptides **3**. The bicyclic [3,5,7]-1*H*-imidazo[1,5-*a*]-imidazol-2(3*H*)-one **4** was obtained following the treatment of the resin-bound acylated dipeptide **3** with phosphorous oxychloride ($POCl_3$) under a variety of conditions in order to optimize the Bischler–Napieralski cyclization.[6] The best yields were obtained using 15 equiv. of freshly distilled $POCl_3$ at 100°C in dioxane for 18 h. The desired products were readily obtained in moderate yield after cleavage using HF/anisole (95/5) (Table 1).[7] The lower yield was caused by a premature cleavage during the cyclization due to the generation of HCl. The products were characterized by electrospray LC-MS under APCI conditions, ^1H and ^{13}C NMR. Fig. 1 illustrates a typical LC-MS spectra of the [3,5,7]-1*H*-imidazo[1,5-*a*]-imidazol-2(3*H*)-one **4b** derived from valine, phenylalanine and acetic acid.

In summary, we have demonstrated the feasibility of the synthesis of [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3*H*)-ones from acylated dipeptides on the solid phase using Bischler–Napieralski reaction conditions. As in earlier studies, the described chemistries will be used to generate individual compounds and mixture-based combinatorial libraries.[8]

Acknowledgements

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7. Typical procedure for the synthesis of an individual [3,5,7]-1*H*-imidazo[1,5-*a*]imidazol-2(3H)-one, **4**: 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) and diisopropylcarbodiimide (DICI). Upon removal of the Boc group with 55% TFA in DCM (30 min), the packet was washed, neutralized with a solution of 5% DIEA in DCM and the second amino acid was coupled under the same conditions as described above. Following removal of the Boc group, the dipeptide was acylated with a carboxylic acid (10 equiv., 0.1 M) in DMF using DICI and HOBt as coupling reagent. The cyclization reactions were performed under nitrogen. The bicyclic [3,5,7]-1*H*-imidazo[1,5-*a*]-imidazol-2(3H)-one **4** was obtained via cyclization using phosphorus oxychloride (15 equiv. 0.1 M) at 100°C in dioxane for 18 h. Following cleavage of the resin with HF/anisole (95/5), the desired product was extracted with acetic acid/water (95/5), and lyophilized. The product was characterized by electrospray LC-MS under APCI conditions, ^1H and ^{13}C NMR. Compound **4b**: MS(APCI) m/z 270($M+H^+$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, d, $J=7.0$), 1.19(3H, d, $J=7.0$), 2.47(1H, m), 2.58(3H, s), 3.97(2H, dd, $J=6.0$), 4.46(1H, d, $J=3.3$), 7.21–7.31(5H, m), 8.90(1H, brs). ^{13}C NMR ($CDCl_3$, 75 M), 170.1(CO), 138.4(C), 135.7, 130.7, 129.2, 128.8, 127.6(Ar), 108.8(C), 64.7(CH), 30.6(CH_3), 29.6(CH), 17.7(CH_3), 16.3(CH_3).
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