Pergamon

Tetrahedron Letters 42 (2001) 2727–2728

TETRAHEDRON LETTERS

A facile synthesis of 2,5-diketopiperazines based on isocyanide chemistry

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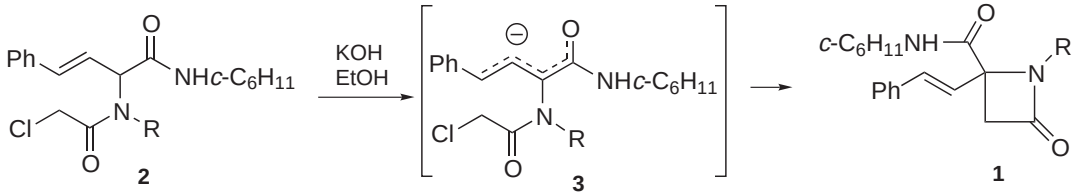
Received 17 July 2000; revised 2 February 2001; accepted 7 February 2001

Abstract—The Ugi four-component condensation (4-CC) between amines **4**, aromatic aldehydes **5**, chloroacetic acid **6** and isocyanides **7** afforded the expected 4-CC adducts **8** which were cyclised to the title compounds **9** upon treatment with ethanolic KOH under ultrasonication.

In a previous work,[1] belonging to a series of papers concerning the synthesis of heterocyclic compounds from isocyanides,[2] we described the synthesis of β-lactams **1** by base-induced cyclization of (*E*)-2-[(*N*-chloroacetyl-*N*-substituted)amino]-4-phenyl-but-3-enoic acid *N*-cyclohexylamides **2** obtained via the Ugi four-component condensation between (*E*)-cinnamaldehyde, chloroacetic acid, amines and cyclohexyl isocyanide. In this synthesis the key intermediates are the highly stabilised anions **3**.

If saturated aldehydes are employed as a starting materials in the Ugi reaction it is reasonable to hypothesise that the anions arising from the corresponding 4-CC adducts are less stable, thus, a different base-induced cyclisation mode, involving the amide nitrogen, appears to be possible.

The first step of the synthesis was the Ugi 4-CC between amines **4**, aromatic aldehydes **5**, chloroacetic acid (**6**) and isocyanides **7** which was performed in the usual manner[1] to afford the expected 2-substituted 2-[(*N*-chloroacetyl-*N*-substituted)amino]acetic acid *N*-cyclohexyl- (or benzyl)amides **8** in good yields.[‡]



Keywords: isocyanides; Ugi–Passerini reactions; piperazine/piperazinones; sonochemistry.

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‡ Compound **8a**: mp 173–174°C (EtOH/DMF), 85% yield; IR (KBr): 3286, 1645 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.25–6.95 (m, $8H_{arom}$), 5.77 (s, 1H, CHN), 5.67 (d, $J=7.4$, 1H, NH), 4.72 (d, $J=17.6$, 1H, CH_2Cl), 4.49 (d, $J=17.6$, 1H, CH_2Cl), 3.99 (d, $J=12.8$, 1H, CH_2Ph), 3.90 (d, $J=12.8$, 1H, CH_2Ph), 3.74 (m, 1H, $1\text{-}H_{cyclohexyl}$), 1.88–1.02 (m, $10H_{cyclohexyl}$). Compound **8b**: mp 188–189°C (DMF/EtOH), 82% yield; IR (KBr): 3274, 1646 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.30–6.99 (m, $9H_{arom}$), 5.78 (s, 1H, CHN), 5.67 (d, $J=7.4$, 1H, NH), 4.75 (d, $J=17.5$, 1H, CH_2Cl), 4.54 (d, $J=17.5$, 1H, CH_2Cl), 4.03 (d, $J=12.8$, 1H, CH_2Ph), 3.93 (d, $J=12.8$, 1H, CH_2Ph), 3.75 (m, 1H, $1\text{-}H_{cyclohexyl}$), 1.83–1.06 (m, $10H_{cyclohexyl}$). **8c**: mp 168–170°C (EtOH), 78% yield; IR (KBr): 3279, 1652 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.25–6.75 (m, $8H_{arom}$), 5.77 (s, 1H, CHN), 5.53 (d, $J=8.1$, 1H, NH), 4.69 (d, $J=17.6$, 1H, CH_2Cl), 4.48 (d, $J=17.6$, 1H, CH_2Cl), 4.02–3.67 (m, 3H, $CH_2Ph+1\text{-}H_{cyclohexyl}$), 3.74 (s, 3H, CH_3), 1.83–1.00 (m, $10H_{cyclohexyl}$). **8d**: mp 194–196°C (DMF/EtOH), 86% yield; IR (KBr): 3277, 1651 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.81–6.96 (m, $11H_{arom}$), 5.98 (s, 1H, CHN), 5.64 (d, $J=8.0$, 1H, NH), 4.74 (d, $J=17.5$, 1H, CH_2Cl), 4.53 (d, $J=17.5$, 1H, CH_2Cl), 4.05–3.78 (m, 3H, $CH_2Ph+1\text{-}H_{cyclohexyl}$), 1.87–1.00 (m, $10H_{cyclohexyl}$). **8e**: mp 138–140°C (DMF/EtOH), 68% yield; IR (KBr): 3283, 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.56–7.15 (m, $9H_{arom}$), 6.63 (m, 1H, NH), 4.86 (s, 1H, CHN), 4.42 (d, $J=5.6$, 2H, CH_2Ph), 4.19 (d, $J=12.1$, 1H, CH_2Cl), 4.05 (d, $J=12.1$, 1H, CH_2Cl), 3.73 (m, 1H, $1\text{-}H_{cyclohexyl}$), 1.99–1.09 (m, $10H_{cyclohexyl}$).

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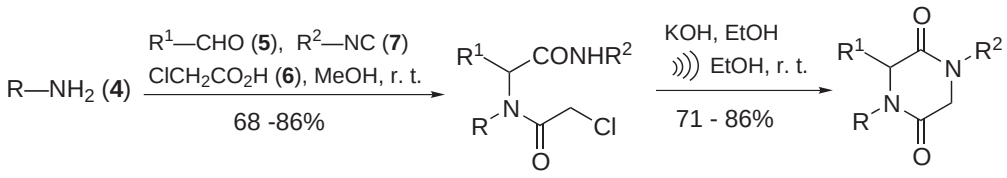
PII: S0040-4039(01)00232-5



4	R
a	4-$ClC_6H_4CH_2$
b	$C_6H_5CH_2$
c	*c*-C_6H_{11}

7	R^2
a	*c*-C_6H_{11}
b	$C_6H_5CH_2$

5	R^1
a	4-ClC_6H_4
b	4-$CH_3OC_6H_4$
c	2-naphthyl
d	4-BrC_6H_4

8, 9	R	R^1	R^2
a	4-$ClC_6H_4CH_2$	4-ClC_6H_4	*c*-C_6H_{11}
b	$C_6H_5CH_2$	4-ClC_6H_4	*c*-C_6H_{11}
c	4-$ClC_6H_4CH_2$	4-$CH_3OC_6H_4$	*c*-C_6H_{11}
d	4-$ClC_6H_4CH_2$	2-naphthyl	*c*-C_6H_{11}
e	*c*-C_6H_{11}	4-BrC_6H_4	$C_6H_5CH_2$

In earlier experiments, we obtained the desired 2,5-diketopiperazines **9** by refluxing compounds **8** in ethanolic KOH or by employing NaOH under phase-transfer catalysis; however, either the yield or the purity of the products obtained were unsatisfactory.

Now we have found that compounds **9** can be obtained in good yields, under very mild conditions, if a suspension of **8** in ethanolic KOH is subjected to ultrasonication.[§]

Although the Ugi four-component condensation was successfully performed by employing aliphatic aldehydes as starting materials, attempts to cyclise the resulting products gave complex reaction mixtures. Cyclisations performed by employing KOD in EtOD showed that epimerisation at the stereogenic centre took place to a large extent. For example, the integral of the NCHCO proton signal of compound **9a** showed that 89% of deuterium was incorporated.

Even though the present method suffers from limitations due to the nature of the aldehyde, it must be underlined that a wide variety in the substitution pattern of **8**, and subsequently in the diketopiperazines **9**, can be easily achieved by changing the components in the Ugi reaction. From this point of view the synthesis of compounds of type **8** by means of alternative methods such as the chloroacetylation of α-amino acid amides[3] appears to be much less important. Furthermore, the facile cyclisation of compound **8** allows us to consider the present method as being of interest for the synthesis of 2,5-diketopiperazines.

References

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[§] A typical procedure is as follows. Compound **8a** (500 mg, 1.07 mmol) was treated with a solution of KOH (66 mg, 1.18 mmol) in EtOH (7 ml). The resulting suspension was transferred to the vessel of a Bausch & Lomb Balsonic apparatus and ultrasonicated at rt for 30 min. The thick reaction sludge was filtered and the collected solid washed with water and dried to give **9a** (307 mg). A further crop (90 mg) was obtained by concentrating the mother liquors. Total yield 397 mg (86%), mp 154–156°C (*i*-PrOH); IR (KBr): 1646 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.36–7.07 (m, $8H_{arom}$), 5.37 (d, $J=14.6$, 1H, CH_2), 4.83 (s, 1H, NCHCO), 4.20 (m, 1H, 1-$H_{cyclohexyl}$), 4.02 (d, $J=17.3$, 1H, CH_2Ph), 3.89 (d, $J=17.3$, 1H, CH_2Ph), 3.59 (d, $J=14.6$, 1H, CH_2), 1.83–1.06 (m, $10H_{cyclohexyl}$). Compound **9b**: mp 151–153°C (*i*-PrOH/*i*-Pr_2O), 80% yield; IR (KBr): 1644 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.37–7.12 (m, $9H_{arom}$), 5.44 (d, $J=14.7$, 1H, CH_2), 4.86 (s, 1H, NCHCO), 4.21 (m, 1H, 1-$H_{cyclohexyl}$), 4.04 (d, $J=17.5$, 1H, CH_2Ph), 3.91 (d, $J=17.5$, 1H, CH_2Ph), 3.59 (d, $J=14.7$, 1H, CH_2), 1.83–1.00 (m, $10H_{cyclohexyl}$). **9c**: mp 126–128°C (*i*-PrOH), 72% yield; IR (KBr): 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.28–6.83 (m, $8H_{arom}$), 5.35 (d, $J=14.6$, 1H, CH_2), 4.78 (s, 1H, NCHCO), 4.21 (m, 1H, 1-$H_{cyclohexyl}$), 3.97 (d, $J=2.2$, 2H, CH_2Ph), 3.78 (s, 3H, CH_3), 3.59 (d, $J=14.6$, 1H, CH_2), 1.82–1.06 (m, $10H_{cyclohexyl}$). **9d**: mp 198–200°C (DMF/*i*-PrOH), 77% yield; IR (KBr): 1646 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.88–7.10 (m, $11H_{arom}$), 5.46 (d, $J=14.8$, 1H, CH_2), 5.03 (s, 1H, NCHCO), 4.21 (m, 1H, 1-$H_{cyclohexyl}$), 4.02 (s, 2H, CH_2Ph), 3.67 (d, $J=14.8$, 1H, CH_2), 1.83–1.01 (m, $10H_{cyclohexyl}$). **9e**: mp 184–186°C (DMF/*i*-PrOH), 71% yield; IR (KBr): 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (ppm, δ): 7.52–6.94 (m, $9H_{arom}$), 5.16 (s, 1H, NCHCO), 4.98 (d, $J=15.0$, 1H, CH_2), 4.37 (m, 1H, 1-$H_{cyclohexyl}$), 4.34 (d, $J=15.0$, 1H, CH_2), 3.84 (d, $J=17.2$, 1H, CH_2Ph), 3.71 (d, $J=17.2$, 1H, CH_2Ph), 1.81–0.92 (m, $10H_{cyclohexyl}$).