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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.
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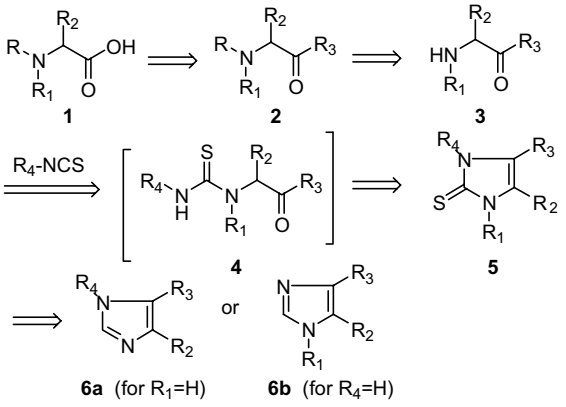
Substituted imidazoles are a class of pharmaceutically important heterocyclic compounds, several of which have been incorporated in marketed drugs such as cimetidine and losartan.[1] There are a number of methods available for the construction of this ring system.[2] However, no practical protocol exists 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

Keywords: Imidazoles; Regio-controlled synthesis; Amino acids; Cyclic thioureas.
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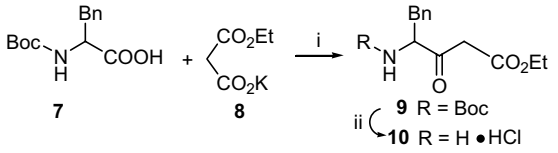


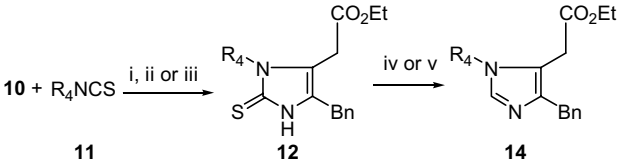
7 8

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

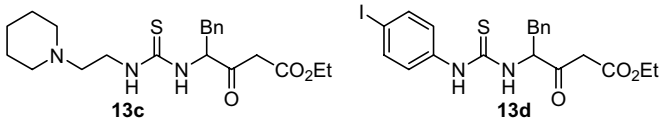


11 12 14

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).



13c 13d

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

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