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Regio-controlled synthesis of *N*-substituted imidazoles

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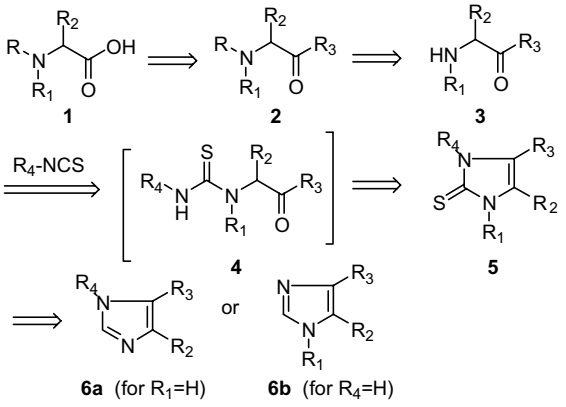
Abstract—A regio-specific synthesis of *N*-substituted imidazoles is described. Readily available α-amino acids are converted to α-aminocarbonyl derivatives and reacted with various isothiocyanates to give *N*-substituted cyclic thioureas. Oxidative or reductive desulfurization of the cyclic thioureas affords structurally diversified imidazoles in good to excellent yields.

Substituted imidazoles are a class of pharmaceutically important heterocyclic compounds, several of which have been incorporated in marketed drugs such as cimetidine and losartan.[1] There are a number of methods available for the construction of this ring system.[2] However, no practical protocol exists for the regio-controlled synthesis of *N*-substituted imidazoles. A conventional way to prepare *N*-alkyl substituted imidazoles is to alkylate the imidazole nitrogen with appropriate electrophiles, such as alkyl halides.[3] Recently, palladium or copper catalyzed imidazole couplings with aryl halides[4] or arylboronic acids[5] are the methods of choice to access *N*-aryl imidazoles. Nonetheless, all these methods suffered from the same intrinsic poor regio-selectivity due to the tautomeric nature of the imidazole ring. Any regio-selectivity seen in the reaction was primarily attributed to the steric effects of the substituents, which are distinct for each reactant.[6] We describe herein a method to synthesize structurally diversified *N*-substituted imidazoles in a regio-specific fashion from readily accessible starting materials.

Within this context, we found that the Marckwald synthesis[7] could be expanded to prepare regio-specific *N*-substituted imidazoles. As detailed in Scheme 1, the protected α-aminocarbonyl analogs **2** can be prepared from the amino acids **1** through many known procedures, such as Weinreb amide method and Nierenstein reaction.[8] Removal of the protecting group R provides the α-aminocarbonyl compounds **3**. Condensation of **3** with various isothiocyanates or a thiocyanate salt (i.e. KSCN, originally used in the Marckwald synthesis) leads to the *N*-substituted cyclic thioureas **5** through the acyclic thiourea intermediates **4**. By choosing either R_1 in amino acids or R_4 in isothiocyanates to be a hydrogen atom, regio-specific thioureas **5** are readily obtained. This regio-specificity is maintained during the following desulfurization step, leading to the desired imidazoles **6a** or **6b**.



Scheme 1. Synthetic approach to *N*-substituted imidazoles from α-amino acids.

We used the β-ketoester **10** as an example for our initial study. As shown in Scheme 2, condensation of Boc-phenylalanine **7** with ethyl malonate potassium salt **8** afforded the intermediate **9** in 95% yield.[9] ^{1}H NMR indicated that

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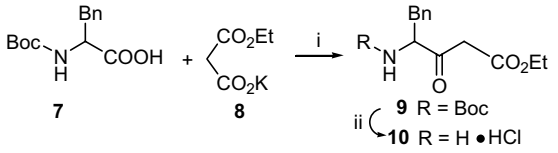
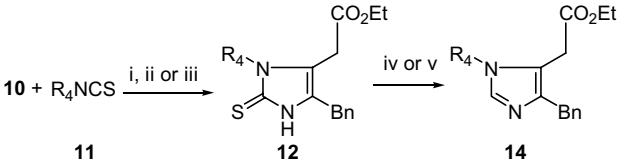


Scheme 2. Reagents and conditions: (i) CDI, $MgCl_2$, 95%; (ii) HCl/EtOAc, rt, 1 h, 100%.

compound **9** exists mainly in keto form in $CDCl_3$ (>99%). Removal of the Boc group with saturated HCl in EtOAc provided the amine salt **10** as a white solid quantitatively. This salt was fairly stable: it could be stored at room temperature for 6 months without noticeable degradation (monitored by HPLC-MS and NMR).

We selected three reagents, methyl, piperidinoethyl, and *p*-iodophenyl isothiocyanates (**11a**, **11c**, and **11d**, respectively), to couple with the salt **10** for their structural diversity. All reactions were performed in hot ethanol, and triethyl amine was used as the base to neutralize the formed hydrogen chloride. As shown in Table 1,

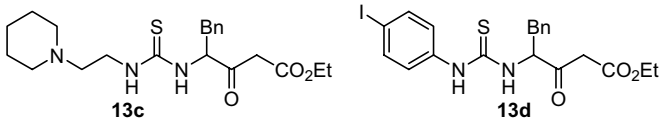
Table 1. Synthesis of cyclic thioureas **12a–d** and imidazoles **14a–d** from phenylalanine



No.	R_4NCS	Cyclic thiourea	Imidazole
1	MeNCS **11a**	**12a** (80%)[a]	**14a** (74%)[d]
2	KNCS **11b**	**12b** (81%)[b]	**14b** (75%)[d]
3	**11c**	**12c** (75%)[c]	**14c** (71%)[d]
4	**11d**	**12d** (80%)[c]	**14d** (82%)[e]

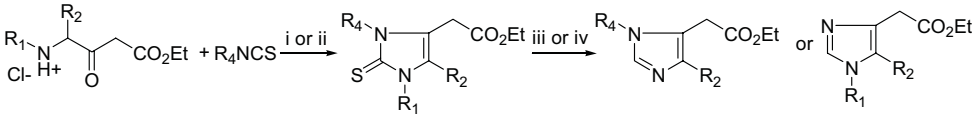
Reagents and conditions: (i) EtOH, Et_3N, reflux, 12 h; (ii) 1:3 *t*-BuOH/H_2O, 90 °C, 12 h; (iii) EtOH, Et_3N, 50 °C, 4 h; then 10% PPTS, toluene, reflux, 4 h; (iv) Raney Nickel, EtOH, reflux, 16 h; (v) H_2O_2, AcOH, rt, 5 min.

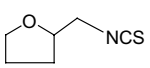
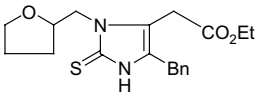
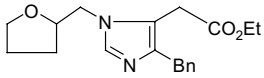
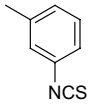
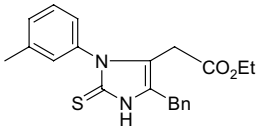
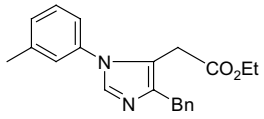
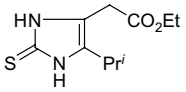
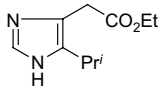
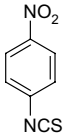
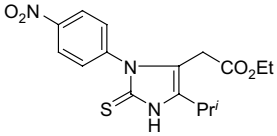
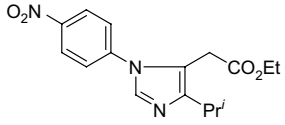
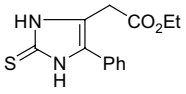
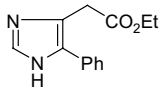
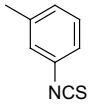
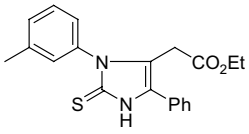
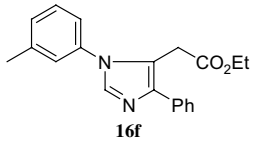
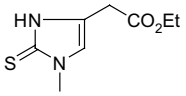
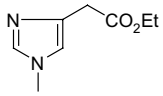
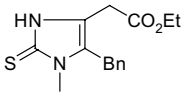
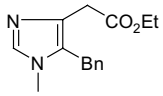
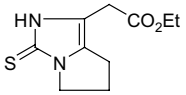
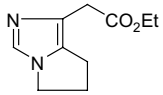
[a] Yield from reaction condition (i).
[b] Yield from reaction condition (ii).
[c] Yield from reaction condition (iii).
[d] Yield from reaction condition (iv).
[e] Yield from reaction condition (v).



Scheme 3. Acyclic thioureas formed in hot ethanol reaction. See text for details.

Table 2. Synthesis of imidazoles from various α-amino acids



Entry	Amino acid	R_4NCS	Cyclic thiourea	Yield(%)	Imidazole	Yield (%)
1	Phenylalanine		 **15a**	68[a]	 **16a**	71[c]
2	Phenylalanine		 **15b**	85[a]	 **16b**	80[d]
3	Leucine	KNCS	 **15c**	84[b]	 **16c**	81[c]
4	Leucine		 **15d**	80[a]	 **16d**	85[d]
5	2-Phenylglycine	KNCS	 **15e**	84[b]	 **16e**	82[d]
6	2-Phenylglycine		 **15f**	83[a]	 **16f**	86[c]
7	Sarcosine	KNCS	 **15g**	80[b]	 **16g**	68[c]
8	*N*-Methyl phenylalanine	KNCS	 **15h**	84[b]	 **16h**	75[d]
9	Proline	KNCS	 **15i**	82[b]	 **16i**	70[d]

Reagents and conditions: (i) EtOH, Et_3N, 50 °C, 4 h; then 10% PPTS, toluene, reflux, 4 h; (ii) 1:3 *t*-BuOH/H_2O, 90 °C, 12 h; (iii) Raney Nickel, EtOH, reflux, 16 h; (iv) H_2O_2, AcOH, rt, 5 min.

[a] Yield from reaction condition (i).

[b] Yield from reaction condition (ii).

[c] Yield from reaction condition (iii).

[d] Yield from reaction condition (iv).

methyl isothiocyanate **11a** reacted with **10** to give the cyclic thiourea **12a** in 80% yield, which is in accordance with the direct formation of the cyclic thiourea in the Marckwald synthesis. Similarly, coupling of **10** with KNCS in hot aqueous *tert*-butanol afforded the cyclic thiourea **12b** in 81% yield (Table 1, entry 2,).[10] Coupling of **11c** and **11d** with **10**, however, led to a 3:2 mixture of the cyclic and acyclic thioureas (**12c** and **13c**) and the acyclic thiourea **13d**, respectively (for structures of **13c** and **13d**, see Scheme 3). In both cases, prolonged heating did not improve the yields of the cyclized products **12c** and **12d** (monitored by LC–MS at 254 and 210 nm).

Clearly, a more effective method was needed for the cyclodehydration of **13c**,**d** to form **12c**,**d**. In a test study, the acyclic thiourea **13d** was dissolved in toluene and heated to 120 °C for 4 h in the presence of 10% pyridinium *p*-toluenesulfonate (PPTS).[11] As expected, the cyclic thiourea **12d** was obtained in 88% isolated yield. To combine the acyclic thiourea formation and the subsequent cyclodehydration into a one-pot process, the reaction mixture of **11c** with **10** was concentrated in vacuo and directly subjected to the PPTS catalyzed cyclization. The desired cyclic thiourea **12c** was isolated in 75% yield after refluxing in toluene for 4 h. Generally, the yields of this one-pot procedure to form cyclic thioureas are good to excellent, as can be seen in Tables 1 and 2.

Conversion of cyclic thioureas to imidazoles can be achieved under either oxidative[12] or reductive[13] conditions. We chose two established methods, that is, Raney Nickel/EtOH and H_2O_2/AcOH, to remove the sulfur. As exemplified in Table 2, the two protocols provided comparable results for the imidazole formation. For molecules that are susceptible to oxidative conditions, a reductive desulfurization is preferred, and vice versa. For example, the tetrahydrofuran analog **15a** favors Raney Nickel reduction, whereas the iodo analog **12d** requires oxidative condition for removal of sulfur atom due to the phenyl iodide functionality.

The method was applied to a variety of amino acids and isothiocyanates, providing structurally diversified imidazoles, as illustrated in Table 2. Disubstituted imidazoles, **16c**, **16e**, and **16g**, were also prepared for comparison. Amino acids with both alkyl and aryl side chains are good substrates, as seen within entries 3 and 5. The substitution on the amino group showed little effect on the cyclization and desulfurization steps, as exemplified by sarcosine, *N*-methyl phenylalanine, and proline (entries 7–9). Thus, the elusive bicyclic imidazole **16i** was conveniently prepared. Most notably, the two imidazole regioisomers, **14a** and **16h**, were readily available with unambiguous regio-specificity using this method.[14]

In summary, we demonstrated that a variety of amino acids are convenient starting materials for the syntheses of *N*-substituted imidazoles in a regio-controlled manner. Many functional groups, such as ester, iodo, nitro, and iodole moieties, are compatible with the process. In addition, reducible or oxidizable functional groups in the cyclic thioureas are tolerated by using different desulfurization conditions. Further elaboration at the 2-position of the imidazole ring is possible with the transition metal catalyzed coupling reactions. We are currently evaluating these reactions and the results will be reported in due course.

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14. A typical procedure for synthesizing the N-substituted imidazoles from α-aminocarbonyl salt **13** is as follows: A solution of salt **13** (3.0 g, 1 equiv), an isothiocyanate (1.2 equiv) and triethylamine (1.5 equiv) in 50 mL of ethanol was heated to 50 °C for 4 h. The reaction mixture was then concentrated in vacuo to dryness. The residue was suspended in 50 mL of toluene with PPTS (0.1 equiv). The mixture was heated to 120 °C for 4 h and then cooled to room temperature. The resulted solution was diluted with 50 mL of ethyl acetate, washed with 50 mL of saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The organic phase was concentrated in vacuo and the residue was re-crystallized with 50% EtOAc/hexanes to give the desired cyclic thiourea.
A suspended solution of cyclic thiourea and Raney nickel (5 equiv) in EtOH (50 mL) was heated to reflux for 8 h.

After cooling the reaction mixture to room temperature, Raney nickel was removed by filtration through a Celite pad. The filtrate was concentrated in vacuo and the residue was treated with 1 N HCl in ether. The imidazole HCl salt was purified by crystallization in an ether/MeOH mixture. Alternatively, the desulfurization step can also be carried out under oxidative condition: to a solution of cyclic thiourea (1.00 mmol) in glacial acetic acid (5 mL) was added 30% H_2O_2 aqueous solution (4 equiv, 4.00 mmol) slowly. After 5 minutes, the reaction was cooled to 0 °C and quenched with 10 mL of 10% K_2CO_3 solution. The pH of the mixture was adjusted to pH ~ 9 with 2 N NaOH solution. The solution was extracted with 50 mL of EtOAc and the organic phase was separated, washed with 20 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was treated with 1 N HCl in ether to form imidazole HCl salt, which was crystallized in an ether/MeOH mixture.

Selected data (^{1}H NMR, 400 MHz, δ ppm): Compound **12d** (chloroform-*d*): 10.97 (1H, s), 7.83 (2H, d, $J = 7.8$ Hz), 7.17–7.34 (5H, m), 7.07 (2H, d, $J = 8.2$ Hz), 4.00 (2H, q, $J = 6.8$ Hz), 3.84 (2H, s), 3.27 (2H, s), 1.62 (1H, s), 1.14 (3H, t, $J = 7.0$ Hz); LC–MS *m/z*: 479.4 $[M+H]^+$. Compound **13d** (chloroform-*d*): 7.76 (2H, d, $J = 7.8$ Hz), 7.22–7.40 (6H, m), (2H, d, $J = 7.8$ Hz), 6.13–6.22 (1H, m), 5.57–5.66 (1H, m), 3.87–4.09 (3H, m), 2.94–3.14 (2H, m), 2.58–2.84 (2H, m), 1.21 (3H, t, $J = 7.3$ Hz); LC–MS *m/z*: 497.4 $[M+H]^+$. Compound **14c** (methanol-d_4): 9.15 (1H, s), 7.20–7.37 (5H, m), 4.75 (2H, m), 4.17 (2H, q, $J = 6.8$ Hz), 4.12 (2H, s), 4.06 (2H, s), 3.70 (3H, m), 3.51 (2H, d, $J = 7.0$ Hz), 1.96 (4H, m), 1.26 (2H, t, $J = 4.0$ Hz), 1.20 (3H, t,$J = 8.0$ Hz); LC–MS *m/z*: 356.3 $[M+H]^+$. Compound **14d** (methanol-d_4): 9.19 (1H, s), 8.03 (2H, d, $J = 7.8$ Hz), 7.34 (7H, m), 4.19 (2H, s), 4.01 (2H, q, $J = 6.8$ Hz), 3.85 (2H, s), 1.12 (3H, t, $J = 6.8$ Hz); LC–MS *m/z*: 446.8 $[M+H]^+$. Compound **16a** (methanol-d_4): 8.91 (1H, s), 7.19–7.38 (5H, m), 4.40 (1H, d, $J = 12.5$ Hz), 4.12–4.23 (4H, m), 4.11 (2H, s), 3.98 (2H, s), 3.90 (1H, q, $J = 6.9$ Hz), 3.79 (1H, q, $J = 6.9$ Hz), 2.11–2.21 (1H, m), 1.90–2.01 (2H, m), 1.60–1.71 (1H, m), 1.24 (3H, t, $J = 7.0$ Hz); LC–MS *m/z*: 329.0 $[M+H]^+$. Compound **16b** (chloroform-*d*): 7.55 (1H, s), 7.08–7.36 (9H, m), 3.94–4.01 (4H, m), 3.48 (2H, s), 2.40 (3H, s), 1.12 (3H, t, $J = 7.2$ Hz); LC–MS *m/z*: 335.3 $[M+H]^+$. Compound **16d** (methanol-d_4): 9.21 (1H, s), 8.45 (2H, d, $J = 8.2$ Hz), 7.82 (2H, d, $J = 8.2$ Hz), 3.97 (2H, q, $J = 6.8$ Hz), 3.85 (2H, s), 2.62 (2H, d, $J = 7.4$ Hz), 1.91–2.01 (1H, m), 1.06 (3H, t, $J = 7.0$ Hz), 0.96 (6H, d, $J = 6.3$ Hz); LC–MS *m/z*: 332.1 $[M+H]^+$. Compound **16h** (DMSO-d_6): 9.06 (1H, s), 7.22–7.37 (4H, m), 7.17 (1H, d, $J = 6.7$ Hz), 4.17 (2H, s), 4.09 (2H, d, $J = 6.7$ Hz), 3.93 (3H, s), 3.60 (2H, s), 1.18 (3H, t, $J = 6.7$ Hz); LC–MS *m/z*: 259.0 $[M+H]^+$. Compound **16i** (chloroform-*d*): 7.32–7.38 (1H, m), 4.16 (2H, q, $J = 7.2$ Hz), 3.97 (2H, t, $J = 7.0$ Hz), 3.50–3.59 (2H, m), 2.72–2.82 (2H, t, $J = 8.0$ Hz), 2.56–2.66 (2H, m), 1.17–1.30 (3H, t, $J = 7.0$ Hz); LC–MS *m/z*: 194.9 $[M+H]^+$.