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High-throughput parallel synthesis of 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-ones on 'volatilizable' supports

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Abstract

A solid-phase synthesis of 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-ones on the 'volatilizable' aminoalkyl functionalized silica gel is reported. The desired products were cleaved by a two-step procedure in good purity and yield.

Combinatorial chemistry using solid-phase synthesis approaches has been a powerful methodology for the synthesis of large numbers of individual compounds as well as mixture-based combinatorial libraries for use in the discovery of pharmaceutical lead compounds.[1] During the past ten years, we have focused on the design and synthesis of diversity-oriented heterocyclic combinatorial libraries on commercial resins using the 'teabag' approach.[2] We have made hundreds of thousands of heterocyclic compounds in individual and mixture-based library formats.[3] Both mixtures and individual compounds need to be cleaved from the resin at the final step, followed by the separation from the spent support through exhaustive extraction, centrifugation, and filtration. This results in reduced yields and increased costs. Recently, we reported a novel solid-phase synthesis support which was based on the functionalized silica gel that was totally transformed into volatile compounds with a HF water solution and/or HF gas.[4] Such 'volatilizable' resins provide a new approach and simplification of solid-phase synthesis.[5]

As part of our ongoing efforts directed toward the use of 'volatilizable' supports for the synthesis of small molecule heterocyclic compounds, we report here the synthesis of a new heterocyclic library. 3,4-Disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-ones were synthesized on the 'volatilizable' support of aminoalkyl functionalized silica gel. The aminoalkyl functionalized silica gel was synthesized using the hydrolysis–condensation approach according to the literature.[6] Tetraethyl orthosilicate (20.8 g; 0.1 mol) was mixed and stirred with 4.75 g of water at 0 °C for 5 min, 1.84 g (8.33 mmol) aminopropyltrimethoxysilane was then added. For aminobutyl functionalized silica gel, 1.97 g (8.3 mmol) of aminobutyltrimethoxysilane was added. White precipitates were formed after 20 min. The reaction mixtures were kept stirring for 2 h and then 'aged' overnight. After washing and vacuum drying at 110 °C, the functionalized silica gels were ready to be used as supports for the parallel synthesis of a heterocyclic library as shown in Scheme 1. The resin bound *N*-acyl peptide **3** was synthesized using standard coupling procedures described elsewhere.[7] The resin bound *N*-acyl peptide **3** was then reduced with borane in THF at 65 °C for 72 h followed by treatment with piperidine overnight to yield the resin bound diamine **4**.[8] The borane–THF reduction was repeated twice. The resin bound diamine **4** was cyclized with carbonyldiimidazole in DCM overnight to yield the resin bound3,4-disubstituted imidazolin-2-one **5**. The cleavage of compound **6** was performed first with 35% HF in

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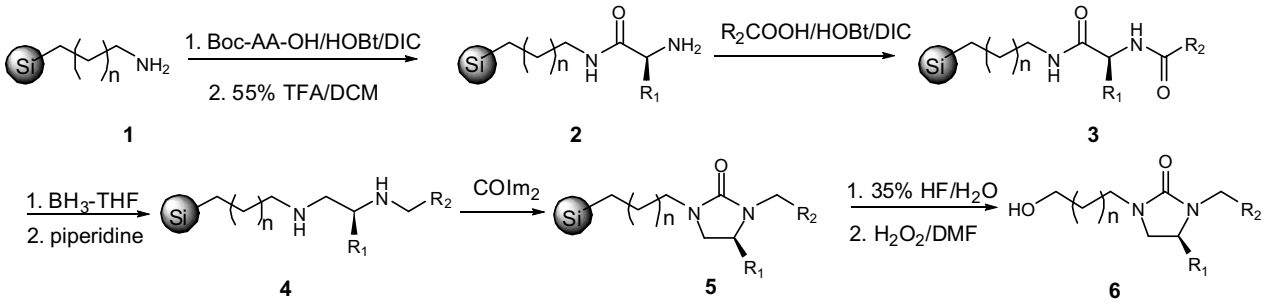

Scheme 1. Synthesis 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-one on aminoalkyl silica gel.

Table 1
Individual 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-one

Entry	R_1	R_2	*n*	Yield[a]	Purity[b]
6a	$-CH_3$	$-CH_2CH_2Ph$	1	79	73
6b	$-CH_2CH(CH_3)_2$	$-CH_2Ph$	1	75	75
6c	$-CH_2CH(CH_3)_2$	$-CH(C_2H_5)C_6H_5$	1	73	72
6d	$-CH_2Ph$	$-C_3H_7$	1	86	85
6e	$-CH_2Ph$	$-C_6H_{13}$	1	76	74
6f	–H	$-CH_2Ph$	1	90	87
6g	–H	$-CH_2CH_2Ph$	1	88	82
6h	$-CH(CH_3)_2$	$-CH(C_2H_5)C_6H_5$	1	72	80
6i	$-CH(CH_3)_2$	$-CH_2Ph$	2	74	80
6j	$-CH(CH_3)_2$	$-CH_2Ph(3\text{-}F)$	2	80	83
6k	$-CH_3$	$-C_3H_4(1\text{-}C_6H_5)$	2	79	85
6l	$-CH_3$	$-CH_2C_{10}H_7$	2	81	75

[a] Yields (in %) are based on the weight of silica gel before cleavage, the weight of crude product, and are relative to the substitution[10] of the resin.
[b] Purity (in %) is determinated by the peak area of HPLC at 214 nm.

water at room temperature for 30 min to decompose the silica forming tetrafluorosilane and water. After removing the solvent and tetrafluorosilane by lyophilization, 1:1 (v/v) hydrogen peroxide in DMF was added to further cleave the Si–C bond and release the final product **6**. After removing the solvent under vacuum and dissolving the product in 1:3 (v/v) acetonitrile in water, mixed bed ion-exchange resin (AG 501-X8(D) from Bio-Rad Laboratories, Inc.) was added to remove the byproduct produced by the partially unreacted linker. The desired products **6** were obtained in good purity[9] and yield. The results are summarized in Table 1.

In conclusion, we report here a new approach for the parallel synthesis of 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-ones on 'volatilizable' aminoalkyl silica gel. Both aminopropyl and aminobutyl silica gels were demonstrated to be good supports for the solid-phase synthesis of the 3,4-disubstituted 1-(ω-hydroxyalkyl) imidazolin-2-ones.

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9. The products were characterized by electrospray LC–MS under ESI conditions and ^1H and ^{13}C NMR. ^1H NMR of compound **6f**: (500 MHz, DMSO-d_6): δ 1.52–1.58 (2H, q), 2.71–2.74 (2H, t), 3.06–3.09 (2H, t), 3.19–3.22 (4H, m), 3.23–3.24 (2H, d), 3.36–3.39 (2H, m), 4.42 (1H, s), 7.18–7.23 (3H, m), 7.27–7.30 (2H, m). ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.5, 33.4, 40.9, 42.3, 42.4, 45.2, 58.4, 126.1, 128.3, 128.6, 139.4, 160.5.
10. The substitution level of the amino-functional silica gel was determined by coupling Boc–Ala–OH and phenylacetic acid. The methods of coupling and cleavage are the same as described in the text. After removing the ionic products with mixed bed ion-exchange resin for 1 h and lyophilization, 42 mg was obtained from the original 800 mg resin. The substitution level is thus 0.2 mmol/g.