JOURNAL OF combinatorial CHEMISTRY

Report

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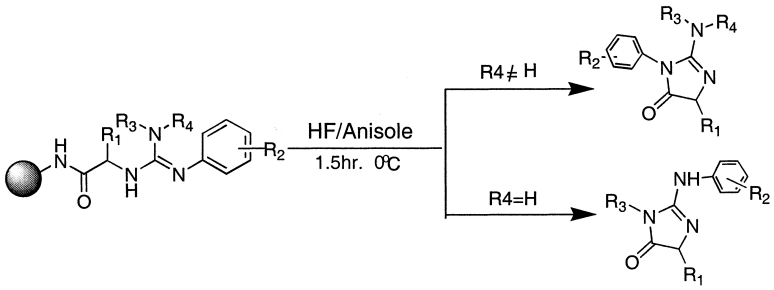
J. Comb. Chem., **2001**, 3 (6), 521-523• DOI: 10.1021/cc010022x • Publication Date (Web): 18 September 2001



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Solid-Phase Synthesis of 2,3,5-Trisubstituted 4*H*-Imidazolones

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Received May 7, 2001

The rapid synthesis of large organic compound collections by combinatorial methods using solid-phase approaches continues to be 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] bicyclic guanidines,[6] have received special attention in combinatorial synthesis because of their biologically relevant properties.[7] This strategy has permitted the rapid synthesis of large numbers of heterocyclic compounds in a short time period, facilitating their use in high-throughput screening.[8]

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.[9] The hydrogen-bonding acceptor and donor abilities of the guanidine group play important roles in supramolecule formation and in the active sites of various proteins, as well as in drug design in medicinal chemistry.[10] As part of our ongoing efforts directed toward the solid-phase synthesis of small-molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[11] we report here an efficient strategy for the synthesis of 2,3,5-trisubstituted 4*H*-imidazolones, which incorporate both the guanidine and imidazole functionalities. The straightforward nature of these synthetic approaches also permits the construction of large combinatorial libraries of such compounds.

The parallel solid-phase synthesis of 2,3,5-trisubstituted 4*H*-imidazolones 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, a Boc amino acid was coupled to the resin. The Boc group was removed using 55% trifluoroacetic acid (TFA) in dichloromethane (DCM). The resin was dried, and the resulting primary amine **2** was reacted with an isothiocyanate to provide the resin-bound thiourea **3**. The reaction was conveniently monitored via the ninhydrin test.[12]

Several methods exist for the preparation of guanidines on the solid phase, but most have not been optimized.[13] For example, when Mukaiyama's reagent was used to convert thioureas to guanidines using aryl isothiocyanates without at least one electron-withdrawing group on the aromatic ring, it was found to be difficult to form the desired corresponding guanidines. It was sometimes necessary to heat the reaction to get the addition to proceed.[13e] We have investigated various methods for the preparation of guanidines **4** and have found that the $HgCl_2$-promoted guanylation reaction gave especially good results. The resin-bound thioureas **3**, in the presence of $HgCl_2$ and a specific primary or secondary amine in dimethylformamide, were shaken overnight at room temperature to give the corresponding guanidines **4**. The desired 2,3,5-trisubstituted 4*H*-imidazolones were obtained via intramolecular cyclization with concomitant cleavage from the resin using HF/anisole (95/5) for 1.5 h at 0 °C in good yield and purity. The products were characterized by electrospray LC−MS under both ESI and APCI conditions, as well as by ^1H and ^{13}C NMR. We found the resin-bound guanidines formed from secondary amines afforded the cyclized products **5**, while the reaction with primary amines yielded the corresponding cyclized products **6**. It is expected that the reaction proceeds via hydrolysis of the intermediate imidazolium salts.[14] The imidazolones were also independently synthesized via Wang resin to verify the structural assignment of **6a**. Although this is an alternative route to the imidazolones, both potential isomers are obtained via this synthetic route (see Supporting Information). The results are summarized in Table 1.

From these results, there appears to be no clear correlation between the electronic effects of the substituent on the *N*-aryl and final yields or purities. Thus, the electron-donating and electron-withdrawing groups on the *N*-phenyl substituents give similar results (entries **6b**, **6g**, **6h**). These observations are consistent with the reaction mechanism proposed for the guanylation of thiourea in solution:[15] $HgCl_2$ promotes the elimination of H_2S from the thiourea starting material to produce a carbodimide intermediate; the amine then adds to the carbodiimide to yield the guanidines. $HgCl_2$ appears to cause the first step to proceed efficiently regardless of the nature of the *N*-phenyl substituents.

Since it is known that a guanidine nitrogen δ to an ester carbonyl can cyclize via an "Edman-like" degradation under acidic conditions,[16] we replicated this reaction in solution to clarify whether the cyclization occurred during the $HgCl_2$-promoted reaction or during the HF cleavage step. Thiourea **7** was reacted with $Ph(CH_2)_3NH_2$ in the presence of $HgCl_2$ at room temperature in DMF overnight. Compound **8** (*m*/*z* 473.6, $M + H^+$) was formed quantitatively, and no cyclized product **9** was found by LC−MS. Compound **8** was cyclized to afford compound **9** (*m*/*z* 352.9, $M + H^+$) by treatment with HF for a period of 1.5 h at 0 °C (Scheme 2).

Following optimization of the synthetic steps, we expanded the number of individual controls by separately

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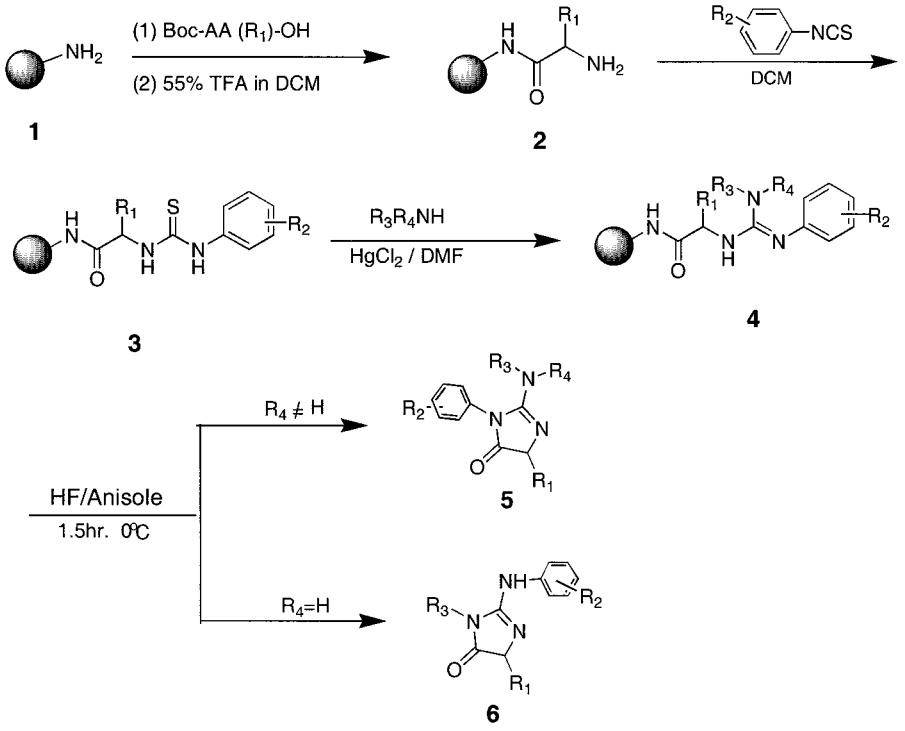
10.1021/cc010022x CCC: $20.00
Published on Web 09/18/2001

Scheme 1. Solid-Phase Synthesis of 2,3,5-Trisubstituted 4*H*-Imidazolones



Scheme 2. Solution-Phase Synthesis of 2,3,5-Trisubstituted 4*H*-Imidazolones

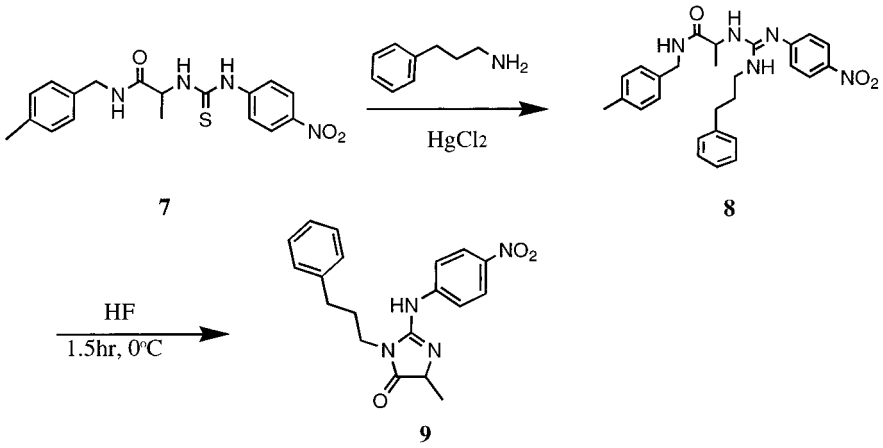


Table 1. Individual 2,3,5-Trisubstituted 4*H*-Imidazolones

entry	R_1	R_2	R_3R_4NH	crude yield,[a] %	HPLC purity, %
5a	$(CH_3)_2CH-$	4-Cl	$Ph(CH_2)_2NHCH_3$	98	92
5b	$PhCH_2-$	H	$-(CH_2)_6-NH$	93	85
5c	CH_3-	H	$CH_3CH_2NHCH_2CH_3$	95	86
6a	$(CH_3)_2CH-$	H	$PhCH_2CH_2CH_2NH_2$	97	77
6b	$PhCH_2-$	H	$PhCH_2CH_2NH_2$	100	72
6c	4-F$-PhCH_2-$	H	$PhCH_2CH_2NH_2$	98	75
6d	$PhCH_2-$	4-CF_3	$PhCH_2CH_2NH_2$	100	86
6e	$PhCH_2-$	H	3-$CH_3-PhCH_2NH_2$	97	89
6f	$(CH_3)_2CH-$	H	$PhCH_2CH_2NH_2$	99	81
6g	$PhCH_2-$	4-NO_2	$PhCH_2CH_2NH_2$	96	83
6h	$PhCH_2-$	4-CH_3	$PhCH_2CH_2NH_2$	94	84

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

varying the substituent at each of these three variable positions. One hundred individual controls were prepared by fixing two positions of diversity while varying the other position. Forty-five amino acids were examined at the first position of diversity (R^1), 25 isothiocynates at the second position of diversity (R^2), and 30 amines at the third position of diversity (R^3).

The building blocks that produced cyclized compounds having purities more than 80% were considered for inclusion in the synthesis of a mixture-based combinatorial library. We selected 40 different amino acids at the first position (R^1) of diversity, 20 isothiocyanates at the second position (R^2), and 20 amines at the third position of diversity (R^3) for synthesis of a positional scanning combinatorial library (SCL).[17] The preparation of the mixture-based positional scanning combinatorial library containing 16 000 (40 R^1 × 20 R^2 × 20R^3) different imidazolones and its screening in different assays for the identification of highly active compounds will be reported elsewhere.

Summary

In summary, we have successfully synthesized 2,3,5-trisubstituted 4*H*-imidazolones from resin-bound amino acids.

Reaction of resin-bound amino acids with isothiocyanates to give resin-bound thioureas that react with $HgCl_2$ and a range of primary and secondary amines to yield resin-bound guanidines was described. The desired products, 2,3,5-trisubstituted 4*H*-imidazolones, were readily obtained via intramolecular cyclization and simultaneous cleavage from the resin in good yield and purity using HF/anisole (95/5) for 1.5 h at 0 °C. The discovery of novel active compounds based on this scaffold will be reported elsewhere.

Acknowledgment. This work was supported by National Cancer Institute Grant No. CA78040 (Houghten).

Supporting Information Available. Typical procedure for the synthesis of 2,3,5,-trisubstituted 4H-imidazolones, a listing of their MS and NMR data, and copies of LC−MS of all compounds, proton and ^{13}C NMR spectra of compounds **5a, 6a, 6b, 6c**, alternative synthesis procedure of compound **6a** from Wang resin, and solution-phase synthesis procedure of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC010022X