Tetrahedron Letters 52 (2011) 4771–4774

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

N-(2-formyl-1-methylimidazol-4-yl)-2,2-dimethylpropanamide: a versatile reagent for preparing imidazole-amine ligands with variable second-coordination spheres

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ARTICLE INFO

Article history:
Received 6 June 2011
Revised 16 June 2011
Accepted 6 July 2011
Available online 19 July 2011

Keywords:
Amide
Imidazole
Nitroimidazole
Non-covalent interactions

ABSTRACT

Two synthetic pathways to *N*-(2-formyl-1-methylimidazol-4-yl)-2,2-dimethylpropanamide from 1-methyl-2-carboxaldehyde are described. The reagent serves as a useful synthon for reductive amination reactions with primary and secondary amines in the presence of sodium cyanoborohydride to yield a series of ligands with second coordination sphere functional groups. Protocols for the syntheses of related imidazole synthons functionalized in the 4-position with amino acids, Schiff bases, and other amides are also reported.

The active site of several metal-containing enzymes extends beyond the donor atoms of the first-coordination sphere to include a second-coordination sphere[1,2] defined by functional groups that participate in non-covalent interactions with metal-bound species, Figure 1. The design and synthesis of organic ligands with multiple functional group shells to represent these coordination spheres in model complexes remain a challenge. In recent years, tripodal nitrogen-based ligands incorporating amide pendant groups have been reported. Masuda,[3–5] Berreau,[6,7] and Mareque-Rivas,[8–10] employed pyridine-based ligands to stabilize reactive metal-bound hydroperoxide or hydroxide intermediates, while Borovik and coworkers[2,11–14] have developed elegant urea-based tripods to stabilize high valent metal-oxo or metal-hydroxo compounds. Additionally, Carrano and co-workers[15,16] explored carboxamide and 3-carboxyethyl functionalized pyrrazolate ligands.

Our laboratory has focused on the ligand tris((1-methylimidazol-2-yl)methyl)amine (tmima)[17–20] as a model for metalloenzymes with histidine-rich primary coordination spheres. The constrained nature of the metal binding pocket of tmima makes it suitable for binding various metals. Recently, we have been interested in modifying the tmima metal binding pocket to include amide pendant groups capable of stabilizing various exogenous ligands bonded to different metals. Toward this goal, we have reported the synthesis and characterization of **L1** and its ferric complex,[21] as well as the bis-functionalized amide tripod, **L2**, and a series of Cu(II) complexes.[22] In the current study, we report improved syntheses of **L1** and **L2** employing 1-methyl-4-pivaloylamidoimidazole-2-carboxaldehyde as a key synthon. The methodology was then extended to develop new ligands, **L3–L5**, and a small library of amide-functionalized imidazole synthons.

A key feature of our design is the introduction of the amide pendant in the 4-position of the imidazole ring. This position is crucial to facilitate the formation of intramolecular six-member hydrogen bonding rings upon metal-coordination, Figure 1. Our strategy involves nitration of 1-methylimidazole-2-carboxaldehyde (**1**) followed by protection (**2**,**3**), reduction (**4**,**5**), and acylation (**6**,**7**) to yield the target compound *N*-(2-formyl-1-methylimidazol-4-yl)-2,2-dimethylpropanamide (**8**), Scheme 1. Synthon **8** was then employed to prepare a variety of amido-functionalized imidazole ligands **L1**–**L5**. All intermediate species were characterized using conventional analytical and spectroscopic methods. The X-ray crystal structures of **1**, **3**, **8**, and **10** are also reported, Figure 2.

The nitration of imidazole was first reported by Pyman and coworkers over nine decades ago.[23] In the 1960s the reaction was revisited by Vaupre,[24] who reported the isolation and biological activity of 2-nitroimidazole. Since then nitroimidazoles have been used in pharmaceuticals including metronidazole,[25] in purine synthesis,[26–28] and in the syntheses of polyimidazole and polypyrrole compounds as DNA minor groove binders.[29–32] Nitration of 1-methylimidazole-2-carboxaldehyde using various NO_2^+ sources (HNO_3/H_2SO_4 or NH_4NO_3/H_2SO_4)[33] yields 1-methyl-4-nitroimidazole-2-carboxaldehyde (**1**). The HNO_3 protocol gives slightly lower yields (35% vs 45%), but allows partial recovery of unreacted **1**.

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doi:10.1016/j.tetlet.2011.07.025

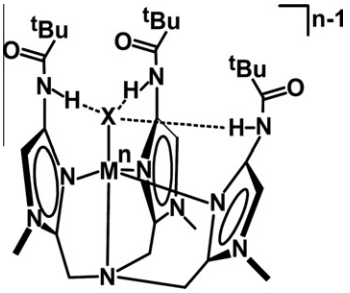
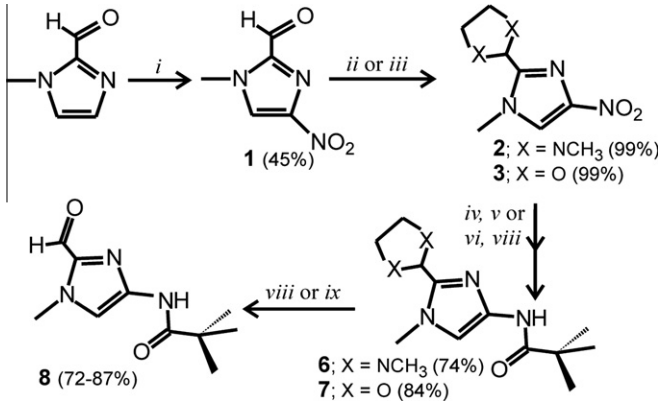


Figure 1. Representation of $[\mathbf{L3}MX]^{n-1}$ highlighting the first coordination sphere of the M–N bonds and the second coordination sphere of H-bonding interactions between the amide functional groups and the anionic donor X. The structure is based on the previously reported complexes $[\mathbf{L1}FeCl]^{2+}$ and $[\mathbf{L2}CuOH]^{+}$, where **L1** and **L2** differ from **L3** by the substitution of one and two amido functional groups by hydrogen, respectively.



Scheme 1. Synthesis of **8**. Reagents and conditions: (i) HNO_3/H_2SO_4, 100 °C, 50 min or NH_4NO_3/H_2SO_4, 90 °C, 12 h; (ii) *N*,*N*′-dimethyl-ethylenediamine; reflux, 2 h; (iii) ethylene glycol, *p*-toluenesulfonic acid, reflux, 6 h; (iv) $Pd/C/H_2$, dioxane, rt, 4 h (v) NEt_3, pivaloyl chloride, rt, 2 h; (vi) $Pd/C/H_2$, toluene, rt, 24 h; (vii) NEt_3, pivaloyl chloride, rt, 4 h; (viii) 3 M HCl, acetone, rt, 2 h; (ix) glacial acetic acid, reflux, 12 h.

With either NO_2^+ source, the reaction occurs regioselectively at the 4-position attributable to the electron-withdrawing carboxaldehyde in the 2-position, which strongly disfavors the cationic intermediate required for nitration at the 5-position.

Several carboxaldehyde protecting methods were investigated including the formation of an 1,3 imidazolidine[34] (**2**), an acetal[35] (**3**), and a thioether.[36] Compounds **2** and **3** are isolated in high yields; 99%. Although **2** is slightly more acid sensitive than **3**, either derivative is suitable for further reactions. Compound **3** is easily crystallized from the reaction mixture upon cooling at −20 °C overnight. Reduction of **2**/**3** to their corresponding amines **4**/**5** readily occurs in 1,4-dioxane or THF using $H_2/Pd/C$.[37] Reaction yields as high as 95% were obtained when dried, freshly distilled solvents are used. Reaction progress was monitored by the NMR resonance frequency of the C5 proton, which shifts upfield by ~1 ppm upon reduction of the electron-withdrawing nitro group. While the amine derivatives **4** and **5** are stable under a H_2 atmosphere, attempts to isolate analytically pure samples were unsuccessful. As such, **4** and **5** are acylated in situ using pivaloyl chloride to yield compounds **6** and **7**, respectively, in 74 and 84% yields, respectively. The direct acylation of **4**/**5** upon reduction of **2**/**3** provides a significant improvement in the reaction yield. The acylated products **6** and **7** are deprotected using either 3 M HCl in acetone/water for 2 h or refluxing acetic acid for 4 h to yield the target synthon *N*-(2-formyl-1-methylimidazol-4-yl)-2,2-dimethylpropanamide (**8**) as a crystalline white solid. The overall yield from **1** is 52% for the 1,3 imidazolidine-protected route and 72% for the acetal-protected pathway.

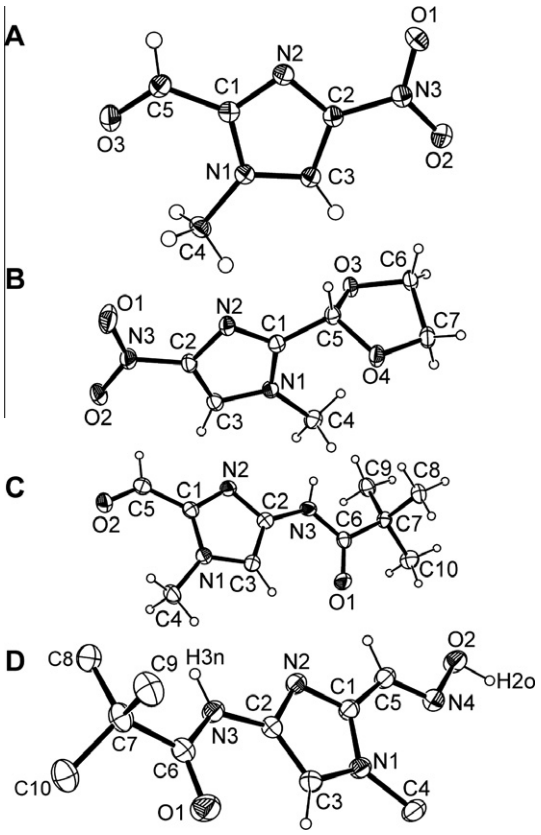
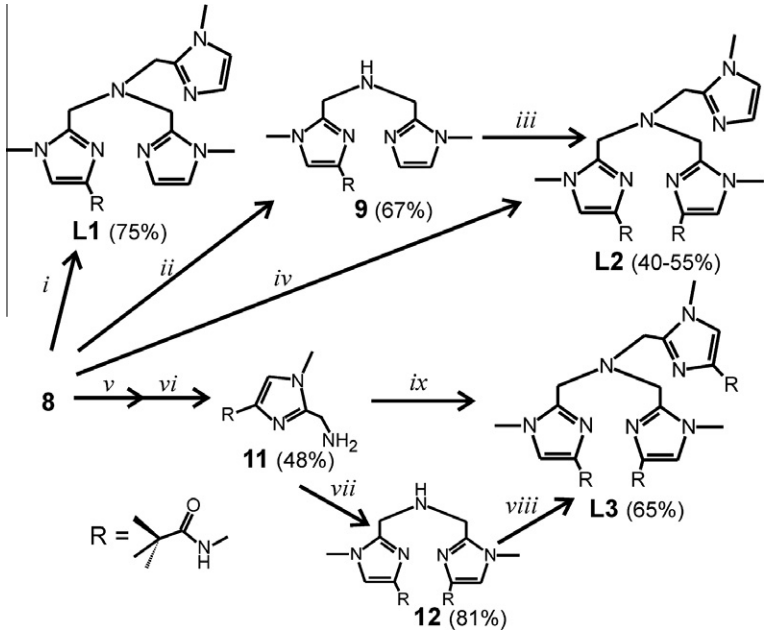


Figure 2. ORTEP representations of **1**, **3**, **8**, and **10**.

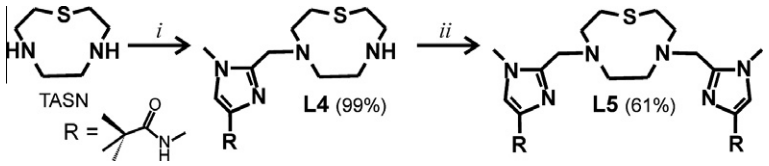
Compound **8** was employed to synthesize the tripodal ligands **L1–L3** with one to three amide-functionalized imidazole donors, respectively, as shown in Scheme 2. Reductive amination of bis((1-methyl-imidazol-2-yl)methyl)amine (bmima) with **8** in the presence of sodium cyanoborohydride gives the monoamide-functionalized tripod **L1** in 75% yield. The diamide-functionalized ligand **L2** is prepared by reductive amination of 2-aminomethyl-1-methylimidazole with two equivalents of **8** and sodium cyanoborohydride in a stepwise or single pot manner. The reaction proceeds via the amide-functionalized bmima derivative, **9**, which is isolated in the stepwise method and used in situ in the one pot method. The overall yield for **L2** ranges from 40 to 55% following column chromatography purification. The triamide-functionalized ligand **L3** requires a slightly different approach. First, **8** is reacted with hydroxylamine to yield oxime **10**. Next, **10** is reduced to 2-aminomethyl-1-methyl-4-pivalamidoimidazole (**11**), which was isolated and stored as the hydrochloric acid salt. The free base of **11** reacts with two equivalents of **8** to yield **L3** either in a stepwise process via **12** or in a one-pot synthesis with yields of 65%.

In addition to tripodal ligands, the synthon **8** can be employed to prepare amido-functionalized imidazole donors based on macrocyclic scaffolds, Scheme 3. As a proof of concept we have isolated **L4**–**L5**, which are derivatives of the previously reported 1-thia-4,7-diazacyclononane (TASN) ligands with mono- and bis-imidazole pendant arms. Reductive amination of **8** with TASN in the presence of sodium borohydride yields **L4** in 99% yield within 3 h. Isolated **L4** reacts more slowly with **8** yielding 61% **L5** after 24 h in methanol at 45 °C followed by reduction with sodium cyanoborohydride for an additional 24 h at the same temperature.

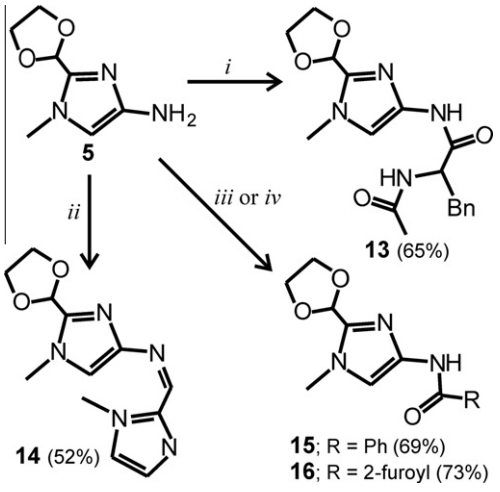
The development of a rational method for the preparation of amide-functionalized imidazole ligands allows further derivation with alternate second coordination sphere motifs. With this in



Scheme 2. Syntheses of **L1--L3**. Reagents and conditions: (i) bmima, $NaBH_3CN$, glacial acetic acid, CH_3OH, rt, 12 h; (ii) 2-aminomethyl-1-methylimidazole; $NaBH_4$, CH_3OH, 12 h; (iii) **8**, $NaBH_3CN$, CH_3OH, rt, 12 h; (iv) 0.5 equiv **8**, $NaBH_3CN$, CH_3OH, rt, 12 h; (v) $NH_2OH{\cdot}EtOH$, rt, 2 h; (vi) $Pd/C/H_2$, CH_3OH, rt, 12 h; (vii) **8**, CH_3OH, reflux, 30 min, $NaBH_4$, 0 °C, 2 h; (vii) **8**, $NaBH_3CN$, CH_3OH, rt, 12 h.; (ix) 2 equiv **8**, $NaBH_3CN$, CH_3OH, rt, 2 h.



Scheme 3. Syntheses of **L4**–**L5**. Reagents and conditions: (i) **8**, CH_3OH, reflux, 3 h, $NaBH_4$, 0 °C, 12 h; (ii) **8**, CH_3OH, 45 °C, 24 h, NaBH3CN, 45 °C, 24 h.



Scheme 4. Syntheses of **13**–**16**. Reagents and conditions: (i) *N*-acetyl-DL-phenylalanine, HBTU/DIEA, DMF, rt, 22 h; (ii) 1-methylimidazole-2-carboxaldehyde, CH_3OH, rt, 2 h; (iii) NEt_3, dioxane, benzoyl chloride, rt, 2 h; (iv) NEt_3, 2-furoyl chloride, rt, 2 h.

mind, we prepared a small library of functionalized imidazole synthons from **5**, Scheme 4, through peptide coupling reactions (**13**), Schiff base condensation with aldehydes (**14**), and acylation with other acyl chlorides (**15**, **16**). Although standard peptide coupling reagents (DCC/HOBt or EDCI/DMAP in DMF)[29,31] give low yields of **13**, HBTU/DIEA yields 65% isolated product after 22 h.[38] Similarly, **6** reacts with 1-methylimidazol-2-carboxaldehyde to form the corresponding Schiff base **14**. Finally, the benzamido- (**15**) and furamido- (**16**) analogs of **8** are prepared in 65 and 73% yields, respectively, under similar reaction conditions.

In conclusion, a facile methodology has been developed to synthesize novel and versatile amide-functionalized imidazole ligands. The synthetic methodology developed herein allows the design of new metal binding pockets that can form intramolecular six-membered hydrogen bonding rings with other endogenous ligands. The systems may be useful in recognition studies modeling the second coordination sphere of metalloenzymes. The development of new amido imidazole synthons containing carboxaldehyde or amine functionalities permits a wide range of control over the structure and electronic properties of metal binding pockets. The molecular environment around the metal can be fine-tuned to include harder or softer ligands as well as ligands possessing hydrophobic, hydrophilic, and charged groups in the second coordination sphere. Another attractive aspect of this synthetic strategy is that the nitration step could be used to easily introduce ^{15}N nucleus in the fourth position of the imidazole ring by using ^{15}N-labeled ammonium nitrate.

Acknowledgments

Acknowledgment is made to the National Science Foundation (CHE-0749965) and the Kentucky Science and Engineering Foundation (KSEF-275-RDE-003) for funding. MSM thanks the Department

of Energy, grant number DE-FG02-08CH11538 and the Kentucky Research Challenge Trust Fund for upgrade of our X-ray facilities.

Supplementary data

Experimental procedures and NMR spectra (^{1}H and ^{13}C) of **1–16** and **L1**–**L5**, and X-ray crystallographic detail in PDF format and crystallographic data in CIF format (CCDC 827412–827415) of **1**, **3**, **8**, and **10**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.025.

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