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A facile and practical solid-phase synthesis of trisubstituted 2-aminoimidazolones

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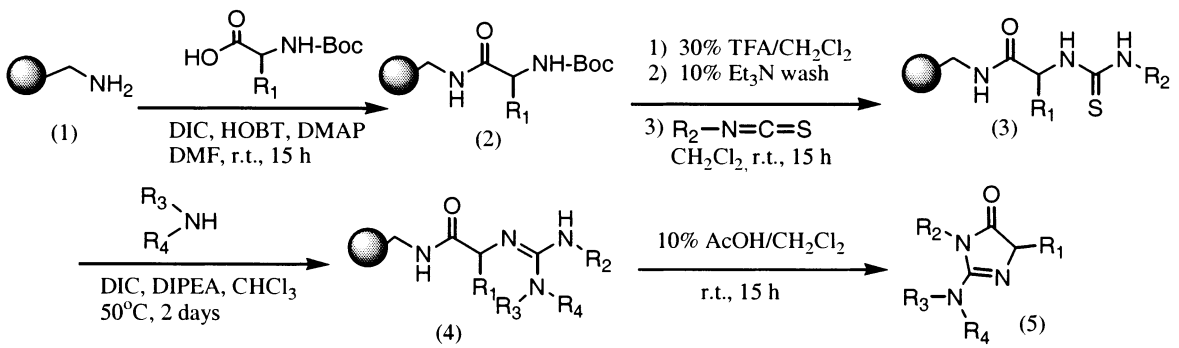
Abstract—The solid-phase synthesis of trisubstituted 2-aminoimidazolones based on the intramolecular cyclization between a δ-guanidinium nitrogen and the amide carbonyl under acidic conditions is described. The method utilizes easily accessible commercial starting materials, mild reaction conditions, as well as a cyclizative–cleavage strategy to afford the desired products in moderate to good overall yields and good to excellent purity.

The 2-aminoimidazolone ring, a derivative of cyclic guanidines, often appears as the core structure in many drug substances, covering a wide range of pharmacological activities.[1] Although the interest in making mono-, di-, and trisubstituted guanidines on solid support have rapidly grown in recent years,[2] there have been few methods to access the 2-aminoimidazolones.[3,4] Herein, We wish to report a facile and practical solid-phase method for the preparation of trisubstituted 2-aminoimidazolones based on the intramolecular cyclization between a δ-guanidinium nitrogen and the amide carbonyl under acidic conditions.[2]

While expanding our interest in the solid-phase synthesis of small heterocyclic rings and substituted guanidines,[5] we found that when starting with a resin bound amino acid moiety, we can easily access guanidino amides, guanidino acids, as well as 2-aminoimidazolones with the same guanidine synthesis procedure, depending on the type of amino acids bound on the resin. The 2-aminoimidazolone formation was especially attractive to us due to its cyclizative–cleavage feature which occurs between the δ-guanidium nitrogen and the resin bound amide carbonyl under acidic conditions. The general procedure (Scheme 1) includes treating a resin bound α-amino amide moiety (**2**) with an isothiocyanate (5 equiv.) in CH_2Cl_2 to give the resin bound thiourea (**3**). The thiourea **3** was then subjected to the guanylation with an amine (5 equiv.) at 50°C in $CHCl_3$ in the presence of DIC (5 equiv.) and DIPEA (5 equiv.) to give the resin bound guanidine (**4**). The desired product (**5**) was obtained upon cleavage under acidic conditions at room temperature. Although both Rink resin and aminomethyl resin can be used as the solid support for the 2-aminoimidazolone synthesis, aminomethyl resin (**1**) is a better choice since it would



Scheme 1. Solid-phase synthesis of trisubstituted 2-aminoimidazolones.

Keywords: 2-aminoimidazolone; solid-phase synthesis; cyclizative–cleavage.

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only allow the cyclized product to be cleaved off the resin. Hydroxymethyl resin was not chosen due to the simultaneous cyclization during the guanylation step. The cyclizative–cleavage occured in either 10% TFA/CH_2Cl_2 or 10% AcOH/CH_2Cl_2. However, the AcOH/CH_2Cl_2 combination is more preferable in generating cleaner products. By starting with an aminomethyl resin bound α-amino acid (**2**) and using the reaction conditions described, we obtained the 2-aminoimidazolones (**5**) in moderate to good overall yields and good to excellent purity.

During the study, we found that the guanylation is the central step in the 2-aminoimidazolone synthesis. The major and the only by-products that we had usually observed from the synthesis were relevant to the guanylation step—thiourea and/or carbodiimide. There have been many reports around guanylation conditions and reagents.[2b,6] Among the reagents tried (EDC, DIC, Mukaiyama's and Sanger's reagents) DIC gave cleaner products. Reaction temperature seemed to have a great impact on the guanylation (Table 1). For the given reaction time (2 days), at room temperature, the guanylation gave both thiourea (**8**) and carbodiimide (**9**) as the by-products (**8** was formed by cyclization then ring opening during MeOH washes) (entry 1); at 70°C, carbodiimide **9** was the major by-product (entry 3); only at 50°C, the guanylation was 100% (entry 2). It was also found that the 2 day reaction time is necessary for 100% guanylation (entry 4 versus 2). This may suggest that whether a carbodiimide intermediate is involved in this transformation, the tetrahedral mechanism must dominate.[6b] The guanylation reaction does not seem to be very solvent dependent. DMF and DMSO both gave a similar result as $CHCl_3$. Other solvents, e.g. 1,2-dichloroethane or THF, etc. could also be applicable.

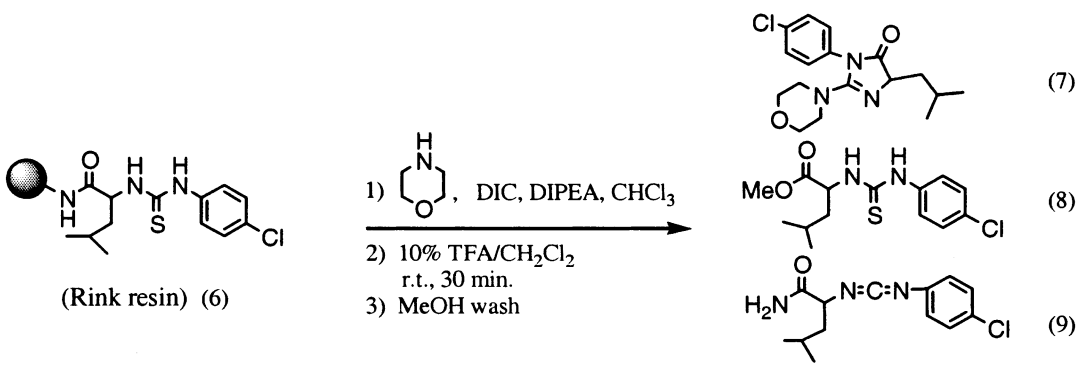
The structural effect of the isothiocyanates and amines on the guanylation has also been investigated. It was found that under these guanylation conditions, aromatic isothiocyanates and aliphatic amines are the most suitable substrates. Some less steric hindered aliphatic isothiocyanates underwent the guanylation in a lower yield. To avoid generating two cyclizable guanidinium nitrogens,[2b] only secondary aliphatic amines were used in the synthesis of the 2-aminoimidazolones.

We also found that some of the 2-aminoimidazolones did not seem to be very stable in MeOH. We have observed some complication in NMR and MS spectrum when the compounds were stored in a MeOH solution. This could be due to the tautomerization or ring opening of the compounds. No further investigations have been carried out in this respect. However, no changes were observed after the same compounds were stored in $CHCl_3$ for weeks.

Table 2 summarizes a set of the 2-aminoimidazolones synthesized via this method by utilizing the Argonaut Quest 210. As shown, most compounds gave a fair five-step overall yield, and good to excellent purity. No further purification would be needed after the simple cyclizative–cleavage in many cases.

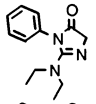
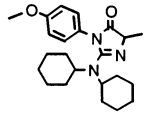
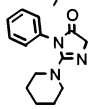
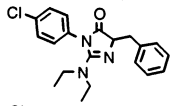
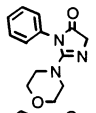
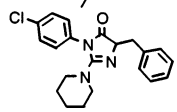
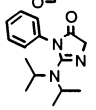
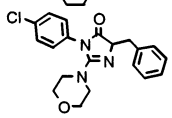
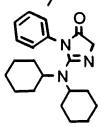
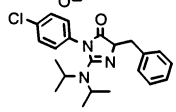
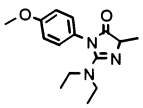
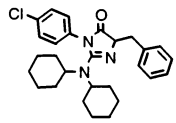
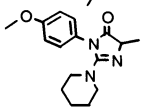
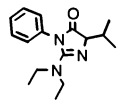
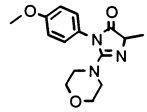
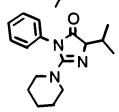
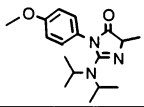
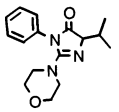
In summary, we have developed a practical solid-phase synthetic method for trisubstituted 2-aminoimidazolones. The method involves simple and mild solid-phase reaction conditions, utilizes easily accessible commercial reagents (amino acids, isothiocyanates and amines), and introduces the diversity points efficiently (in each step). Most importantly, the method takes advantage of the intramolecular cyclization to afford the desired products in good quality with no need for further purification in many cases. The method could be easily applied to the combinatorial synthesis of large numbers of trisubstituted 2-aminoimidazolone compounds and libraries.

Table 1. Guanylation temperature and time optimization



Entry	Temp. (°C)	Time (days)	Ratio (by LC/MS)		
			7	**8**	**9**
1	Rt	2	4.5	3	1
2	50	2	100%		
3	70	2	6	0	1
4	50	1	Major	Trace	Trace

Table 2. Examples of the trisubstituted 2-aminoimidazolones synthesized by this method[7]

	Product	Overall Yield (%)[a]	Purity (%)[b]		Product	Overall Yield (%)[a]	Purity (%)[b]
5a		73	89	**5j**		31	77
5b		66	87	**5k**		89	83
5c		76	87	**5l**		89	75
5d		32	100	**5m**		77	98
5e		33	95	**5n**		60	71
5f		49	93	**5o**		57	84
5g		30	88	**5p**		60	100
5h		25	67	**5q**		37	100
5i		43	76	**5r**		27	100

a) Crude 5-step overall yield as a mono-TFA salt. Determined by weight based on the loading of the commercial aminomethyl polystyrene resin. b) Determined by HPLC at 210 nm.

Acknowledgements

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References

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4. While we were in the process of submitting this manuscript, a similar solid-phase route appeared (Drewry, D. H.; Ghiron C. *Tetrahedron Lett.* **2000**, *41*, 6989). The key differences in our work are: (1) amide linker instead of ester linker; (2) isolated resin bound guanidine intermediate; and (3) the lack of need for scavenger resin use to clean up the products.
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7. **General procedure for the synthesis of 2-aminoimidazolones (each step was repeated once)**: To a slurry of aminomethyl polystyrene resin (1 equiv.; 1.16 mmol/g; Advanced ChemTech) in DMF (10 ml/g) was added Boc-amino acid (3 equiv.), DIC (3 equiv.), HOBT (3 equiv.) and DMAP (0.3 equiv.). The mixture was agitated at room temperature overnight (~15 h). The resin was filtered and washed successively with DMF (three times), CH_2Cl_2 (three times), MeOH (three times) and CH_2Cl_2 (three times). The resin was then treated with 30% TFA/CH_2Cl_2 (10 ml/g) at room temperature for 1 h, filtered, washed with 10% Et_3N/

CH_2Cl_2 (three times), then same as above. To a slurry of the deprotected resin in CH_2Cl_2 (10 ml/g) was added isothiocyanate (5 equiv.), and the mixture was agitated at room temperature overnight (~15 h). The resin was filtered and washed in the same way as above. To a slurry of the resin in $CHCl_3$ (10 ml/g) was added secondary amine (5 equiv.), DIC (5 equiv.) and DIPEA (5 equiv.), and the mixture was agitated at 50°C for 2 days. The resin was filtered and washed in the same way as above. The resin was cleaved with 10% $AcOH/CH_2Cl_2$ (10 ml/g) at room temperature overnight (~15 h), filtered and washed with $CHCl_3$. The filtrate was evaporated to dryness to give the desired product in yield and purity as shown in Table 2. Analytical data for representative compounds:

5d: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.08 (m, 5H), 4.25 (s, 2H), 3.56–3.47 (m, 2H), 1.07 (d, 12H, $J=6.8$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.1, 158.1, 134.9, 130.3, 129.8, 127.8, 53.3, 50.0, 21.2; HRMS (FAB) m/z for $C_{15}H_{21}N_3O$ ($M+H^+$) calcd: 260.1763, found: 260.1757.

5f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, $J=8.9$ Hz), 6.88 (d, 2H, $J=8.9$ Hz), 4.31 (q, 1H, $J=14.4$, 7.2 Hz), 3.70 (s, 3H), 3.13 (q, 4H, $J=14.2$, 7.1 Hz), 1.42 (d, 3H, $J=7.2$ Hz), 0.92 (t, 6H, $J=7.1$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.0, 160.8, 157.2, 128.9, 126.1, 115.7, 57.3, 56.0, 44.5, 17.8, 12.8; HRMS (FAB) m/z for $C_{15}H_{21}N_3O_2$ ($M+H^+$) calcd: 276.1712, found: 276.1717.

5m: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 7H), 6.70 (d, 2H, $J=8.5$ Hz), 4.56 (t, 1H, $J=4.5$ Hz), 3.52–3.47 (m, 4H), 3.28 (dd, 2H, $J=6.6$, 1.8 Hz), 3.00–2.92 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.8, 158.6, 135.4, 134.6, 132.8, 130.7, 130.1, 128.2, 127.5, 127.3, 66.3, 66.1, 47.7, 38.0; HRMS (FAB) m/z for $C_{20}H_{20}ClN_3O_2$ ($M+H^+$) calcd: 370.1322, found: 370.1316.

5q: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.06 (m, 5H), 4.35 (d, 1H, $J=3.4$ Hz), 3.22 (bs, 4H), 2.25–2.20 (m, 1H), 1.42 (bs, 6H), 0.97 (d, 3H, $J=6.9$ Hz), 0.85 (d, 3H, $J=6.8$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.8, 158.3, 133.1, 130.8, 130.5, 126.7, 64.8, 49.6, 31.7, 25.3, 23.5, 18.3, 16.8; HRMS (FAB) m/z for $C_{17}H_{23}N_3O$ ($M+H^+$) calcd: 286.1919, found: 286.1910.