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Synthesis of Tetrasubstituted Imidazoles via α-(*N*-acyl-*N*-alkylamino)-β-ketoamides on Wang Resin

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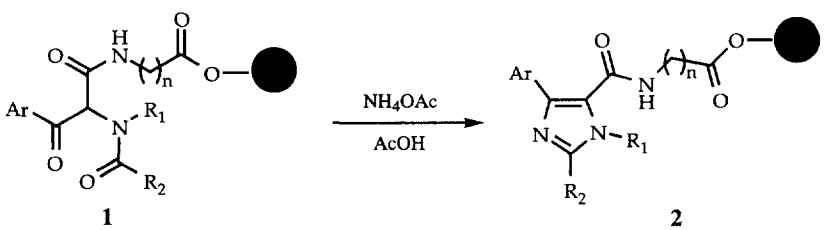
Abstract: *The first example of a four component condensation of arylglyoxals, 1° amines, carboxylic acids and isocyanides on Wang resin is described. These products can be cyclized in the presence of NH_4OAc-AcOH to yield tetrasubstituted imidazoles.*

Combinatorial chemistry is a rapidly evolving discipline in the field of medicinal chemistry.[1] The use of radio frequency encoded[2] and spatially dispersed combinatorial libraries[3] of small organic molecules promises to drastically shorten lead discovery and optimization times. Diversity within such libraries is highly desirable and constitutes a pivotal aspect of library design. Such diversity may be achieved *via* multi-component condensation strategies involving numerous, readily available starting materials. Previously we reported the first solid phase synthesis of tetrasubstituted imidazoles *via* a four component condensation of aldehydes, 1° amines, 1,2-diones and NH_4OAc.[4] The condensation product of a β-Carbonyl-*N*-acyl-*N*-alkylamines was cyclized to the corresponding imidazoles using known procedures.[5] We now describe an efficient attractive approach: the first one step synthesis of α-(*N*-acyl-*N*-alkylamino)-β-ketoamides **1** *via* an Ugi four component condensation (U-4CC)[6] on Wang[7] resin, and the subsequent cyclization in the presence of NH_4OAc-AcOH to yield tetrasubstituted imidazoles **2** (Figure 1).[8]



1 **2**

Figure 1

In solution, the reaction of phenylglyoxal, isobutylamine, benzoic acid and *n*-butylisocyanide gave amide **3**[8] which was cyclized to imidazole **4** (100°C, 16 h) in 43% overall yield (Figure 2). A synthetic strategy beginning with the attachment of the isocyanide component to Wang resin was developed for two reasons. First, the stability of Wang[7] resin compared to Rink[9] resin was previously observed, i.e. in AcOH at 100°C for up to 30 h.[4] Second, a very limited number of commercially available isocyanides exists today.

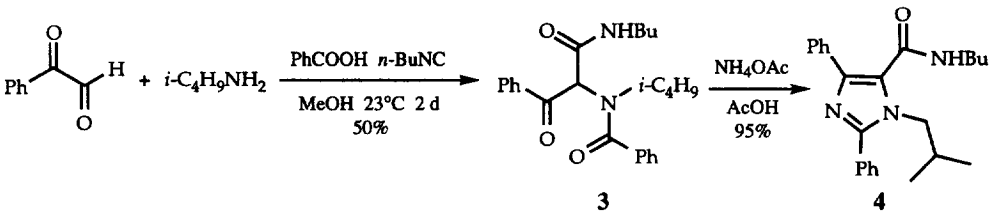


Figure 2

A series of aliphatic amino acids (Figure 3, n=2 or 10) were formylated[10] with HCO_2Et or HCO_2H-Ac_2O, attached to Wang resin (DIC-DMAP),[11] and dehydrated (Ph_3P-Et_3N-CCl_4)[12] to provide resins **6a** and **6b**. The extent of the dehydration step was monitored by ^1H NMR of the resin bound reactants in $CDCl_3$.[13] The disappearance of the formyl proton signal at 8.20 ppm indicated complete conversion of **5** to **6**.[14] These dehydration conditions did not cause any linker loss, as indicated by a comparison of the mass balance of recovered *N*-formylamino acids from the TFA cleavage of resins **5** and **6**.[12b]

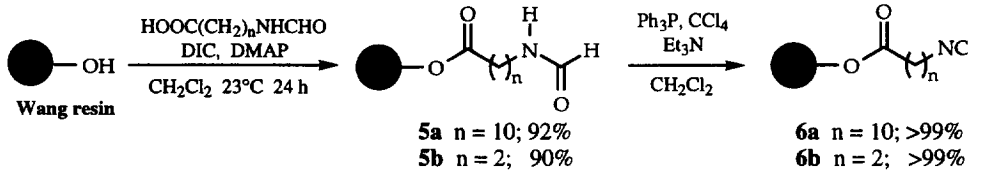


Figure 3

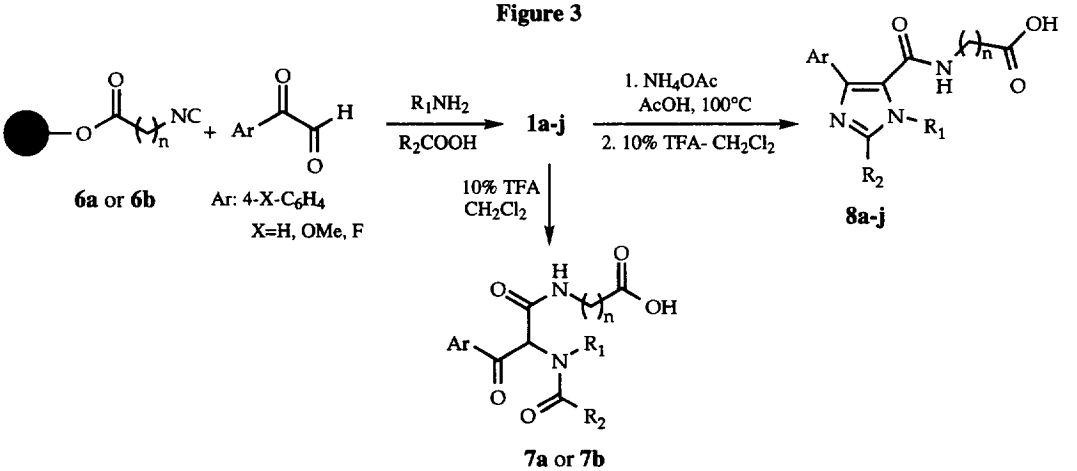


Figure 4. Synthesis of Imidazoles with the Isocyanide Component Attached to Wang Resin.

Resins **1a** and **1b** were obtained respectively from the reactions of **6a** and **6b** with phenylglyoxal, isobutylamine and benzoic acid in 1:1:1 $CHCl_3$-MeOH-pyridine, at 65°C for 3 days (Figure 4).[15] After treatment of **1a** and **1b** with 10%TFA-CH_2Cl_2 (23°C, 20 min), the corresponding amides **7a** and **7b** were isolated in 47 and 45% yield, respectively (Table 1, entries 1 and 3).[16] Treatment of **1a** and **1b** with 60 equiv of NH_4OAc in AcOH (100°C for 20 h), followed by 10%TFA-CH_2Cl_2 (23°C, 20 min) provided imidazoles **8a** and **8b** in 45 and 44% yield after purification, respectively (Table 1).[17] These yields are consistent with the solution

phase results which reflect a 96 and 98% conversion of the U-4CC products to the corresponding imidazoles. Enhanced yields were observed for the U-4CC carried out at room temperature in 1:1 $CHCl_3$-MeOH (entries 1 and 2). The U-4CC step is being further optimized.

The length of the isocyanide linker had no effect on the yield of the imidazoles (entries 1 and 3). Both aromatic and aliphatic carboxylic acids are good substrates (entries 1, 4, 5 and 6). With the exception of aniline (entry 7), there do not seem to be any limitations on the nature of the 1° amines (entries 1, 8 and 9). The electronic nature of the arylglyoxals does not effect the yield of the cyclization step (entries 1, 10 and 11). Given the number of carboxylic acids, 1° amines, isocyanides and arylglyoxals,[18] a combinatorial library of over ten million unique imidazoles could be synthesized.

Table 1. Imidazoles **8** Generated on Solid Support[a]

Entry	**8**	Ar (4-X-C_6H_4)	n	R_1	R_2	U-4CC[b]	% Yields[c]
1	**8a**	X = H	10	*i*-C_4H_9	C_6H_5	A, 47%[d]	45
2	**8a**	X = H	10	*i*-C_4H_9	C_6H_5	B	56
3	**8b**	X = H	2	*i*-C_4H_9	C_6H_5	A, 45%[d]	44[e]
4	**8c**	X = H	10	*i*-C_4H_9	4-F-C_6H_4	A	35
5	**8d**	X = H	10	*i*-C_4H_9	n-C_4H_9	A	36
6	**8e**	X = H	10	*i*-C_4H_9	$C_6H_5CH_2$	A	47
7	**8f**	X = H	10	C_6H_5	C_6H_5	A	16
8	**8g**	X = H	10	4-MeO-C_6H_4	C_6H_5	A	43
9	**8h**	X = H	10	$C_6H_5CH_2$	C_6H_5	A	36[e]
10	**8i**	X = MeO	10	*i*-C_4H_9	C_6H_5	A	51[e]
11	**8j**	X = F	10	*i*-C_4H_9	C_6H_5	A	49[e]

[a]The imidazole formation was carried out at 100°C with 60 equiv of NH_4OAc in AcOH for 20 h.
[b]Ugi reaction was performed either in 1:1:1 $CHCl_3$-MeOH-pyridine at 65°C (Method A) or in 1:1 $CHCl_3$-MeOH at 23°C (Method B) with resin **6** (0.75 mmol/g) and 10 equiv of each of the reagents.
[c]Overall yield of purified imidazoles based on the original loading of the isocyanide linker on resin **6**.
[d]U-4CC products were cleaved with 10% TFA-CH_2Cl_2 and purified by preparative TLC.
[e]Compounds **8b**, **8h**, **8i** and **8j** were transformed to their methyl esters prior to purification.

In summary, we have developed a one step strategy for synthesizing α-(*N*-acyl-*N*-alkylamino)-β-ketoamides and the subsequent cyclization to the corresponding imidazoles on Wang resin. This is a vast improvement over traditional multistep syntheses which would require a minimum yield of 85% per step.[5] Furthermore, the construction of the imidazole nucleus using this methodology greatly increases the overall diversity and size of the library.

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13. ^{1}H NMR of compounds bound to solid support are usually very broad and uninformative. In this case quite reasonable linewidths could be achieved with a judicious combination of exponential, gaussian and sine bell apodisations.
14. When kept in a vacuum dessicator, these resins are stable for up to 6 months at 23°C.
15. Mjalli, A. M. M.; Sarshar, S.; Baiga, T. J. *J. Am. Chem. Soc.* **1995**, submitted.
16 Yields correspond to preparative TLC purified material. ^{1}H NMR showed that the crude isolate contained unreacted linker as the sole impurity.
17. All the compounds listed have ^{1}H NMR and mass spectral data consistent with the proposed structure. The data of compound **8e** is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3H), 0.81 (s, 3H), 1.00--1.33 (m, 14H), 1.54--1.61 (m, 2H), 1.87--1.98 (m, 1H), 2.28 (t, J = 7.2 Hz, 2H), 3.18 (dt, J = 13.2, 6.8 Hz, 2H), 3.96 (d, J = 8.0 Hz, 2H), 4.17 (s, 2H), 5.64 (t, J = 6.0 Hz, 1H), 7.16--7.40 (m, 8H), 7.58 (d, J = 7.2 Hz, 2H); ESIMS, *m/z* for $C_{32}H_{42}O_3N_3$ $[M\text{-}H]^-$: 516.
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