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Parallel synthesis of 1,2,4-trisubstituted imidazoles via *N*-alkyl-*N*-(β-keto)amides using a carbazate linker

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Abstract—The synthesis of 1,2,4-trisubstituted imidazoles was demonstrated via the solid phase synthesis of *N*-alkyl-*N*-(β-keto)amides using a carbazate linker. The approach enabled the assembly of a diverse number of *N*-alkyl-*N*-(β-keto)amide intermediates in good yield and purity. Subsequent cyclisation in solution using NH_4OAc led to the preparation of 1400 1,2,4-trisubstituted imidazoles. © 2002 Published by Elsevier Science Ltd.

The imidazole ring system is of much interest since it is a component of histidine and its decarboxylation metabolite histamine.[1] The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor–acceptor capability. Examples of imidazoles include p38 inhibitor **I** (SB 203580)[2] and COX-2 inhibitor **II** (Fig. 1).[3]

Within the field of combinatorial chemistry there is much interest in the development of methods for solid-phase synthesis of small molecule libraries for drug discovery.[4a,b] As part of our project needs, the synthesis of arrays of imidazoles was sought. The existing methodologies for the combinatorial preparation of imidazoles include the preparation of 2,4,5-trisubstituted imidazoles on solid support by direct resin-attachment to the imidazole core,[5a,b] as well as the preparation of 1,2,4,5-tetrasubstituted imidazoles via an Ugi four component condensation reaction.[6] We were initially attracted to the preparation of tertiary amides via *N*-acylation of resin bound tertiary amine intermediates.[7] The modest yields obtained using this approach prompted us to explore alternative strategies for the synthesis of tertiary amides. The keto-moiety of the tertiary amide is essential for cyclisation to the imidazole (compound **3**, Scheme 1). Hence a general solid-phase synthesis approach to display diverse functionality about a ketone would enable the preparation of libraries of keto-amides and subsequently imidazoles.

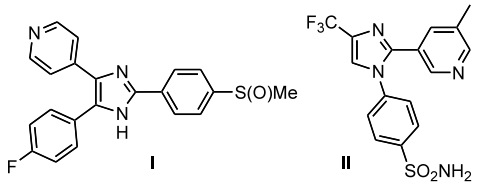
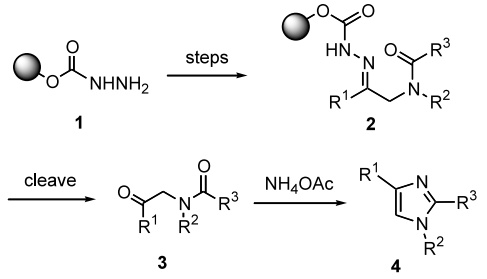


Figure 1.

This letter describes the preparation of 1,2,4-trisubstituted imidazoles **4** in arrays via *N*-alkyl-*N*-(β-keto)amide **3** as the key intermediate. Keto-amides **3** are prepared using the carbazate linker **1**. After cleavage, cyclisation of the keto-amide **3** was effected by treatment with NH_4OAc under elevated temperatures[7] to furnish the imidazole **4** (Scheme 1).

The linkage of a ketone to a solid support using the carbazate linker has been described by Ellman.[8] Car-



Scheme 1.

Keywords: *N*-alkyl-*N*-(β-keto)amide; 1,2,4-trisubstituted imidazole; carbazate linker; solid phase synthesis.

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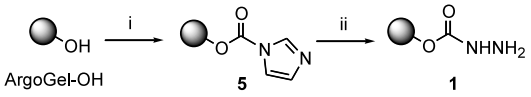
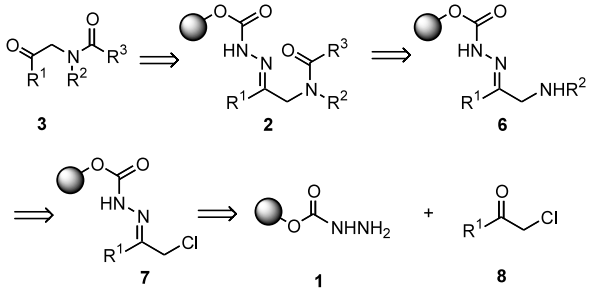
bazate linker **1** was prepared from commercially available polystyrene-poly(ethylene glycol) resin (ArgoGel-OH, Argonaut Technologies). It was reported that 60 equiv. of anhydrous hydrazine were required to provide near quantitative loading levels (0.3–0.4 mmol g^{-1}).[8] The use of hydrazine monohydrate was examined and the reaction followed by FTIR analysis.[9] It was observed that similar loadings could be obtained with only 10 equiv. of hydrazine monohydrate (Scheme 2).



Scheme 2. (i) CDI, CH_2Cl_2, rt, 3 h; (ii) $H_2NNH_2{\cdot}H_2O$, DMF, rt, 1 h.

Retrosynthetic analysis of keto-amide **3** is shown in Scheme 3. It was envisaged that the resin-bound hydrazone amide **2** would be prepared from resin-bound secondary amine **6**, which would be prepared by displacement of a chloro group from resin-bound α-chloro hydrazone intermediate **7**. Hydrazone **7** would be prepared from condensation of the α-chloroketone **8** with the carbazate **1**. From the analysis, it was also evident that cleavage of the intermediates to monitor the synthetic route would not be conclusive, as this would require determining mass recovery of the α-chloroketone **8** from the cleavage of hydrazone **7**, or isolation of an unstable aminoketone from cleavage of **6**. Hence the synthesis would be taken through to the resin-bound hydrazone amide **2** before cleavage to examine the overall yield and purity.

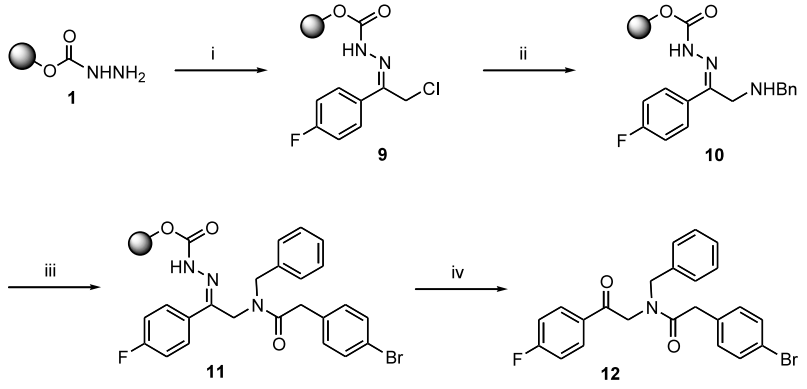


Scheme 3.

The validation study (Scheme 4) was carried out using 2-chloro-4′-fluoroacetophenone, benzylamine and 4-bromophenylacetic acid. Condensation with 2-chloro-4′-fluoroacetophenone was investigated at 45°C and room temperature. Aminolysis, acylation and cleavage gave quantitative mass return from the condensation at 45°C, and in >85% purity.[10] Similar results were obtained for the condensation at room temperature, but in slightly reduced yield (85%) and purity (80%). Different solvents for the condensation reaction were also examined. It was observed that whilst THF and DMF gave similar results, dioxane gave poorer yields (30–40% less by comparison). The limited commercial availability of α-chloroketones led to further exploration of this step. One option was the preparation of α-chloroketones from the corresponding α-methylketones.[11] Alternatively, it was noted that this condensation was also applicable to α-bromoketones, even though they yielded 30–50% less product when directly compared with the corresponding α-chloroketones. Nevertheless the ability to use α-bromoketones in the synthesis further increased the choice for monomer selection in the library production.

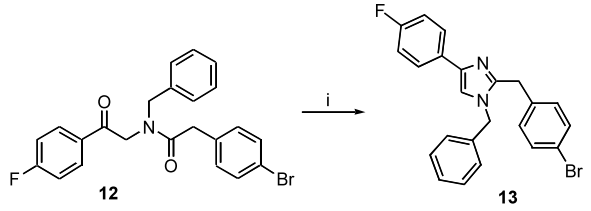
The aminolysis reaction proceeded well and did not require further studies. Acid coupling conditions were examined using either HOAt or HOBt in combination with PyBOP, or HATU. All gave similar results. Hence HOBt and PyBOP were selected due to availability and economic reasons.

As reported by Ellman, cleavage from the resin was successfully carried out using a mixture of 1:4:4:15 TFA/H_2O/MeCHO/TFE, in which MeCHO is utilised as a hydrazine scavenger.[8] However, the volatility of the carcinogen MeCHO meant that its safe removal on a library production scale would not be feasible. Hence alternative solutions were sought. Cleavage could be carried out using 20% TFA in acetone but lower yields and purities were observed. The cleavage success using this mixture was also dependent on the nature of R^1. The optimum conditions identified were the direct replacement of MeCHO in the original cleavage mixture with acetone. The keto-amides were analysed[12] to verify the success of the synthesis before being taken through to the imidazole. Typically, the purity of these compounds were >95% by ELS.



Scheme 4. (i) 2-Chloro-4′-fluoroacetophenone, THF, 45°C, 4 h; (ii) benzylamine, DMF, rt, 30 min; (iii) 4-bromophenylacetic acid, PyBOP, HOBt, DiPEA, DMF, rt, 2×4 h; (iv) 1:4:4:15 TFA:H_2O:acetone:TFE, rt, 2×2 h.

Overnight treatment of the keto-amide with a saturated solution of NH_4OAc in AcOH and DMF (6:1) at 90°C furnished the desired 1,2,4-trisubstituted imidazoles. Using the example from keto-amide **12**, cyclisation to imidazole **13**[13] is depicted in Scheme 5. The excess NH_4OAc was removed by employing an aqueous work-up and re-extraction of the product into EtOAc. This method was generally successful when R^1 = aryl (see Scheme 1). However, when R^1 = alkyl the higher aqueous solubility of the products resulted in poor compound recovery after aqueous extraction. This was circumvented by removal of the excess NH_4OAc by freeze-drying.



Scheme 5. (i) 6:1 sat. NH_4OAc (AcOH):DMF, 90°C, 24 h.

In conclusion, the preparation of *N*-alkyl-*N*-(β-keto)amides on solid phase using a carbazate linker[8] followed by cyclisation to 1,2,4-trisubstituted imidazoles in solution was successfully accomplished. This has enabled the synthesis of 1400 diverse imidazole compounds.

In general from resin-bound α-chloro carbazate **7**, the imidazoles were obtained over four steps in >30% yield and >95% purity (Table 1).

Acknowledgements

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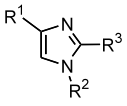
References

1. Ganellin, C. R. In *Medicinal Chemistry*: *the Role of Organic Chemistry in Drug Research*; Roberts, S. M.; Price, B. J., Eds.; Academic Press: New York, 1985; p. 93.
2. For a recent review, see: Adams, J. L.; Lee, D. *Curr. Opin. Drug Discov. Dev.* **1999**, *2*, 96.
3. Khanna, I. K.; Yu, Y.; Huff, R. M.; Weier, R. M.; Xu, X. D.; Koszyk, F. J.; Collins, P. W.; Cogburn, J. N.; Isakson, P. C.; Kobolt, C. M.; Masferrer, J. L.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Yuan, J.; Yang, D.; Zhang, Y. Y. *J. Med. Chem.* **2000**, *43*, 3168.
4. For a recent review, see: (a) Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383; (b) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
5. (a) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800; (b) Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835.
6. Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 751.
7. Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323.
8. Lee, A.; Huang, L.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 9907.
9. FTIR indicated hydrazide formation by a shift in the absorption peak from 1762 to 1719 cm^{-1}.
10. Purity based on analysis by ELS.
11. Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Fujisaki, S.; Maeno, K.; Okamoto, T. *Synthesis* **1988**, 545.
12. The compounds were determined by LC MS using Waters Symmetry (4.6×50 mm) column and eluted isocratically using a mixture of MeOH and water with 10 mM NH_4OAc as the mobile phase (flow rate 1.5 ml min^{-1}).
13. *Typical experimental procedure*: A mixture of ketoamide (0.022 mmol), DMF (0.2 ml) and acetic acid saturated with ammonium acetate (1.2 ml) were heated to 90°C for 24 h. The cooled mixture was diluted with EtOAc (10 ml) and washed with saturated aqueous sodium bicarbonate (10 ml) and water (10 ml). The aqueous layers were re-extracted with EtOAc (10 ml). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford pure 1,2,4-trisubstituted imidazole. Spectro-

Table 1. Yield and purity data for representative analogues from the imidazole library



Entry	R^1	R^2	R^3	Purity[a] (%)	Yield[b] (%)
13a	Ph	$PhCH_2$	$PhCH_2$	>95	32
13b	Ph	*p*-$CF_3C_6H_4CH_2$	$PhCH_2$	>95	35
13c	Ph	*n*-Bu	*p*-$BrC_6H_4CH_2$	>95	30
13d	*p*-FC_6H_4	*n*-Bu	*p*-$BrC_6H_4CH_2$	>95	49
13e	*p*-FC_6H_4	$PhCH_2$	*p*-$BrC_6H_4CH_2$	>95	79
13f	*p*-FC_6H_4	*i*-Pr	*p*-$CF_3C_6H_4CH_2$	>95	60
13g	*p*-FC_6H_4	*p*-$MeOC_6H_4CH_2$	$MeOCH_2$	>95	17
13h	CH_3	*p*-$MeOC_6H_4CH_2CH_2$	$PhCH_2CH_2$	>95	80
13i	CH_3	CH_2:$CHCH_2$	$PhCH_2$	>95	70

[a] Determined by ELS.
[b] Overall yield of solid and solution phase reactions.

scopic data for product **13e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 2H), 4.92 (s, 2H), 7.09–6.97 (m, 7H), 7.41–7.32 (m, 5H), 7.72–7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.09 (CH_2), 50.38 (CH_2), 115.79 (CH), 116.01 (CH), 116.62 (CH), 116.69 (CH), 121.17 (C_{quat}), 126.83 (CH), 126.91 (CH), 127.22 (CH), 128.62 (CH), 129.42 (CH), 130.02 (CH), 130.07 (CH), 130.32 (CH), 132.22 (CH), 132.27 (CH), 135.75 (C_{quat}), 135.94 (C_{quat}), 139.69 (C_{quat}), 147.08 (C_{quat}), 161.08 (C_{quat}), 163.62 (C_{quat}); MS (ES+) m/z 421 (100), isotope pattern to confirm Br.