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Imidazole Libraries on Solid Support

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Abstract: *The method of synthesis of highly substituted imidazole libraries on solid support using an aldehyde, an amine and a 1,2-dione in the presence of NH_4OAc is described. The synthesis was accomplished by attaching the aldehyde or amine component to Wang resin via ester or ether linkages. A class of unsymmetrical bis-imidazoles has also been prepared without any need for selective protection of the synthetic intermediates.*

The promise of combinatorial chemistry as an efficient tool in the early stages of drug discovery has been described.[1] A variety of small molecule, non-peptide combinatorial libraries have been synthesized on solid phase, yet the number of heterocyclic compound libraries has been limited.[2] Furthermore, many biologically active therapeutics contain five-membered ring heterocycles.[3] The imidazole ring system is of particular interest since it is a component of histadine and its decarboxylation metabolite histamine.[4] The potency and wide applicability of the imidazole phamacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals which are present in many protein active sites (e.g. Zn, Fe, Mg).[5] Also, improved pharmacokinetics and bioavailability of peptide based protease inhibitors have been observed by replacing an amide bond with an imidazole.[6] As part of a program which applies spatially dispersed[7] and radio frequency encoded combinatorial libraries[8] to the discovery of novel therapeutic agents, we have devised an efficient strategy for the rapid synthesis of diverse and highly substituted imidazole libraries on solid support.

The condensation of an aldehyde, NH_4OAc, a 1,2-diarylethanedione and a 1° amine in refluxing AcOH is a well established procedure for the preparation of 2,4,5-trisubstituted-(1H)-imidazoles **1** and 1,2,4,5-tetrasubstituted-imidazoles **2** (Figure 1).[9] In general, this method yields crude imidazoles with varying levels of purity. Additionally, highly functionalized and polar imidazoles synthesized in solution require laborious work up and purification.[10] However, when prepared on solid support, imidazoles **1** and **2** are routinely isolated in good yield and high purity.

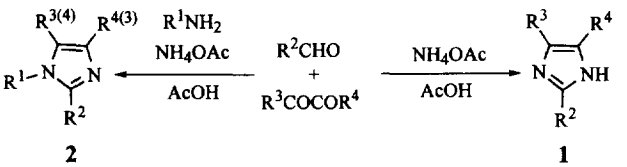

Figure 1. Solution phase synthesis of imidazoles **1** and **2**.

Our preliminary studies had indicated that Wang resin[11] was stable to AcOH at reflux. Hence, functionalized polymers **A** and **B** were prepared by standard DIC-DMAP coupling[12] of carboxybenzaldehyde (**4**) and *N*-fmoc-6-aminohexanoic acid[13] (**5**) respectively to Wang resin (Figure 2). **C** was synthesized via a

modified Mitsunobu coupling of 4-hydroxybenzaldehyde (**6**) to Wang resin.[14] In fact, when **A**, **B** and **C** were heated in AcOH at 100°C for 4 h, less than 10% cleavage of the linkers was observed.[15]

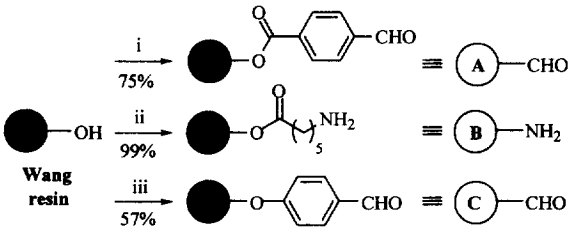

Figure 2. i) **4**, DIC, DMAP, THF, 23°C, 48 h; ii) a) **5**, DIC, DMAP, CH_2Cl_2, 23°C, 24 h; b) 20% piperidine-DMF; iii) **6** , N-ethylmorpholine, DIAD,Ph_3P, sonicate for 1 h then stir 23°C for 16 h.

A typical experimental procedure for the preparation of imidazoles of general formula **2** involves heating a stirred mixture of 0.07 mmol (1 equiv) of resin **A** or **C**, 0.1mmol (1.4 equiv) of NH_4OAc, 1.4 mmol (20 equiv) of the 1,2-dione and 1.4 mmol (20 equiv) of the 1° amine in 1.2 mL of AcOH at 100°C for 4 h (Figure 3). The resin was filtered, washed (CH_2Cl_2-CH_3OH) and treated with 20%TFA in CH_2Cl_2. Imidazoles of general formula **1** were prepared in the same manner by replacing the 1° amine with NH_4OAc (40 equiv). In the case of resin **B**, the 1° amine was replaced by an aldehyde, and 40 equiv of NH_4OAc were used.

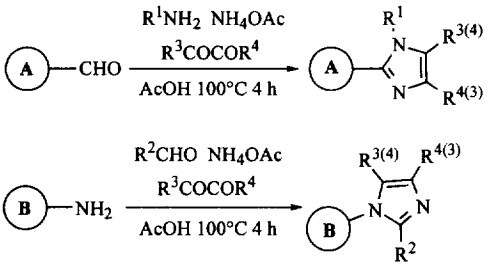

Figure 3. Preparation of imidazoles on solid support.

^1H NMR of TFA cleavage products showed that the reactions were between 80-90% complete in 2 h. After 4 h at 100°C, less than 1% of linker could be detected by ^1H NMR and HPLC analysis. There does not seem to be any limitations on the nature of the 1° amine, or aldehyde components. All of the imidazoles prepared so far were isolated in good yield even after SiO_2 chromatography (Figure 4).[16] Most importantly, comparison of the product ^1H NMRs before and after chromatography showed that the imidazoles are of high purity (90-95%) as isolated after TFA cleavage. Therefore, post-cleavage purification of these imidazole libraries is unnecessary and the isolated compounds are suitable for primary biological screening.[17] Centigram quantities of highly functionalized and very polar imidazole derivatives have been synthesized in this manner without the need for costly purification schemes such as reversed phase chromatography.

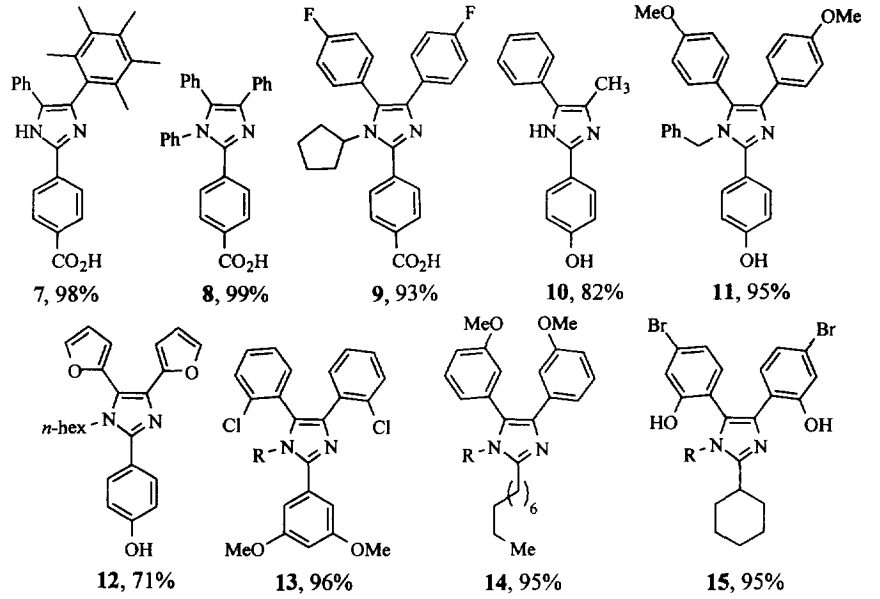

Figure 4. Examples of imidazoles synthesized on solid support (R=$(CH_2)_5CO_2H$). Yields represent the mass balance of crude isolated material (90-95% pure) based upon the loading levels of resins **A**, **B** or **C**.[18]

More notably, unsymmetrical 1,4-*bis*-imidazole **16**[19] can be prepared by this method without the use of any protective groups (Figure 5). In this case, a 1 mL stirred AcOH mixture of 0.06 mmol (1 equiv) of resin **C** containing 2 mmol (33 equiv) of NH_4OAc and 1.2 mmol (20 equiv) of 1,4-*bis*-benzil (**17**) was heated to 100°C for 6 h to give resin **18**. When **18** was treated with 20% TFA in CH_2Cl_2 (23°C, 20 min) imidazole **19** was isolated in 95% yield. When 0.06 mmol (1 equiv) of **18** was reacted with 2.4 mmol (40 equiv) of NH_4OAc and 2.4 mmol (40 equiv) of 4-ethylbenzaldehyde (1 mL of AcOH, 100°C, 8 h), **16** was isolated in 75% overall yield and 92% purity.

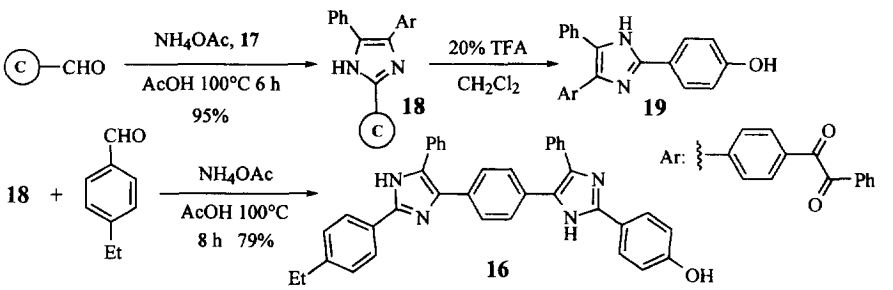

Figure 5. Synthesis of unsymmetrical 1,4-*bis*-imidazoles on solid support.

In conclusion, this method provides a very efficient way to access large libraries of highly functionalized imidazoles. Centigram quantities of high purity material may be synthesized rapidly and used directly in a

variety of biological assays. Other heterocyclic systems have been synthesized using this method and those results will be reported shortly.

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15. After 4 h at 100°C, resin **C** decomposed faster than resins **A** or **B**.
16. The more Lewis basic imidazoles accelarate the cleavage of the linkers from the polymer support.
17. The most active components of the libraries are usually purified for detailed biological evaluation.
18. All compounds were were fully characterized by ^{1}H and ^{13}C NMR as well as high resolution MS after purification by SiO_2 chromatography.
19. Analytical data for product **16**: ^{1}H NMR (1:10 CD_3OD-$CDCl_3$,400 MHz) δ (1.18,t,3H), (2.62,q,2H), (6.6,d,2H), (7.1-7.4,m,16H), (7.65,d,2H), (7.87,d,2H). ^{13}C NMR (1:10 CD_3OD-$CDCl_3$,100 MHz) δ 15.5, 29.5, 113.5, 116.7, 120.4, 127.2, 127.4, 127.7, 127.8, 127.94, 127.98, 128, 128.2, 129.2, 129.4, 129.5, 129.7, 129.8, 130.6, 130.7, 130.8, 145.4, 145.6, 150, 161.8. HRMS *m/z* $[M+H]^+$ calculated: 559.2498; observed: 559.2520 (±3.9ppm). For examples of symmetrical 1,4-*bis*-imidazoles see reference 9.

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