Solid-Supported Synthesis of Imidazoles: A Strategy for Direct Resin-Attachment to the Imidazole Core

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Received January 9, 1998

Within the field of combinatorial chemistry there is a flourishing interest in the development of methods for the solid-phase synthesis of heterocycles.[1] In the most useful examples, a wide range of chemical functionality is tolerated, and independent variation of several substituents is possible. In many cases, substituent-based functional group handles are employed for resin attachment, and this inherently limits library diversity. In contrast, linking directly to a heterocyclic structure is a valuable approach since the substituents around the pharmacophore can be freely varied.[2] In this paper, we describe new resin-based chemistry for the straightforward construction of 2,4,5-triarylimidazoles where the three substituents are independently varied on the solid support. Our process relies on a new imidazole linking method where attachment is achieved through an imidazole core nitrogen.[3] In addition, we have developed a strategy for the purification of the imidazoles before cleavage from the resin.

Our route utilizes a münchnone 3 + 2 cycloaddition reaction in the key bond-forming step.[4] Münchnone cycloaddition reactions with activated alkynes to form pyrroles (after elimination of carbon dioxide) have been developed for the solid phase.[5] While the analogous reaction of a münchnone with a nitrile to provide an imidazole is not viable due to the low reactivity of nitriles, Ferraccioli et al. have reported that in solution aryltosylimines will react with münchnones to provide imidazoles.[6] While the yields of these reactions are generally low, this is at least partly due to the potential for münchnones to self-condense.[4,6] Self-condensation is a side reaction that can be readily suppressed in a solid-phase approach.

Our successful translation of this chemistry to the solid-phase is shown in the generic reaction sequence in Scheme 1. The commercially available polystyrene−poly(ethylene glycol) graft copolymer resin **1**[7] was employed in a standard reductive alkylation protocol with an amino acid methyl ester (5 equiv) until such a time as the aldehyde functionality was consumed (as judged by IR and a qualitative 2,4-dinitrophenylhydrazine test[8]) to provide **2**. The resulting amino ester was efficiently acylated with a carboxylic acid chloride (10 equiv) employing diisopropylethylamine as the base in CH_2Cl_2. Cleavage of representative samples at this stage indicated that resin loading approximated the manufacturer's specification (0.41 mmol/g). The resulting α-amido ester was then subjected to KOH hydrolysis in 3:1 dioxane/H_2O to provide the carboxylic acid **3**.[9]

Treatment of the resin-bound acid **3** under modified conditions of EDC (10 equiv) and tosylimine (10 equiv) in CH_2Cl_2 at ambient temperature for 24−48 h led initially to the intermediate münchnone **4**. Subsequent cycloaddition of this münchnone **4** with the tosylimine, followed by elimination of toluenesulfinic acid and CO_2, provided the polymer-linked imidazole.

Scheme 1

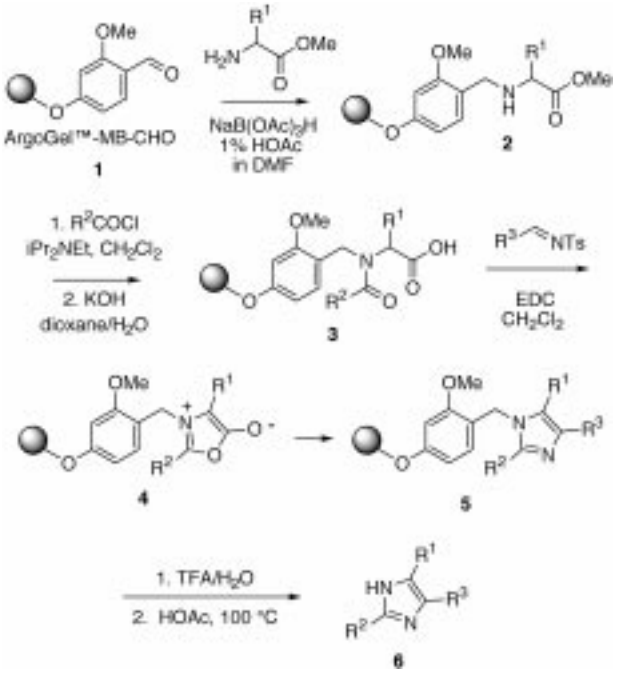
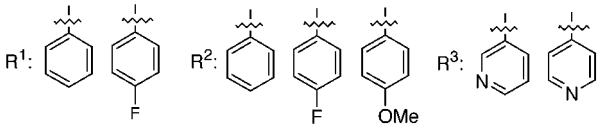


Table 1. Results from a Library of Twelve Triarylimidazoles



entry	R^1	R^2	R^3	yield,[a] %	purity,[b] %
1	phenyl	phenyl	3-pyridyl	72	94
2	phenyl	phenyl	4-pyridyl	99	96
3	phenyl	4-F-phenyl	3-pyridyl	63	94
4	phenyl	4-F-phenyl	4-pyridyl	73	96
5	phenyl	4-MeO-phenyl	3-pyridyl	82	96
6	phenyl	4-MeO-phenyl	4-pyridyl	76	98
7	4-F-phenyl	phenyl	3-pyridyl	53	95
8	4-F-phenyl	phenyl	4-pyridyl	90	97
9	4-F-phenyl	4-F-phenyl	3-pyridyl	49	96
10	4-F-phenyl	4-F-phenyl	4-pyridyl	65	95
11	4-F-phenyl	4-MeO-phenyl	3-pyridyl	66	95
12	4-F-phenyl	4-MeO-phenyl	4-pyridyl	89	97

[a] Yield based on theoretical loading of 0.41 mmol/g. [b] Purity of unpurified material determined by HPLC at 215 nM.

(1) For a recent review see: Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337.

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S0022-3263(98)00027-9 CCC: $15.00
Published on Web 04/07/1998

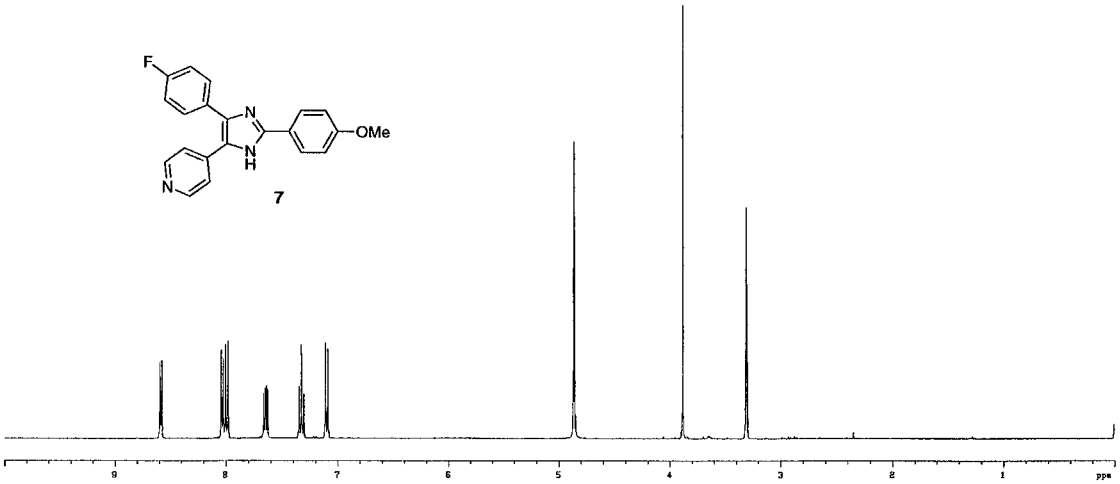

Figure 1. ^{1}H NMR of compound **7** after cleavage from the resin.

The 4-alkoxy-2-methoxybenzylic group is a very robust linker for imidazoles, but we were able to take advantage of this to obtain products of high purity. We followed the cycloaddition step with a washing step employing 90% TFA/H_2O for 1 h. Importantly, the imidazole (**5**) was not removed from the resin; rather, unreacted starting materials and non-imidazole byproducts were removed during this washing. This effectively served as a purification step of the resin-bound imidazole. The imidazole was then found to be efficiently and cleanly liberated from the resin by treatment with glacial acetic acid at 100 °C for 2 h to provide **6**.

A triarylimidazole library of 12 compounds was constructed to demonstrate the viability and generality of this chemistry. The substituent variations that were employed are shown in Table 1. Two arylglycines, three acid chlorides, and two pyridyltosylimines[10] were employed in the library for a 2 × 3 × 2 matrix. All product combinations were obtained in good to excellent yields after cleavage from the resin. The average yield was 73% over the six-step sequence (based on a theoretical loading of 0.41 mmol/g). More importantly, the products were obtained in uniformly high purity without purification. The average HPLC purity (UV detection at 215 nM) for the 12 imidazoles in the library was 96%. All products were characterized by ^{1}H NMR and by mass spectrometry. The ^{1}H NMR spectra also indicated the products were formed in high purity, and a representative example is shown for compound **7** in MeOH-d_4 (Table 1, entry 12) in Figure 1.

It is particularly notable that under the cleavage conditions very little, if any, poly(ethylene glycol) impurities were observed in the ^{1}H NMR spectra (generally a broad signal at ~3.6 ppm). This is a clear indication of the stability of resins such as **1**. Resin **1** contains an inert bis-homobenzylic ether bond between the poly(ethylene glycol) and polystyrene moieties.[11] In traditional peg-grafted polystyrene resins the attachment is a more labile benzylic ether bond. We had previously followed a similar synthetic route employing a resin of this latter type and observed very large quantities of poly(ethylene glycol) contaminants in our cleaved products.

Comparison of the products also demonstrated that the reactions were completely regioselective as they have been reported to be in solution.[6] In a nonregioselective reaction, entries 3 and 7 (as well as 4 and 8) would be expected to produce products in common. However, the products produced were unique, and neither product showed any level of contamination by the other (by HPLC or NMR).

Our linking strategy, while requiring fairly harsh cleavage conditions, was dependent on the use of the 4-alkoxy-2-methoxybenzylic linking group. The attempted use of more electron-rich potential imidazole linking groups (such as Rink or PAL-type linkers) failed in the münchnone formation/cycloaddition step.[12] It appears in these cases that the münchnone is cleaved from the resin during the reaction as no material can be recovered from the resin after this step. However, as described above, the robustness of the current linker proved to be an advantage to obtaining pure products.

In summary, we have developed a very efficient sequence for the solid-phase synthesis of imidazoles employing a new linking strategy involving direct linkage to the imidazole core. The process utilizes a münchnone cycloaddition in the key bond-forming step and allows for the independent variation of three substituents on the resin. The method also includes a strategy for the purification of the imidazoles on the resin before cleavage. While we anticipate that this chemistry will be compatible with a large range of chemical functionality, the true test of this assertion will come with future efforts to create large libraries employing this method.

Acknowledgment. We appreciate the helpful suggestions of Professor David A. Evans (Harvard University). Dr. Charles W. Ross III is acknowledged for obtaining mass spectral data.

Supporting Information Available: Experimental details for synthesis of the tosylimines and the library and ^{1}H NMR, mass spectral, and HPLC data for all compounds (15 pages).

JO980027P

(10) Tosylimines were formed by azeotropic removal of water from a refluxing toluene mixture of the appropriate aldehyde, toluenesulfonamide, and catalytic toluenesulfonic acid. See the Supporting Information for details.

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(12) The same observation has been reported for the Rink linker; see ref 5a, footnote 11.