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Solid-Phase Synthesis of 2-Aminoimidazolones

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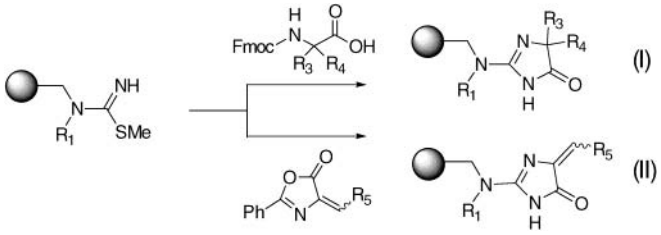
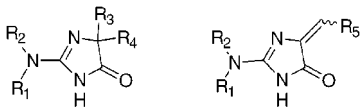
ABSTRACT



A solid-phase route for the preparation of 2-aminoimidazolones has been developed which can incorporate diverse functionality at each position of the molecule. Resin-bound *S*-methyl isothioureas were converted to structures of type I by using commercially available Fmoc-protected amino acids. Products of structure II were accessed by reaction of the *S*-methyl isothiourea with 5-substituted oxazolones.

The 2-aminoimidazolone ring (**1**, **2**) is a structural component of compounds that inhibit NF-κB activation[1] and protein kinase C.[2] In the context of our program to generate libraries



1 **2**

of small heterocyclic rings with potential intracellular biological activity, we report the synthesis of 2-aminoimidazolones on the solid phase. There are several reports of solution-phase routes to these compounds.[3] Our priority was to develop a method that utilized diversity reagents that are commercially available. Consistent with this goal, Fmoc-protected amino acids were coupled to a resin-bound *S*-methyl isothiourea to produce 2-aminoimidazolones **1**. Aldehydes were used to synthesize 5-substituted oxazolones, which were added to the *S*-methyl isothiourea to produce compounds of structure **2**.

Scheme 1 shows our general procedure for the synthesis of 2-aminoimidazolones. For our initial studies, Rink Amide MBHA resin was used (Scheme 1, R_1 = H) to produce compounds that were unsubstituted in the 2-amino position. The reaction of Fmoc-NCS in methylene chloride with the free amino group of Rink Amide MBHA resin was rapid, reaching completion in 15 min, as indicated by a negative ninhydrin test.[4] The resin was deprotected using 20% piperidine in DMF, and methyl iodide treatment yielded the *S*-methyl isothiourea **4**. Fmoc-protected amino acids (5 equiv) were coupled to the resin using HOBT/HBTU/NMM (1:1:2) to yield **5**, and the resin was deprotected using 20% piperidine in DMF. The intramolecular cyclization was accomplished by heating the resin at 80 °C for 24 h in DMSO. The resin was washed (DMF, CH_2Cl_2) and dried for 10 min under a stream of nitrogen to yield **6**. Modest

(1) (a) Roshak, A.; Jackson, J. R.; Chabot-Fletcher, M.; Marshall, L. A. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 955−961. (b) Breton, J. J.; Chabot-Fletcher, M. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 459−466.

(2) DiMartino, M.; Wolff, C.; Patil, A.; Nambi, P. *Inflamm. Res.* **1995**, *44*, S123−S124.

(3) (a) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933−5936. (b) Dalkafouki, A.; Ardisson, J.; Kunesch, N.; Lacombe, L.; Poisson, J. E. *Tetrahedron Lett.* **1991**, *32*, 5325−5328. (c) Garratt, P. J.; Thorn, S. N.; Wrigglesworth, R. *Tetrahedron Lett.* **1991**, *32*, 691−694. (d) Kwon, C.-H.; Tahir Iqbal, M.; Wurpel, J. N. D. *J. Med. Chem.* **1991**, *34*, 1845−1849.

(4) (a) Kearney, P. C.; Fernandez. M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663−2666. (b) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196−200.

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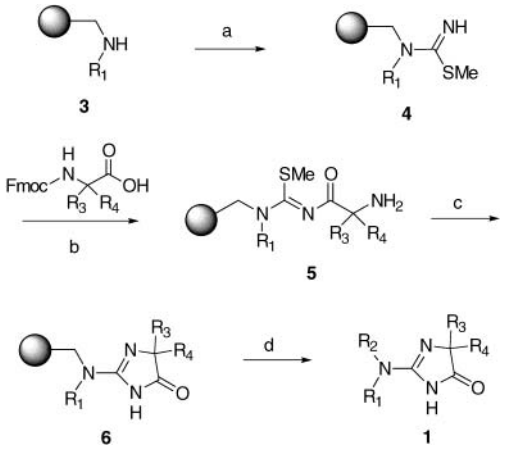
Scheme 1[a]

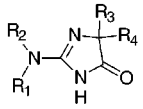


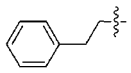
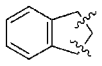
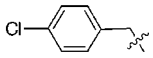
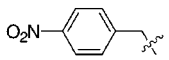
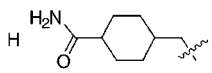
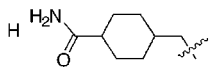
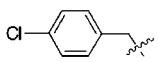
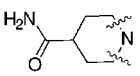
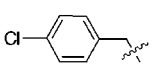
[a] Legend: (a) (i) Fmoc−NCS, CH_2Cl_2, (ii) 20% piperidine in DMF, (iii) MeI, DMF; (b) (i) HOBT, HBTU, NMM, DMF, (ii) 20% piperidine in DMF; (c) DMSO, 80 °C; (d) 95% aqueous TFA, 60 °C.

heating (60 °C) was required to cleave the 2-aminoimidazolone from the resin with 95% aqueous trifluoroacetic acid.[5]

Table 1 summarizes the yields and substrates used for this reaction. Bulky substituents such as a *tert*-butyl group in the R_4 position (compound **1a**) are still able to complete the intramolecular cyclization. Compounds **1f**−**h** were generated from amino acids linked to the Rink Amide MBHA resin. For these compounds the 2-amino group of the 2-aminoimidazolone did not serve as the attachment point to the resin. Despite the additional step of coupling this group to the resin, the yields and purities of these compounds compare well with those that are not substituted in this position. In general, the isolated yields and purities of all entries are high, demonstrating the efficiency of each step in the sequence.

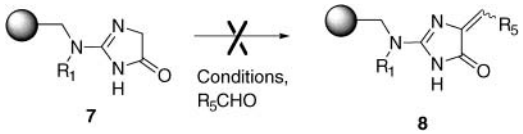
Table 1. Synthesis of 2-Aminoimidazolones



Compound	R_1	R_2	R_3	R_4	Yield[a] (%)
1a	H	H	H		79
1b	H	H	H		88
1c	H	H			97
1d	H	H	H		87
1e	H	H	H		66
1f			H	H	78
1g			H		85
1h			H		80

[a] Yields were determined using the loading level of the starting resin and are based on isolated product.

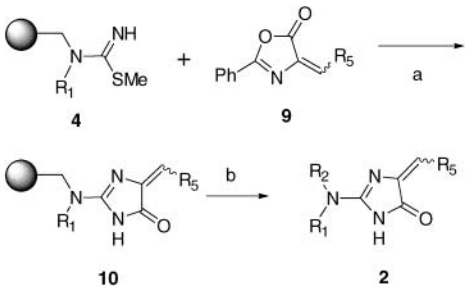
To access unsaturated structures of the general type **2**, we initially attempted to add an aldehyde to the resin-bound 2-aminoimidazolinone **7**, generated from Fmoc−glycine.



Although there are reports of solution-phase reactions that accomplish a similar transformation,[6] all of our efforts to carry out this reaction on the solid phase failed.

To overcome this problem, an oxazolone was added to the resin bound S-methyl isothiourea **4** as shown in Scheme 2.

Scheme 2[a]



[a] Legend: (a) DMF, EtONa (2 equiv), 100 °C; (b) 95% aqueous TFA, 60 °C.

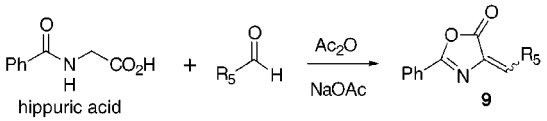
The *S*-methyl isothiourea **4** was generated from Rink Amide MBHA resin in a procedure identical with that outlined in Scheme 1. Treatment of **4** with the oxazolone **9**

(5) General procedure for the synthesis of 2-aminoimidazolones: Rink Amide MBHA resin (0.5 g, 0.34 mmol) was placed into a plastic syringe, and DMF (10 mL, 5 min, 3×) was added. The resin was treated with 20% piperidine in DMF (10 mL, 20 min, 2×) and washed with DMF (10 mL, 30 s, 3×), MeOH (10 mL, 30 s, 3×), and CH_2Cl_2 (10 mL, 30 s, 3×). Fmoc−NCS in CH_2Cl_2 (0.25 M, 10 mL, 2 h) was added to the resin followed by CH_2Cl_2 (10 mL, 30 s, 3×) and DMF (10 mL, 30 s, 3×) washes. A mixture of 20% piperidine in DMF (10 mL, 20 min, 2×) was added, the resin was washed with DMF (10 mL, 30 s, 3×), and a DMF solution of CH_3I (0.5 M, 7 mL, 1 h, 3×) was added. The resin was washed with DMF (10 mL, 30 s, 3×), 17 mL of a DMF solution of HOBT(0.1 M)/HBTU(0.1 M)/NMM(0.2 M) was added followed by Fmoc−α-*tert*-butyl glycine (0.6 g, 5 equiv) (Table 1, compound **1a**), and the resin was agitated for 4 h. The resin was washed with DMF (10 mL, 30 s, 5×) and treated with 20% piperidine in DMF (10 mL, 20 min, 2×), followed by a DMF wash (10 mL, 30 s, 5×). DMSO was added (10 mL), and the resin was heated at 80 °C for 24 h. After it was cooled to room temperature, the resin was washed with DMF (10 mL, 30 s, 3×), MeOH (10 mL, 30 s, 3×), and DCM (10 mL, 1 min, 5×). The resin was dried under nitrogen for 10 min and cleaved with 95% aqueous TFA at 60 °C for 4 h. The cleavage eluant was collected,

and sodium ethoxide yielded the unsaturated 2-aminoimidazolone **10**.[7] The long reaction times (10 h) were necessary to ensure that the product was completely deacylated. If the reaction was stopped earlier, products were isolated with a phenylacetate group on the one position of the imidazolone ring. Cleavage of **10** with 95% aqueous trifluoroacetic acid yielded the unsaturated 2-aminoimidazolone **2**.

Table 2 summarizes the yields and substrates used for this reaction. The proton NMR spectra of the product alkenes showed that they were formed as a 1/1 mixture of *E*/*Z* isomers. Although the diversity of the R_5 position is limited by the small number of commercially available oxazolones, these compounds can be synthesized readily from the corresponding aldehyde.

Following a literature procedure,[8] hippuric acid was treated with an aldehyde in the presence of acetic anhydride and sodium acetate and heated to 80 °C for 2 h:



The oxazolone precipitated from the crude reaction mixture when the solution was poured into water. This allowed us to incorporate aldehydes as the diversity unit in the R_5 position.

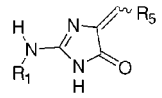
and the resin was washed with 95% aqueous TFA (5 mL, 1×) and MeOH (5 mL, 2×). The eluant and washes were combined and dried with a Speedvac. The compound was purified with preparative HPLC (Dynamax-60A C18 column, 0.1% solutions of TFA, water/acetonitrile 9/1 to 2/8 eluant gradient over 40 min, 21 mL/min flow rate), to yield the product as a crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.02 (s, 1H), 0.95 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.88, 158.17, 66.88, 34.52, 25.00. FAB HR-MS: calcd *m*/*z* for $C_7H_{13}N_3O$ 156.1137 ($M + H^+$), obsd 156.1137.

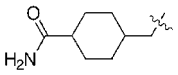
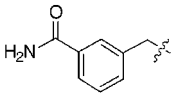
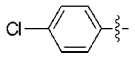
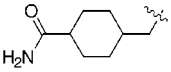
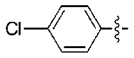
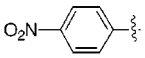
(6) Schuisky, P.; Twistel, W.; Grivas, S. *Heterocycles* **1998**, *48*, 1431−1444.

(7) Mukerjee, A. K.; Joseph, K.; Homami, S.-S.; Tikdari, A. M. *Heterocycles* **1991**, *32*, 1317−1325.

(8) (a) Homani, S.-S.; Mukerjee, A. K. *Indian J. Chem* **1991**, *30B*, 288−289. (b) Kumar, P.; Mishra, H. D.; Mukerjee, A. K. *Synthesis* **1980**, 836−838.

Table 2. Synthesis of Unsaturated 2-Aminoimidazolones



Compound	R_1	R_5	Yield[a] (%)
2a			49
2b			89
2c	H		46
2d			91
2e	H		63

[a] Yields were determined using the loading level of the starting resin and are based on isolated product.

In summary, we have shown that 2-aminoimidazolones can be produced in good yields and with acceptable purities from a resin-bound *S*-methyl isothiourea. The procedure utilizes Fmoc-protected amino acids and aldehydes as the diversity agents in the construction of the rings. The chemistry involved occurs under mild conditions and should find use in combination with other solid- and solution-phase chemistries.

Supporting Information Available: Procedures for the formation of 2-aminoimidazolones **1** and **2** and characterization data for **1a**−**h** and **2a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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