Imidazole Acid Chlorides: Preparation and Application in the Syntheses of Biomimetic Heme Models

James P. Collman,* Martin Bröring, Lei Fu, Miroslav Rapta, and Reinhold Schwenninger

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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The design of biomimetic metalloporphyrins has long been a successful strategy to study the structural requirements and mechanistic details of the multiple functions of heme proteins in nature. Among the amino acid residues that heme proteins employ to modulate the heme environments, the imidazole moiety of histidine is the most common one. Three important tasks, axial ligation of the heme iron, coordination of nearby metal centers, and stabilization of heme dioxygen complexes, are fulfilled in nature by this heterocycle.[1,2] Numerous attempts to mimic these functions by metalloporphyrins with covalently attached imidazole pickets have been reported.[3−5] However, none of these approaches can be regarded as a general method. The selective functionalization of porphyrins with customized imidazoles remains a synthetic challenge.

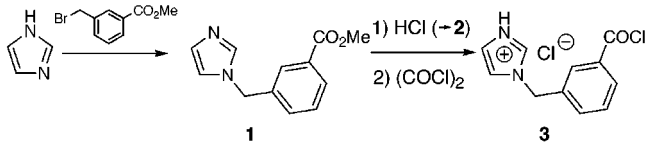
In principle, the most straightforward way to prepare porphyrins with pendant imidazoles would be the reaction of *o*-aminophenylporphyrins with imidazole acid chlorides. These, however, have been used only in a limited number of cases, and their synthesis is generally achieved in situ in order to avoid the handling of these particularly sensitive compounds.

Herein we report a versatile solution to this problem, based on the preparation of stable imidazole acid chlorides and their high yield attachement to *o*-aminophenylporphyrins in an acidic medium.

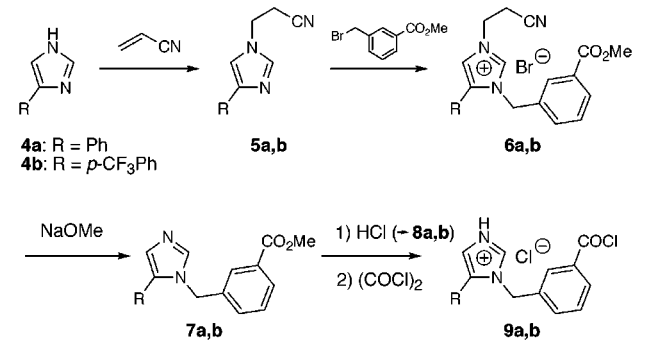
For the design of imidazole pickets which must fulfill different purposes, the nature of the linker is of great importance. A benzylic linker, known to be of an appropriate length and geometry to fasten a proximal axial imidazole to an *o*-aminophenylporphyrin,[4] was chosen for our synthetic scheme. The formation of the acid chloride **3** from the acid **2** using oxalyl chloride in acetonitrile constitutes the key step in the synthesis as shown in Scheme 1. This particular route allows a simple workup, resulting in **3** as a stable solid. Scheme 2 outlines the application of this approach to the 5-substituted imidazoles **7a** and **7b**, giving **9a** and **9b** in excellent yields. The intermediates **7a** and **7b** can be prepared in a regiospecific manner using Horvath's protection strategy.[6,7] The aromatic substituents were chosen to meet the need for less polar and more soluble final compounds. They also offer a convenient handle for a spectroscopic probe, i.e., CF_3 in **9b** for ^{19}F NMR spectroscopy.

In contrast to the proximal face imidazole axial ligands, the pendant imidazoles on the distal face of a porphyrin require special design in order to prevent them from coordinating to the central metal ion of the porphyrin for most applications. This can be accomplished by using shorter linking units ($<C_3$) as demonstrated in **15** and **17** (Scheme 3) or by introducing a steric bulk, such as diphenylimidazole derivative **19**, if a longer imidazole-to-porphyrin distance is desired. The preparation of the acid chlorides **15**, **17**, and **19** as stable, solid materials from the respective acid hydrochlorides is best performed using the same conditions as for **3**, **9a**, and **9b**.

Scheme 1



Scheme 2



Our initial attempts to attach the new imidazole acid chlorides to *o*-aminophenylporphyrins under standard conditions (excess acid chloride, solvent, non nucleophilic base) failed to produce the desired products. Most likely, this failure results from deprotonation of the imidazolium salts, followed by immediate attack of the acid chloride, producing oligomeric acyl imidazolium species. A control experiment with 1-acetyl-3-methylimidazolium chloride[8] showed that this acylating agent is incapable of reacting with the porphyrin at room temperature, probably as a result of steric hindrance. In acetic acid, however, the nucleophilic imidazole nitrogen remains protonated and thus sufficiently protected, allowing the desired transformation to occur. As a scavenger for the HCl build-up in the course of the reaction, sodium acetate was found to be the base of choice, and its slow addition to the reaction mixture drives the acylation to completion. *N*-Acetylamidophenylporphyrins are formed as the only byproducts in ca. 10% yield.

Scheme 3 illustrates the application of this new method to the syntheses of the novel cytochrome *c* oxidase model ligands **16**, **18**, and **20**, using the recently developed *β*-tritylated porphyrin **10** as the starting point.[9] The problem encountered in the acid-lability of the trityl protective group can be circumvented by the introduction of the well-known trifluoroacetamido protective group into the porphyrin structure and its selective removal with methanolic ammonia at a later stage. As shown in Scheme 4, this new acylation approach is also well-suited to append imidazole axial ligands on superstructured porphyrins, such as **21** and **23**, in good yield.

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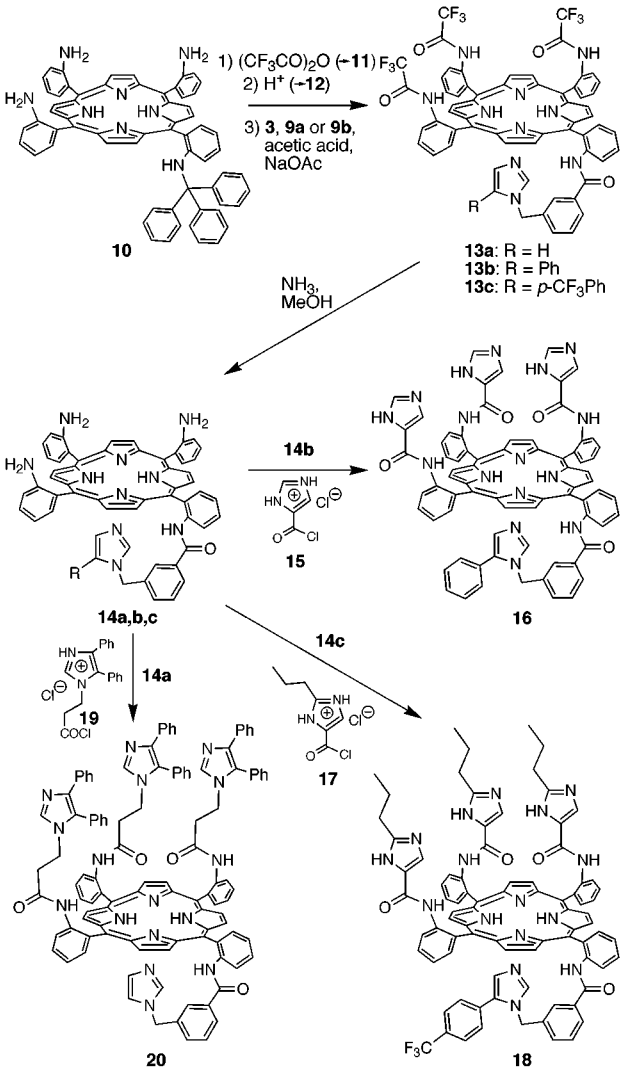
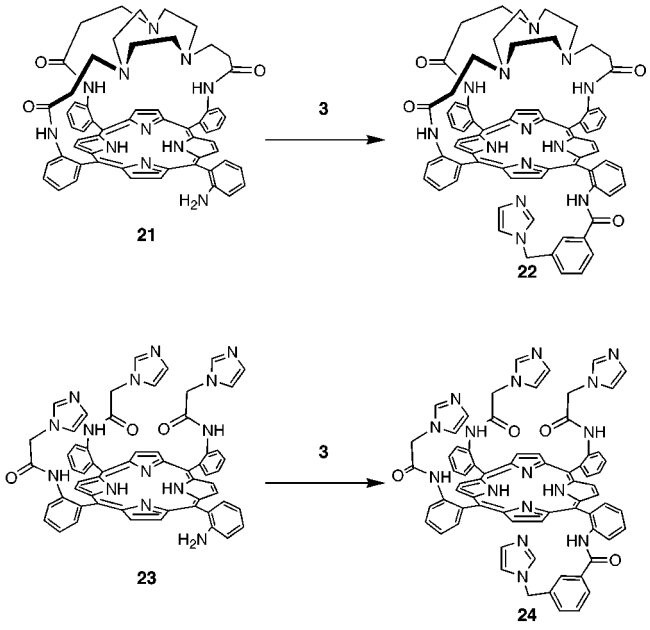
Scheme 3



The generality and versatility of this new approach has allowed us to prepare a unique set of valuable porphyrin ligands with hitherto inaccessible complexity. The advent of these novel porphyrins opens up new possibilities in our studies of enzyme active-site analogues and can thus be expected to have a great impact on structural and functional heme model chemistry.

Scheme 4



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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**3**, **5b**−**9b**, **11**−**20**, **22**, **24** (39 pages).

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