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A Solid-Phase Combinatorial Method for the Synthesis of Novel 5- and 6-Membered Ring Lactams

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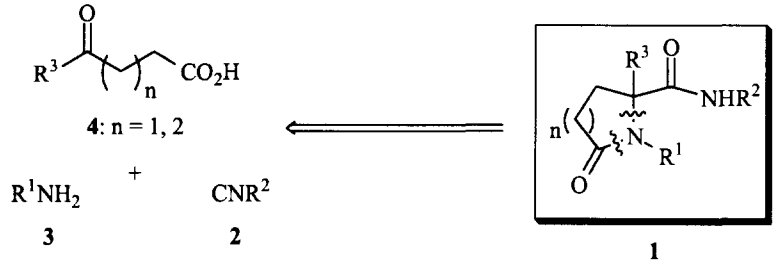
Abstract *The synthesis of small-ring lactams* via *the condensation of ω-ketoacids, isocyanides and amines is reported. This process is shown to proceed well in a combinatorial fashion, by immobilization of the isocyanide component on Wang resin. The product is then released from the support on treatment with 10% TFA/CH_2Cl_2.* Copyright © 1996 Elsevier Science Ltd

Combinatorial chemistry has emerged as a powerful tool for rapid identification and optimization of lead compounds in drug discovery.[1] We have recognized the utility of the four-component condensation (4CC) reaction[2] for the rapid introduction of diversity within small ring heterocyclic libraries such as imidazoles[3] and pyrroles.[4]

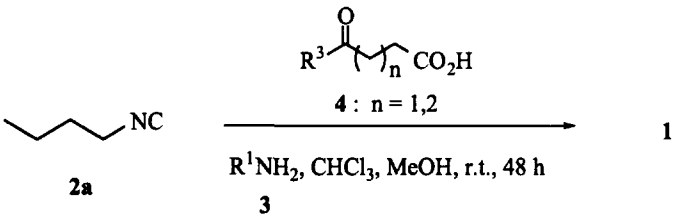
As part of our combinatorial chemistry program in the discovery of biologically active small molecules, a highly efficient method for the synthesis of lactams was needed. Aside from the well-known antibacterial properties of β-lactams,[5] other therapeutic uses have been found for γ-lactams, such as cholesterol absorption modulators,[6] analgesics[7] and bronchodilators.[8]

In a retrosynthetic analysis, we envisioned lactams **1** resulting from a 4CC reaction, wherein both carbonyl and acid components are tethered (i.e. ω-ketoacids)(Scheme 1).[9,10] We now wish to report a combinatorial method for the synthesis of multisubstituted 5- and 6-membered ring lactams **1**, using a novel condensation reaction between ω-ketoacids **4**, isocyanides **2** and amines **3**.



Scheme 1

Indeed, *n*-butyl isocyanide **2a** (CAUTION: STENCH!) was found to react with a series of primary amines **3** and ω-ketoacids **4** in $CHCl_3$/MeOH (3:1) to provide the corresponding 5- and 6-membered ring lactams **1** (Scheme 2) in moderate to excellent yields; as can be predicted, 5-membered ring formation is quite facile (entries **a**,**b**,**c**) (Table 1). However, the reaction is quite dependent upon stereoelectronic factors. For example, the yields for entries **b** and **e** perhaps reflect the sluggish tendency of the intermediate imine to undergo further reaction with the incoming isocyanide **2a**. Entry **f** reflects the sensitivity of the reaction to ring size (Table 1).



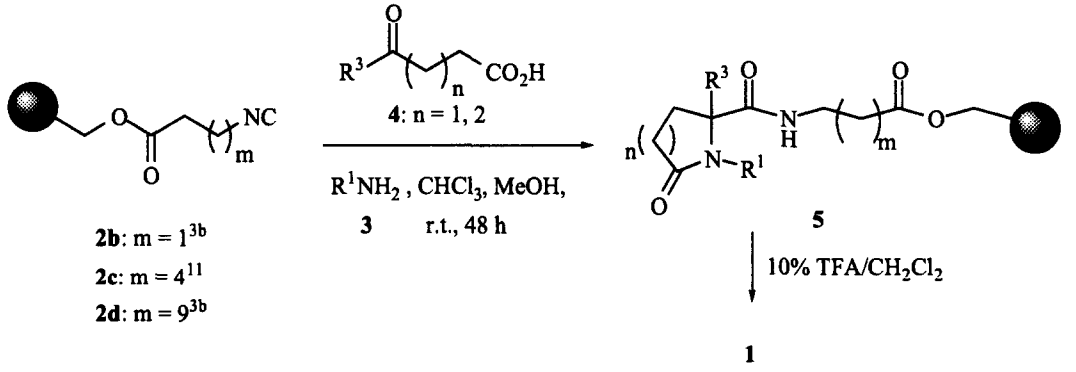
Scheme 2

Table 1. Yields for Lactams **1** Formed from Four-Component Condensation Reaction

entry	n	R^1	R^2	R^3	1(% Yield)
a	1	Bn	*n*-Bu	Me	98
b	1	Bn	*n*-Bu	*p*-BrPh	33
c	1	*n*-Bu	*n*-Bu	Me	83
d	2	Bn	*n*-Bu	Me	70
e	2	*n*-Bu	*n*-Bu	Ph	20
f	3	Bn	*n*-Bu	Me	0[a]

[a] The ω-ketoacid was recovered unchanged from the reaction mixture.

In order to synthesize relatively pure compounds and without the need for tedious chromatographic purification techniques, we recognized that one of the three components needed to be immobilized on solid support. The isocyanide bound Wang resins **2b-d**[3b] were reacted with ω-ketoacids **4** and primary amines **3** in a 3:1 $CHCl_3$/MeOH mixture (Scheme 3). After stirring for 48 h, the resin **5** was washed ($CHCl_3$ (3x), MeOH (3x)) then treated with 10% TFA/CH_2Cl_2 (2 x 20 min.); solvent was removed, leaving an oily residue. ^1H, ^{13}C NMR and tlc analyses of many of the crude residues showed the expected lactams **1g-n** (Table 2) to be practically homogeneous.

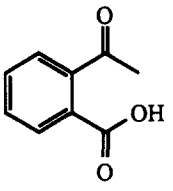


Scheme 3

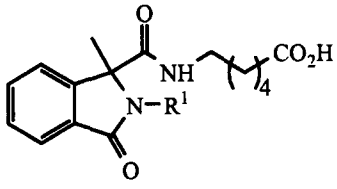
Table 2. Yields for Lactams **1** Formed from Solid-Phase Four-Component Condensation

entry	n	R^1	R^2	R^3	**1** (% Yield)
g	1	Bn	$(CH_2)_{10}CO_2H$	Me	93
h	1	n-$C_{11}H_{23}$	$(CH_2)_5CO_2H$	Me	98
i	1	$CH_2C{\equiv}CH$	$(CH_2)_5CO_2H$	Me	47
j	1	Ph	$(CH_2)_{10}CO_2H$	CO_2H	84
k	1	Bn	$(CH_2)_2CO_2H$	Me	91
l	2	Bn	$(CH_2)_2CO_2H$	Me	60
m	2	Bn	$(CH_2)_{10}CO_2H$	Me	96
n	1	n-Bu	$(CH_2)_{10}CO_2H$	Me	94

As can be seen, the Ugi 4CC reaction proceeds well for a range of primary amines, alkyl- and carboxy-substituted ω-ketoacids, in yields of 47-98%. In addition, we have found that resin **2c** reacts with *o*-acetylbenzoic acid **6** and primary amines **3** to form the benzo-fused lactams **7** in 35 and 38% yields, respectively. This reaction is currently being optimized to include the synthesis of substituted benzo-fused lactams **7**.



6



7a: $R^1 = n\text{-}C_8H_{17}$

7b: R^1 = allyl

A representative experimental is as follows: To a dry, pre-silylated scintillation vial (initial rinse with 1% Me_3SiCl/PhMe, followed by regular rinse with water, acetone, ether) was added resin **2d** (0.4830 g, 0.36 mmol), followed by levulinic acid (0.18 mL, 1.76 mmol, 4.4 mol eq), benzylamine (0.19 mL, 1.74 mmol, 4.4 mol eq), chloroform (4 mL) and methanol (2 mL). The heterogeneous mixture was stirred for 48 hours; the contents were then washed with CH_2Cl_2 (3 x 10 mL), methanol (3 x 10 mL), and a final wash with CH_2Cl_2 (5 mL). The resin was then agitated with 10% CF_3CO_2H/CH_2Cl_2 (10 mL, 20 minutes), and then drained. This process was then repeated once more. The resultant solution was then evaporated, yielding a light brown residue. Passage through a silica gel plug furnished the required lactam **1g** (0.1394 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10-1.32 (m, 14 H), 1.40 (s, 3H, C<u>H</u>$_3$), 1.50-1.58 (m, 2H), 1.84-1.92 (m, 2H), 2.23-2.30 (m, 3H), 2.43-2.48 (m, 2H), 2.88 (ddd, J = 13.2, 13.2, 6.8 Hz, 1H), 3.05 (ddd, J = 13.2, 13.2, 6.8 Hz, 1H), 4.19, 4.60 (AB quartet, J_{gem} = 15.2 Hz, 2H, NC<u>H</u>$_2$Ph), 6.24 (t, J = 5.2 Hz, 1H, C(O)N<u>H</u>CH$_2$), 7.18-7.25 (m, 5H, aromatics) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 24.8, 26.9, 29.0, 29.1 (m), 29.2, 29.3 (m), 29.9, 33.6, 34.2, 40.1, 45.0, 68.4, 127.9, 128.2, 129.0, 137.7, 163.8, 173.3, (177.5, 178.3, <u>C</u>(O)NHCH$_2$ rotameric doublet) ppm; ESIMS, m/z for $C_{24}H_{35}N_2O_4$ $[M\text{-}H]^-$: 415.

Conclusion

We have demonstrated that the condensation of ω-ketoacids **4** with isocyanides **2** and amines **3** provides a combinatorial method for the synthesis of novel multisubstituted 5- and 6-membered lactams **1**. This reaction was carried out on solid phase, by attachment of isocyanides **2** to Wang resin *via* an ester linkage, to provide relatively pure compounds without the need for tedious chromatographic techniques. One could expect that a large combinatorial library can be prepared based upon the number of commercially available amines (300), ω-ketoacids (250) and isocyanides (10).

Acknowledgements

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11. Prepared in an analogous manner in three steps from 6-aminohexanoic acid (see ref. 3(b)).

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