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Synthesis of thiomorpholines by an intramolecular Ugi reaction

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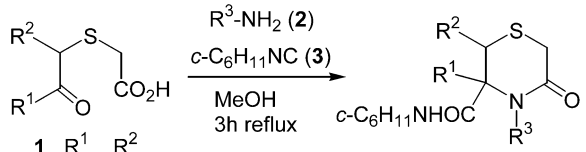
Abstract—The Ugi four-component condensation between 5-oxo-3-thiacarboxylic acids, benzylamines and cyclohexyl isocyanide gave 5-oxothiomorpholine-3-carboxamides. The configuration of bicyclic thiomorpholine derivatives was established by NOESY experiments.

The thiomorpholin-3-one is a well-known heterocycle that has been the subject of an intense research after its first preparation in 1950[1] because of its unique pharmacological properties. This nucleus is present in the 1,4-benzothiazine calcium antagonist Semotiadil[2] as well as in a pyrimido[1,4]thiazine derivative[3] designed as an inhibitor of the glycinamide ribonucleotide transformylase with a potent cell growth inhibition. Modern approaches to this nucleus were performed by base-promoted aminoethylation of ethyl thioglycolate with 2-oxazolidinones[4] and from glycidic esters,[5] among others.[6] 5-Oxothiomorpholine-3-carboxylic acid derivatives were prepared for the first time in 1944.[7] They have been the target of many synthetic methods[8] after their pioneering incorporation into peptidic thyrotropin-releasing hormone analogues that were used for proving structure–activity relationships.[9] A solid phase synthesis of 5-oxothiomorpholine-3-carboxamides has been reported,[10] but several steps and expensive reagents are required. The usefulness of these kinds of compounds as pharmaceutical tools calls for rapid and atom-economical[11] methods that give access to molecular diversity in parallel to modern protein structure-based design of new medicinal leads. Multicomponent reactions are best suited to achieve this goal.[12] In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides,[13] we wish to report a synthesis of thiomorpholines based on an intramolecular Ugi four-component condensation between 5-oxo-3-thiacarboxylic acids **1a**–**b**, benzylamines **2a**–**d**, and cyclohexylisocyanide **3** (Scheme 1).

The Ugi four-component condensation between bifunctional oxoacids **1a**–**b**, obtained following known methods,[14] commercial benzylamines **2a**–**d**, and the commercial cyclohexyl isocyanide **3** took place smoothly in boiling methanol to give monocyclic and bicyclic 5-oxothiomorpholine-3-carboxamides **4a**–**d** and **5a**–**d**, respectively, in good yields (76–85%) (Table 1). In a typical experiment, a solution of cyclohexyl isocyanide **3** (4 mmol) in methanol (4 mL) was added to a solution of **1a**–**b** (4 mmol) and **2a**–**d** (4 mmol) in methanol (4 mL). The resulting mixture was refluxed for 3 h and then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (30 ml) and washed with 0.5% NaOH in water. The organic



1 R1 R2
a Me H
b -(CH2)4-

2 R3
a C6H5CH2
b 4-ClC6H4CH2
c 3,4-CH2O2C6H3CH2
d (S)-C6H5CH(CH3)

4 R1 R2 R3
a Me H C6H5CH2
b Me H 4-ClC6H4CH2
c Me H 3,4-CH2O2C6H3CH2
d Me H (S)-C6H5CH(CH3)

5 R1 R2 R3
a -(CH2)4- C6H5CH2
b -(CH2)4- 4-ClC6H4CH2
c -(CH2)4- 3,4-CH2O2C6H3CH2
d -(CH2)4- (S)-C6H5CH(CH3)

Scheme 1. 5-Oxothiomorpholine-3-carboxamides by the Ugi reaction.

Keywords: Ugi reaction; thiomorpholine; isocyanide.

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Table 1. One-pot synthesis of 5-oxothiomorpholine-3-carboxamides by the Ugi reaction

Entry	Keto-acid	R^3	Reaction product (%)	d.e.[a]
1	**1a**	$C_6H_5CH_2$	**4a** (85)	
2	**1a**	4-$ClC_6H_4CH_2$	**4b** (79)	
3	**1a**	3,4-$CH_2O_2C_6H_3CH_2$	**4c** (76)	
4	**1a**	(*S*)-$C_6H_5CH(CH_3)$	**4d** (80)	0
5	**1b**	$C_6H_5CH_2$	**5a** (85)	36
6	**1b**	4-$ClC_6H_4CH_2$	**5b** (81)	16
7	**1b**	3,4-$CH_2O_2C_6H_3CH_2$	**5c** (81)	30
8	**1b**	(*S*)-$C_6H_5CH(CH_3)$	**5d** (79)	68[b]

[a] Diastereomeric excesses were determined by integration of the ^1H NMR signals of the reaction mixtures.
[b] Relative relation *cis:trans* of C-4a and C-8a.

layer was separated, washed with water and dried (Na_2SO_4). Removal of the solvent left a residue, which was recrystallized from ^{i}PrOH/^{i}Pr$_2$O to give the products.

The structure of compounds **4a–d** and **5a–d** was confirmed by their analytical and spectral data. In these syntheses a new stereocenter is created, so it is interesting to note the stereochemical outcome of the reaction. The configuration of bicyclic compounds **5a–c** was established by NOESY experiments on the major diastereomer. These showed that the proton at C-4a was *trans* to the proton NH of the amide at C-8a.

To improve the diastereoselectivity of the method we performed the Ugi four-component reaction with the chiral amine **2d**. By starting from **1a** and **2d** (entry 4) the reaction gave a 1:1 mixture of both diastereomers, but the reaction of **1b** and **2d** (entry 8) gave a mixture of the four possible diastereomers in the proportion 42:42:8:8, therefore the obtained diastereomeric ratio was 84:16 (*trans*:*cis*). This experiment showed the possibilities of the reported method for the selective synthesis of enhanced mixtures of chiral compounds by employing enantiopure starting materials. One of the major diastereomers of **5d** was isolated as an optically pure material by recrystallization, from which the growth of a single crystal was possible. From the X-ray diffraction study of **5d** (Fig. 1) we assigned the absolute configuration at the C-4a as *R* and 8a as *S*.

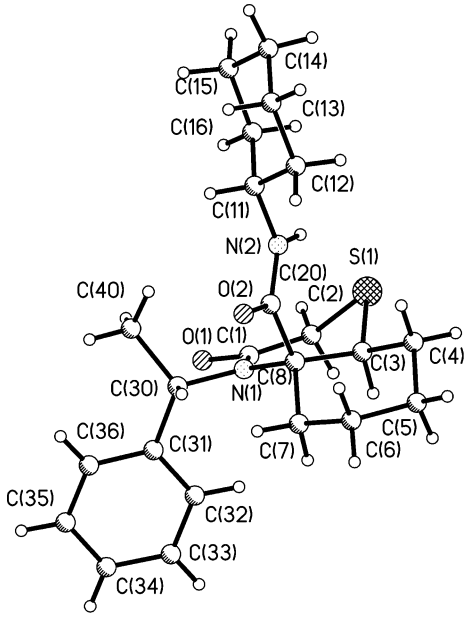

Figure 1. The molecular structure of **5d**.

In conclusion, we have shown that the Ugi four component reaction permitted a simple and fast one-pot procedure for the preparation of monocyclic and bicyclic 3-oxo-thiomorpholin-5-carboxamides from commercial or easily prepared reagents, and with good stereoselection when chiral starting amines were used. A simple hydrolysis of the cyclohexyl amide bond should give the free carboxylic acids, that are considered as useful pharmaceutical tools.[15]

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15. All new compounds gave satisfactory spectral and elemental analysis (selected examples are given). **4-Benzyl-3-methyl-5-oxothiomorpholin-3-(*N*-cyclohexylcarboxamide) 4a**: White solid, mp 130–131°C. IR (KBr, cm^{-1}) ν 3327 (NH), 1636 (CO), 1624 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91–1.98 (m, 13H), 2.89 (d, $J=14.2$, 1H), 3.16 (d, $J=14.2$, 1H), 3.36 (d, $J=16.0$, 1H), 3.52 (d, $J=16.0$, 1H), 3.63–3.78 (m, 1H), 4.06 (d, $J=16.2$, 1H), 5.12 (d, $J=16.2$, 1H), 6.16 (br s, 1H, NH), 7.13–7.32 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8 (CH_2), 25.0 (CH_3), 25.4, 32.2, 32.6, 32.8, and 38.1 (5×CH_2), 49.0 (CH), 68.4 (Cq), 126.6, 127.1, and 128.6 (3×CH_{Ar}), 137.8 (C_{Ar}), 167.5 and 170.6 (2×CO). HRMS $M^+_{found}=346.1690$, $C_{19}H_{26}N_2O_2S$ requires 346.1715. Anal. calcd for $C_{19}H_{26}N_2O_2S$: C, 65.86; H, 7.56; N, 8.08. Found: C, 65.98; H, 7.67; N, 8.00%. **4-(4-Chlorobenzyl)-3-methyl-5-oxothiomorpholin-3-(*N*-cyclohexylcarboxamide) 4b**: White solid, mp 170–171°C. IR (KBr, cm^{-1}) ν 1661 (CO), 1618 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91–1.98 (m, 13H), 2.90 (d, $J=14.2$, 1H), 3.12 (d, $J=14.2$, 1H), 3.36 (d, $J=16.8$, 1H), 3.50 (d, $J=16.8$, 1H), 3.61–3.83 (m, 1H), 3.94 (d, $J=16.2$, 1H), 5.09 (d, $J=16.2$, 1H), 6.21 (d, $J=8.4$, 1H, NH), 7.07–7.26 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8 (CH_2), 25.0 (CH_3), 25.4, 32.2, 32.7, 32.8, 38.2, and 48.7 (6×CH_2), 49.1 (CH), 68.4 (Cq), 128.1 and 128.7 (2×CH_{Ar}), 132.9 and 136.3 (2×C_{Ar}), 167.4 and 170.4 (2×CO). **3-Methyl-4-(3,4-methylenedioxy)benzyl-5-oxothiomorpholin-3-(*N*-cyclohexylcarboxamide) 4c**: White solid, mp 211–213°C (dec). IR (KBr, cm^{-1}) ν 1657 (CO), 1617 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.97–1.98 (m, 13H), 2.86 (d, $J=13.8$, 1H), 3.14 (d, $J=13.8$, 1H), 3.34 (d, $J=16.6$, 1H), 3.48 (d, $J=16.6$, 1H), 3.61–3.82 (m, 1H), 3.99 (d, $J=15.8$, 1H), 5.01 (d, $J=15.8$, 1H), 5.90 (s, 2H), 6.14 (d, $J=8.0$, 1H, NH), 6.60–6.78 (m, 3H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8 (CH_2), 25.0 (CH_3), 25.4, 32.1, 32.6, 32.8, 38.0, and 48.7 (6×CH_2), 49.0 (CH), 68.3 (Cq), 101.1 (CH_2), 107.6, 108.3, and 120.1 (3×CH_{Ar}), 131.8, 146.6, and 147.9 (3×C_{Ar}), 167.5 and 170.6 (2×CO). **4-Benzyl-3-oxoperhydrobenzo[1,4]thiazin-4a-(*N*-cyclohexylcarboxamide) 5a**: White solid, mp 171–172°C. IR (KBr, cm^{-1}) ν 1662 (CO), 1639 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.73–1.88 (m, 16H), 2.18–2.23 (m, 1H), 2.52–2.58 (m, 1H), 3.23 (dd, $J=12.2$, 3.0, 1H), 3.40 (d, $J=11.4$, 1H), 3.61–3.82 (m, 1H), 3.74 (d, $J=11.4$, 1H), 4.30 (d, $J=15.6$, 1H), 5.06 (d, $J=15.6$, 1H), 7.13–7.32 (m, 5H, H_{Ar}), 7.57 (d, $J=7.0$, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.4, 24.5, 24.7, 25.4, 29.2, 32.3, 32.5, 32.7, and 36.5 (9×CH_2), 42.7 (CH), 47.1 (CH_2), 48.4 (CH), 68.5 (Cq), 126.8, 127.6, 128.5 (3×CH_{Ar}), 138.7 (C_{Ar}), 166.1 and 168.4 (2×CO). **4-(4-Chlorobenzyl)-3-oxoperhydrobenzo[1,4]thiazin-4a-(*N*-cyclohexylcarboxamide) 5b**: White solid, mp 170–171°C. IR (KBr, cm^{-1}) ν 1657 (CO), 1622 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.80–2.13 (m, 17H), 2.50–2.56 (m, 1H), 3.16–3.42 (m, 2H), 3.61–3.77 (m, 2H), 4.21 (d, $J=16.2$, 1H), 4.98 (d, $J=16.2$, 1H), 7.04–7.23 (m, 4H, H_{Ar}), 7.72 (d, $J=7.4$, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.4, 24.5, 24.7, 25.4, 28.8, 29.2, 32.5, 32.7, 36.6 (9×CH_2), 42.9 (CH), 47.6 (CH_2), 48.4 (CH), 68.5 (Cq), 126.8, 127.6, 128.5 (3×CH_{Ar}), 138.7 (C_{Ar}), 166.1 and 168.4 (CO). **4-(3,4-Methylenedioxy)benzyl-3-oxoperhydrobenzo-[1,4]thiazin-4a-(*N*-cyclohexylcarboxamide) 5c**: White solid, mp 176–177°C. IR (KBr, cm^{-1}) ν 1662 (CO), 1642 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75–2.22 (m, 17H), 2.53–2.59 (m, 1H), 3.20 (dd, $J=14.6$, $J=3.0$, 1H), 3.39 (d, $J=16.8$, 1H), 3.61–3.82 (m, 1H), 3.72 (d, $J=16.8$, 1H), 4.22 (d, $J=15.8$, 1H), 4.93 (d, $J=15.8$, 1H), 5.88 (s, 2H), 6.60–6.93 (m, 3H, H_{Ar}), 7.51 (d, $J=7.6$, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.4, 24.5, 24.7, 25.5, 29.2, 32.3, 32.6, 32.7, 36.5 (9×CH_2), 42.6 (CH), 46.8 (CH_2), 48.4 (CH), 68.5 (Cq), 100.9 (CH_2), 107.7, 108.1, 120.2 (3×CH_{Ar}), 132.7, 146.4, and 147.7 (3×C_{Ar}), 166.2 and 168.4 (2×CO). HRMS, $M^+=430.1912$ $C_{23}H_{30}N_2O_4S$ requires 430.1926. Anal. calcd for $C_{23}H_{30}N_2O_4S$: C, 64.16; H, 7.02; N, 6.51. Found: C, 64.18; H, 7.15; N, 6.39%. HRMS, $M^+_{found}=430.1912$ $C_{23}H_{30}N_2O_4S$ requires 430.1926. **(a*S*,4a*R*,8a*S*)-4-(α-Methylbenzyl) - 3 - oxoperhydrobenzo[1,4]thiazin - 4a - (*N*-cyclohexylcarboxamide) 5d**: White solid, mp 187–189°C. $[\alpha]_D=+22.5$ (*c* 10.2 g/100 mL, $CHCl_3$); IR (KBr, cm^{-1}) ν 3256 (NH), 1667 (CO), 1631 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07–1.93 (m, 20H), 2.67–2.74 (m, 1H), 3.21 (dd, $J=12.0$, $J=2.4$, 1H), 3.31 (d, $J=16.8$, 1H), 3.68 (d, $J=16.8$, 1H), 3.84–3.91 (m, 1H), 4.77 (q, $J=7.0$, 1H), 7.10–7.28 (m, 5H, H_{Ar}), 8.23 (d, $J=7.8$, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.7 (CH_3), 22.8, 24.5, 25.6, 25.8, 29.4, 32.6, 32.9, 34.0, 36.3 (9×CH_2), 48.4, 49.1, and 55.8 (3×CH), 68.6 (Cq), 126.0, 126.1, 128.0 (3×CH_{Ar}), 142.3 (C_{Ar}), 164.5 and 168.1 (2×CO). HRMS, $M^+=400.2179$ $C_{23}H_{32}N_2O_2S$ requires 400.2184. **Crystal data for 5d**: $C_{23}H_{32}N_2O_2S$, $M_r=400.57$, space group $P2_12_12_1$, $a=9.212(2)$, $b=14.546(4)$, $c=16.238(4)$ Å, $V=2175.8(9)$ Å^3, $Z=4$, $D_x=1.226$ Mg m^{-3}, MoKα radiation (graphite crystal monochromator, $\lambda=0.71073$), $\mu=0.169$ mm^{-1}, $F(000)=864$, $T=299(2)$. Absolute structure parameter = 0.00. Final conventional $R=0.0445$ (for 1577 $F_o>4$ sigma (F_o)), and $wR_2=0.0532$ (for all 3145 reflections), and $w=1/[s^2(F_o^2)+(0.0082P)^2]$ where $P=(F_o^2+2F_c^2)/3$. Total number of parameters 257. CCDC 192749 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).