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A General Route to 4-Imidazolyl-Containing Multidentate Ligands for Biomimetic Studies

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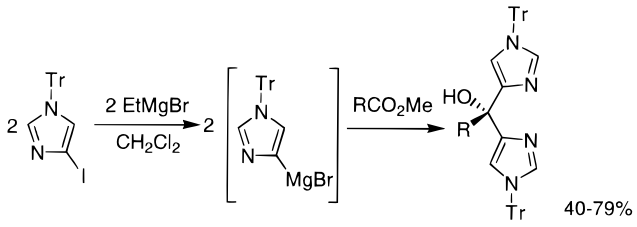
ABSTRACT



4-Iodo-1-tritylimidazole undergoes magnesium−iodine exchange with a Grignard reagent to give selectively the 4-magnesioimidazole derivative, which reacts with esters to form a variety of poly-4-imidazolyl carbinol compounds in 40−79% yields. A wide range of bi-, tri-, and pentadentate ligands featuring 4-substituted imidazole units have been efficiently synthesized.

Imidazole rings of histidine residues often form part of the metal-binding site in metalloproteins.[1] The ubiquitous histidine ligation in metalloenzymes has stimulated syntheses of imidazole-containing multidentate ligands for biomimetic studies. Because imidazole C(2)-H is more acidic than C(4)-H and C(5)-H, it can be readily deprotonated to form a carbanion at the 2-position. On the basis of this chemistry, a large number of bi-,[2] tri-,[3] and tetradentate[4] metal chelating ligands containing imidazole substituted at the 2-position have been developed. However, ligands with the less accessible 4-imidazolyl units are better suited for mimicking biological metal-binding sites because the histidine imidazole ring is attached via the 4-position to the side chain when the imidazole is coordinated to a metal. Previous syntheses of 4-imidazolyl-containing multidentate ligands have mostly relied on the manipulation of histidine derivatives[5] or have invoked double protection of the imidazole 1- and 2-positions followed by lithiation and nucleophilic reaction at C5 (Figure 1, **1**).[6,7] Alternatively, Katritzky et al. employed the imidazole-1,4-dianion **2**, generated by direct lithiation of 4(5)-bromoimidazole, to synthesize a number of 4(5)-substituted imidazoles including a bisimidazole compound.[7] In this paper

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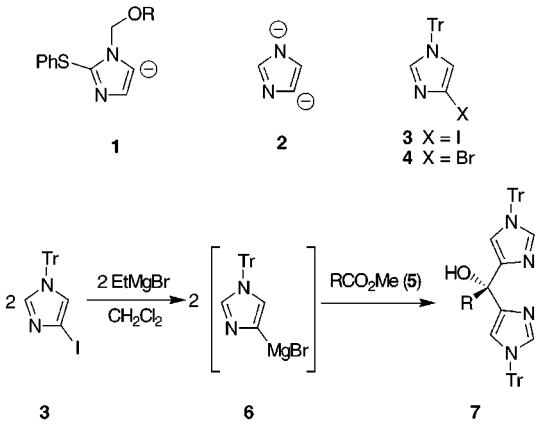


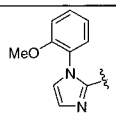
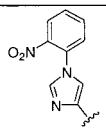
Figure 1.

we present a facile, general method for the synthesis of multidentate ligands containing 4-imidazolyls from readily available 4-iodo-1-tritylimidazole.

4-Iodo-1-tritylimidazole (**3**) and the corresponding 4-bromo derivative **4** can be readily prepared in large scale using a literature method.[8] Lithiation of **3** or **4**, however, is not selective and generates a 2-lithiated species via equilibrium deprotonation.[9] On the other hand, the more reactive **3** can undergo metal−iodine exchange with a Grignard reagent and selectively form the 4-magnesioimidazole derivative,[10] which will then react with aldehydes and ketones[10] or undergo Pd-catalyzed coupling reactions.[11] Despite the well-developed magnesium−iodine exchange method and its wide application in synthesizing monoimidazole compounds of pharmaceutical significance,[10,11] to our knowledge there is no previous study exploiting the use of **3** in the synthesis of polyimidazole ligands which are important entities for biomimetic studies. Thus, we set forth to investigate the reaction of 4-magnesio-1-tritylimidazole with esters and herein report our results.

Methyl benzoate **5a** was first selected as a prototype substrate. When **5a** (0.20 mmol) was treated with the imidazolyl Grignard reagent **6** generated from **3** (0.44 mmol) and EtMgBr (0.44 mmol) in CH_2Cl_2 at room temperature, two subsequent nucleophilic additions of the 4-imidazolyl anion to the ester group furnished the bis-4-imidazolyl carbinol **7a** in 73% yield (Figure 1). No intermediate ketone was isolated from the reaction, which is consistent with the higher reactivity of a ketone carbonyl than an ester group. The good yield and clean reaction prompted us to study the reaction of **6** with other ester substrates. A wide range of esters react with **6** to give polyimidazole compounds in moderate to good yields (Table 1). The reaction yield is affected by the electronic nature of R: **5a** (entry 2) with electron-donating *p*-MeO affords a lower yield than the simple benzoate (entry 1) and *p*-nitrobenzoate (entry 3). Due to their ability to mimic biological metallosites,[12] "tripod" ligands with three N-containing heterocycles are interesting targets. It is significant that a series of "tripod" ligands can be readily obtained by using pyridine and imidazole esters (entries 6−9). A 3-fold addition to methyl chloroformate led to the symmetric trisimidazole compound **7e** with a reasonable yield of 40% (entry 5).

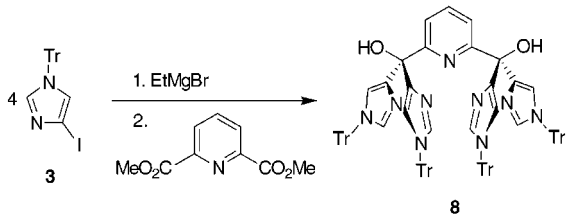
Table 1. Synthesis of Poly-4-imidazolyl Carbinols from **3**, EtMgBr, and RCO_2Me (**5**)[a]

Entry	RCO_2Me		Product	Isolated
	R	**5**	**7**	Yield (%)
1	C_6H_5	**5a**	**7a**	73
2	*p*-$MeOC_6H_4$	**5b**	**7b**	56
3	*p*-$NO_2C_6H_4$	**5c**	**7c**	79
4	H	**5d**	**7d**	67
5[b]	Cl	**5e**	**7e**[c]	40
6	2-pyridyl	**5f**	**7f**	54
7		**5g**	**7g**	52
8		**5h**	**7h**	65
9		**5i**	**7i**	44

[a] Reaction conditions: **3** (0.44 mmol) and EtMgBr (0.44 mmol) react in CH_2Cl_2 at room temperature for 2 h; then **5** (0.20 mmol) was added and the solution stirred for 24−48 h. [b] Substrate = $ClCO_2Me$, and 3.3 equiv of **3** and EtMgBr were used. [c] In **7e**, R = 1-trityl-4-imidazolyl.

The following examples further illustrate the versatility of this methodology (Scheme 1 and Figure 2): when dimethyl 2,6-pyridinedicarboxylate was used, a pentadentate

Scheme 1



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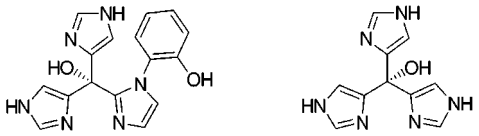

9 10

Figure 2.

ligand, **8**, could be synthesized. Such ligand structures form highly stable complexes with metals in an octahedral geometry[4,13] and have been used as model compounds for non-heme iron enzyme active sites.[14] One trisimidazole product, **7h**, has an *o*-methoxyphenyl-substituted imidazole structure. This imidazole tripod is a precursor to **9** (Figure 2), a close mimic of cytochrome *c* oxidase Cu_B binding site, which features a Tyr-cross-linked imidazole.[15] Biomimetic studies with **9** should help us understand the role the cross-linked Tyr in the function of cytochrome *c* oxidase.[16]

The trityl protecting groups can be removed under acidic conditions. Refluxing **7e** with 85% aqueous CF_3COOH cleanly cleaved the trityls to give **10** (Figure 2), which was previously synthesized in 3−16% overall yield via additional protection/deprotection at the imidazole C2 position.[6,7] The facile preparation of **10** from 4-iodo-1-tritylimidazole (**3**) clearly shows the advantage of the present method.

In summary, we have studied the reaction of esters with Mg−I-exchanged 4-imidazolyl Grignard reagent and have developed a facile, general synthesis for 4-imidazolyl-containing multidentate ligands. This method affords efficient syntheses of an array of important chelating imidazole ligands from readily available starting materials and reagents. The good yield, simplicity of operation, and the versatility to access a variety of structural types make this an attractive method for biomimetic synthesis.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5h**−**i**, **7a**−**i**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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