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Rapid assembly of 2-aminoimidazolones on solid support

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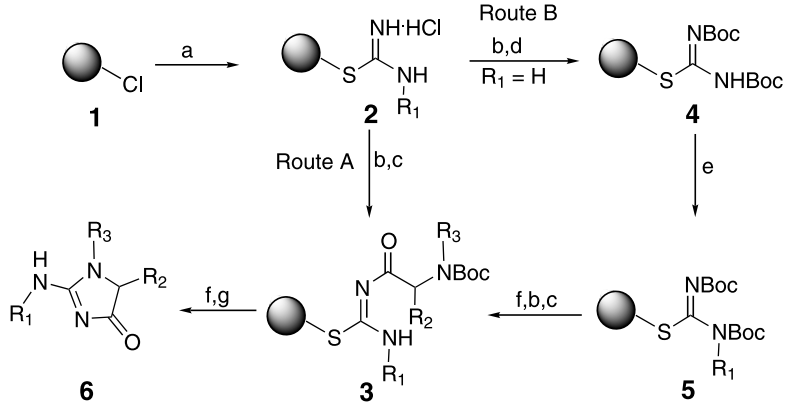
Abstract—A straightforward solid-phase synthesis of 2-aminoimidazolone derivatives is described. The synthesis starts with immobilization of thioureas onto solid support, followed by HBTU/DIEA assisted coupling of Boc-protected amino acids. Upon removal of the Boc group, intramolecular cyclization and simultaneous cleavage are promoted by polyamine resin to give the 2-aminoimidazolone derivatives in good yields and excellent purity.

Guanidine and imidazole are common skeletons in a wide range of biologically active molecules.[1,2] A combination of these two important moieties leads to a single conformationally constrained ring structure, 2-aminoimidazolone, which is an attractive scaffold to be utilized for exploiting chemical diversity and generating a broad drug-like screening library. In fact, the 2-aminoimidazolone core structure can be found in several classes of compounds which inhibit NF-κB activation[3] and protein kinase C.[4] Thus, several methods dealing with the solid-phase syntheses of diverse 2-aminoimidazolone libraries have been reported recently.[5] However, these methods were associated with the following limitations: the harsh cleavage conditions,[5a,c] the extended heating time,[5b] the use of a heavy metal reagent $HgCl_2$,[5c] and the structural restriction of some inputs such as isothiocyanates.[5b,d] We wish to report an efficient and straightforward method for a rapid assembly of this important scaffold on solid support and its extension to the automated synthesis of the corresponding combinatorial library.

As illustrated in Scheme 1, the synthesis (Route A) started with immobilization of readily available substituted thioureas onto Merrifield resin via a nucleophilic substitution reaction as reported by Yang.[6] Subsequent coupling of various Boc-protected amino acids onto the resin-bound isothioureas **2** proceeded smoothly in the



Scheme 1. *Reagents and conditions*: (a) thiourea (5 equiv.), NMP, 85°C, overnight; (b) 10% DIEA in DCM, rt, 5 min; (c) Boc-amino acid (5 equiv.), HBTU (5 equiv.), DIEA (10 equiv.), THF/DMF, rt, overnight; (d) $(Boc)_2O$ (10 equiv.), DIEA (10 equiv.), THF/DCM, rt, 40 h; (e) R_1OH (5 equiv.), PPh_3 (5 equiv.), DIAD (5 equiv.), THF, rt, 24 h; (f) 25% TFA in DCM, rt, 30 min; (g) polymer-supported polyamine, rt, 30 min.

Keywords: 2-aminoimidazolones; solid-phase combinatorial synthesis; cyclative cleavage.

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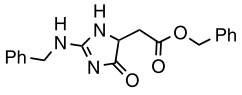
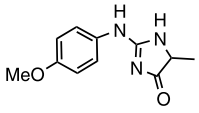
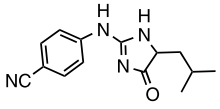
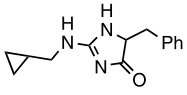
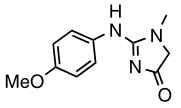
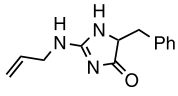
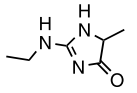
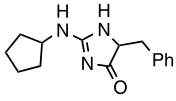
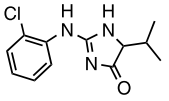
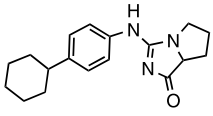
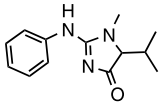
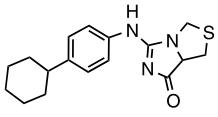
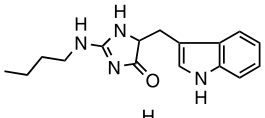
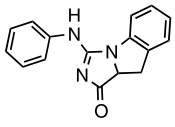
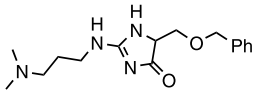
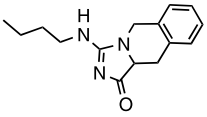
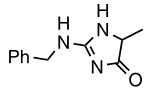
presence of HBTU/DIEA. The Boc-protecting group was then removed by the standard TFA treatment. Upon treatment of polymer-supported polyamine,[7] the free amino group attacks the isothiourea moiety to cleave the desired 2-aminoimidiazolones **6** from the solid support. In contrast to the known methods which relied on the formation of the guanidine intermediates via the displacement of isothioureas by amines under the harsh conditions,[5a,b] our intramolecular ring closure strategy offered a very smooth cyclative-cleavage to give the desired products at room temperature within 30 min.

It is noteworthy that, other than from substituted thioureas (Route A), diversity element at the 2-amino position (R_1) can also be introduced via the Mitsunobu reaction of polymer-bound Boc-protected isothiourea **4** with various alcohols R_1OH (Route B) according to the literature procedure.[8] The resin-bound intermediate **5** was then de-protected followed by the coupling of the amino acids leading to the intermediate **3**.

Table 1 illustrates some examples selected from a small set of a combinatorial library. Since the products were released in a cyclization–cleavage fashion, high purity was achieved as expected. The starting thioureas with aromatic or aliphatic substituents all gave satisfactory results. When cyclic amino acids, such as Boc-proline, were used, interesting ring-fused bicyclic imidazolone derivatives were formed (entries 14–17 in Table 1).

We observed that the coupling reaction of Boc-protected amino acids with the polymer-bound isothioureas **2** occurred exclusively on the unsubstituted nitrogen atom, regardless the nature of the substituents on the other nitrogen (R_1 = aromatic or aliphatic

Table 1. 2-Aminoimidazolones prepared from various thioureas, alcohols and amino acids

Entry	Products[a]	Yield[b] (Purity[c])	Entry	Products[a]	Yield[b] (Purity[c])
1		64% (>95%)	10		94% (>90%)
2		53% (>95%)	11[d]		76% (>80%)
3		92% (>80%)	12[d]		89% (>95%)
4		100% (>90%)	13[d]		63% (>80%)
5		80% (>90%)	14		63% (>90%)
6		74% (>95%)	15		56% (>70%)
7		86% (>90%)	16		65% (>70%)
8		82% (>80%)	17		60% (>90%)
9[d]		89% (>95%)			

[a] prepared from Route A unless otherwise indicated.

[b] determined by weight of the crude products based on the loading of the starting resins.

[c] determined by LC-MS using both UV and ELS detectors; further confirmed by ^1H NMR analysis;

[d] prepared from Route B.

groups). This regio-selectivity was confirmed by synthesizing the same imidazolone compounds, entries 9 and 10 in Table 1, based on the known method reported by Flygare.[5a]

In conclusion, we have developed a straightforward method for solid phase synthesis of 2-aminoimidazolone derivatives.[9,10] This protocol was easily adapted for the automated library synthesis. A diverse 2-aminoimidazolone library was then synthesized with a variety of thioureas, amino acids and alcohols. Syntheses of other heterocyclic scaffolds based on this polymer-bound isothiourea template will be reported in due course.

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9. A typical procedure for preparing compound **10** via Route A: Merrifield resin (**1**) (100 mg, from Advanced ChemTech, loading 0.94 mmol/g) was heated in 2 mL of 0.5 M 1-(*p*-methoxyphenyl)thiourea in NMP at 85°C overnight. After the suspension was cooled to room temperature, the resulting resin (**2**) (R_1=*p*-MeOPh) was filtered and washed with NMP, 10% DIPEA in DCM, then with DCM and MeOH several times. The resin was dried at room temperature, and then treated with 1 mL of 0.5 M Boc-alanine in THF, 2 mL of 0.25 M HBTU in DMF, and 0.5 mL of 2 M DIEA in THF, the resulting slurry was shaken at room temperature overnight to afford resin (**3**) (R_1=*p*-MeOPh, R_2=Me, R_3=H) which was filtered and washed with DMF, DCM and MeOH several times and dried at room temperature. The Boc-group was removed by treating the dried resin with 2 mL of 25% TFA/DCM at room temperature for 30 min. The resin was filtered, washed once with DCM and dried at room temperature. The dried resin was then mixed with 100 mg of polymer-bound tris(2-aminoethyl)amine in 3 mL of THF at room temperature for 30 min. The resin was filtered off and washed with 2 mL of THF. The filtrate and washing were combined and evaporated to afford crude product of compound **10** (19.4 mg, 94% yield, >90% purity). LC/MS (ES, *m*/*z*, relative intensity): 220 (M+H, 100%). ^{1}H NMR ($CDCl_3$, ppm): 8.59 (s, 1H), 7.16–7.18 (d, *J*=9.0 Hz, 2H), 6.90–6.92 (d, *J*=9.0 Hz, 2H), 3.84 (m, 1H), 3.77 (s, 3H), 1.43–1.45 (d, *J*=7 Hz, 3H).
10. A typical procedure for preparing compound **9** via Route B: Merrifield resin (**1**) (100 mg, from Advanced ChemTech, loading 0.94 mmol/g) was heated in 2 mL of 0.5 M thiourea in NMP at 85°C overnight. After the suspension was cooled to room temperature, the resin **2** (R_1=H) was filtered and washed with NMP, 10% DIEA in DCM, then with DCM and MeOH several times, then dried at room temperature. The dried resin was treated with 1 mL of 0.5 M $(Boc)_2O$ in DCM and 1 mL of 0.5 M DIPEA in THF at room temperature for 40 h to afford resin **4** which was filtered and washed with DMF, DCM and MeOH several times and dried at room temperature.

The dried resin (**4**) was then suspended in a mixture of 1.0 mL of 0.5 M benzyl alcohol in THF and 1.0 mL of 0.5 M triphenylphosphine in THF, to it was added 1 mL of 0.5 M DIAD in THF. The resulting slurry was shaken at room temperature for 24 h to give resin **5** ($R_1 = PhCH_2$) which was washed and dried as described previously. Resin **5** was then treated with 2 mL of 25% TFA/DCM at room temperature for 30 min to remove the two Boc groups. The resulting resin was filtered and washed with NMP, 10% DIEA in DCM, then with DCM and MeOH several times, dried at room temperature. The dried resin was treated with 1 mL of 0.5 M Boc-alanine in THF, 2 mL 0.25 M HBTU in DMF, and 0.5 mL of 2 M DIEA in THF, the resulting slurry was shaken at room temperature overnight to give resin **3** ($R_1 = PhCH_2$, $R_2 = Me$, $R_3 = H$) which was filtered and washed with DMF, DCM and MeOH several times and then dried at room temperature. The Boc-group was removed by treating the dried resin with 2 mL of 25% TFA/DCM at room temperature for 30 min. The resin was filtered, washed once with DCM and dried at room temperature. The dried resin was then mixed with 100 mg of polymer-bound tris(2-aminoethyl)amine in 3 mL of THF at room temperature for 30 min. The resin was filtered off and washed with 2 mL of THF. The filtrate and washing were combined and evaporated to afford crude product of compound **9** (17 mg, 89% yield, >95% purity). LC/MS (ES, m/z, relative intensity): 204 (M+H, 40%), 91 ($PhCH_2^+$, 100%). ^1H NMR (CD_3OD, ppm): 7.29–7.34 (bs, 5H), 4.53 (s, 1H), 4.45 (s, 1H), 4.00 (m, 1H), 1.34–1.35 (d, $J = 7$ Hz, 3H).