Pergamon

*Tetrahedron Letters*, Vol. 38, No. 14, pp. 2519-2520, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00389-4

# A Facile Synthesis of β-Lactams Based on the Isocyanide Chemistry

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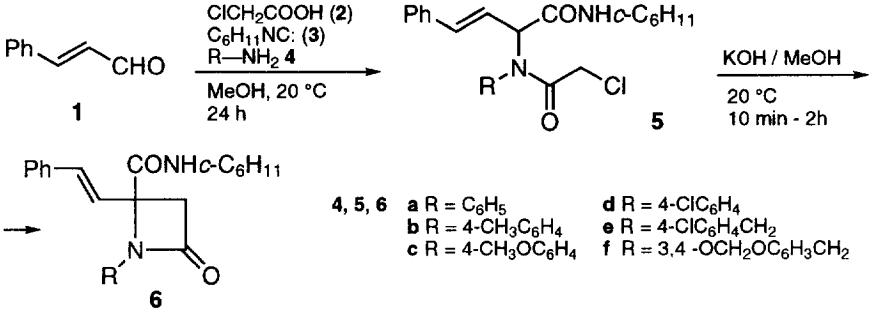
***Abstract:*** The reaction between (*E*)-cinnamaldehyde (**1**), chloroacetic acid (**2**), cyclohexyl isocyanide (**3**), and amines **4** afforded the expected Ugi 4-CC products **5**, which were easily cyclised to (*E*)-1-substituted *N*-cyclohexyl-2-(1-phenylethen-2-yl)-4-oxoazetidine-2-carboxamides **6** upon treatment with methanolic KOH. © 1997 Elsevier Science Ltd.

Among the various reactions that lead to the formation of β-lactams, the Ugi four-component condensation between β-aminocarboxylic acids, carbonyl compounds, and isocyanides is one of the most important and has been largely employed in the synthesis of antibiotics and natural products[2].

Isocyanides have been even used in two-step syntheses of β-lactams. Thus, the Passerini three-component reaction between α-chloroketones, isocyanides, and carboxylic acids afforded 2-acyloxy-3-chlorocarboxamides which was cyclised to 3-acyloxy-2-azetidinones in the presence of CsF[3]. The reaction between aldehydes and isocyanides in molar *ratio* 1:2 in the presence of $BF_3$ afforded 2,3-*bis*-alkyliminooxetanes[4] that reacted with bromoacetic acid to give 1,*N*-disubstituted 2-acyl-4-oxoazetidine-2-carboxamides[5].

In continuation of our investigations on the synthesis of heterocyclic compound from isocyanides[6] we wish to report a facile two-step synthesis of β-lactams starting from isocyanides. The first step consisted in the reaction between (*E*)-cinnamaldehyde (**1**), chloroacetic acid (**2**), cyclohexyl isocyanide (**3**), and amines **4** which afforded the expected (*E*)-2-[(*N*-chloroacetyl-*N*-substituted)amino]-4-phenyl-but-3-enoic acid *N*-cyclohexylamides **5** in fair to good yields. Compounds **5** were isolated from the reaction mixture by filtration and were pure enough to perform the successive reaction on the crude product.




**4, 5, 6** **a** R = $C_6H_5$ **d** R = 4-$ClC_6H_4$
**b** R = 4-$CH_3C_6H_4$ **e** R = 4-$ClC_6H_4CH_2$
**c** R = 4-$CH_3OC_6H_4$ **f** R = 3,4 -$OCH_2OC_6H_3CH_2$

Upon treatment with methanolic KOH under very mild conditions, compounds **5** underwent a ring-

closure reaction to give the hitherto unknown (*E*)-1-substituted *N*-cyclohexyl-2-(1-phenylethen-2-yl)-4-oxoazetidine-2-carboxamides **6** in high yields[7].

**Acknowledgement**

C. F. M. wishes to thank financial support from the Consejería de Educación de la Junta de Extremadura and Fondo Social Europeo (refs. EIA94–43 and BRV9610A043).

**References and Notes**

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7. A typical procedure is as follows. A solution of **2** (1.82 g, 19.3 mmol) in MeOH (5 ml) was added to a well-stirred solution of **4a** (1.80 g, 19.3 mmol) in MeOH (5 ml). The resulting solution was treated as quickly as possible with a solution of **1** (2.55 g, 19.3 mmol) in MeOH (5 ml) and then with a solution of **3** (2.08 g, 19.1 mmol) in MeOH (5 ml). The resulting solution was stirred for 24 h at r. t. and then cooled and filtered to give **5a** (6.06 g, 77%), mp 174-175 °C from EtOH.
The above product (2.06 g, 5.01mmol) was added to a solution of KOH (294.6 mg, 5.25 mmol) in MeOH (10 ml). The resulting mixture was stirred for 2 h and then cooled and filtered. The collected solid was washed with water and dried to give **6a** (1.56 g, 83%), mp 189-190 °C from EtOH; IR (KBr): 1760, 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 3.34 (m, 2 H, $CH_2$); 3.85 (m, 1 H, H-$1_{cyclohex.}$); 5.91 (m, 1 H, NH); 6.58 (d, 1 H, $J$ = 16.4 Hz, PhCH=C<u>H</u>); 6.99 (d, 1 H, $J$ = 16.4 Hz, PhC<u>H</u>=CH).
Compound **5b**: mp 166–167 °C (MeOH), 73% yield; **5c**: mp 170–171 °C (EtOH), 75% yield; **5d**: mp 170–172 °C (EtOH), 72% yield; **5e**: mp 147–148 °C (EtOH), 51% yield; **5f**: mp 130–131 °C (EtOH), 56% yield. Compound **6b**: mp 183–184 °C (DMF/EtOH), 78% yield; IR (KBr): 1740, 1658 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 2.31 (s, 3 H, $CH_3$); 3.31 (m, 2 H, $CH_2$); 3.84 (m, 1 H, H-$1_{cyclohex.}$); 5.90 (m, 1 H, NH); 6.56 (d, 1 H, $J$ = 16.5 Hz, PhCH=C<u>H</u>); 6.98 (d, 1 H, $J$ = 16.5 Hz, PhC<u>H</u>=CH). **6c**: mp 170–171 °C (EtOH), 79% yield; IR (KBr): 1736, 1661 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 3.31 (m, 2 H, $CH_2$); 3.66-3.94 (m, 4 H, H-$1_{cyclohex.}$ + $CH_3$); 5.90 (m, 1 H, NH); 6.57 (d, 1 H, $J$ = 16.5 Hz, PhCH=C<u>H</u>); 6.97 (d, 1 H, $J$ = 16.5 Hz, PhC<u>H</u>=CH). **6d**: mp 157–158 °C (EtOH), 76% yield; IR (KBr): 1739, 1658 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 3.35 (m, 2 H, $CH_2$); 3.84 (m, 1 H, H-$1_{cyclohex.}$); 5.88 (m, 1 H, NH); 6.55 (d, 1 H, $J$ = 16.4 Hz, PhCH=C<u>H</u>); 6.95 (d, 1 H, $J$ = 16.4 Hz, PhC<u>H</u>=CH). **6e**: mp 159–160 °C (EtOH), 72% yield; IR (KBr): 1742, 1672 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 3.25 (m, 2 H, $CH_2$); 3.64 (m, 1 H, H-$1_{cyclohex.}$); 3.91 (s, 2 H, $NCH_2$); 4.45 (d, 1 H, $J$ = 13.9 Hz, PhCH=C<u>H</u>); 4.95 (d, 1 H, $J$ = 13.9 Hz, PhC<u>H</u>=CH); 5.37 (m, 1 H, NH). **6f**: mp 126–128 °C (*i*-PrOH), 63% yield; IR (KBr): 1671, 1632 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) (ppm, δ): 3.31 (m, 2 H, $CH_2$); 3.63 (m, 1 H, H-$1_{cyclohex.}$); 3.90 (s, 2 H, $NCH_2$); 4.30 (d, 1 H, $J$ = 13.9 Hz, PhCH=C<u>H</u>); 5.01 (d, 1 H, $J$ = 13.9 Hz, PhC<u>H</u>=CH); 5.45 (m, 1 H, NH); 5.92 (s, 2 H, $OCH_2O$).

(*Received in UK* 11 *November* 1996; *revised* 21 *February* 1997; *accepted* 28 *February* 1997)