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Synthesis of spiro-annelated pyroglutamides by the Ugi reaction

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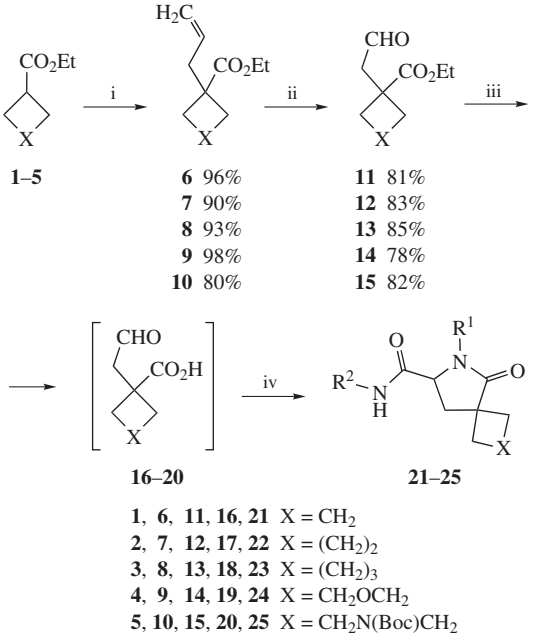
Three component Ugi reaction between 1-(2-oxoethyl)cycloalkanecarboxylic acids, amines and isocyanides affords spirocyclic N-substituted 5-carbamoyl-2-pyrrolidones.

Spirocyclic fragment is not uncommon among low-molecular biologically active compounds. For example, minalrestat is used for the treatment of diabetes,[1] RS-86 is a neurological drug,[2] tiaspirone is an anti-migraine drug,[3] buspirone is a drug for attention deficit – hyperactivity disorder treatment.[4] γ-Lactam cycle is the fundamental structural moiety within a wide class of drugs called 'racetams' which exhibit neurophysiological activity. N-Substituted γ-lactams are known as nootropic drugs (piracetam,[5] aniracetam[6]). Compounds of the same class with various substituents in the pyrrolidone cycle possess anticonvulsant and antiepileptic properties (seletracetam[7]). Therefore, compounds based on spirocyclic N-substituted γ-lactams can be of a great interest in the sight of their potential biological activity.

The Ugi reaction[8] of oxo acids with amines and isocyanides results in a lactam formation thus affording various classes of aromatic,[9,10] heteroaromatic[11–13] and aliphatic[10,14–16] compounds.

However, application of oxo acids in the Ugi reaction, leading to spirocyclic products, have not been explored. Herein, we synthesized new γ-oxo acids **16**–**20** of 1-(2-oxoethyl)cycloalkanecarboxylic type and used them as bifunctional reactants in the Ugi reaction (Scheme 1). Reaction of these compounds under the Ugi conditions gave 5-carboxamide-substituted spirocyclic γ-lactams **21**–**25** which can be regarded as spiro-annelated pyroglutamic acid derivatives.



Scheme 1 *Reagents and conditions*: i, LDA, allyl bromide, THF, –60 °C; ii, $NaIO_4$, OsO_4 (cat.), 2,6-lutidine, dioxane, water, room temperature; iii, $LiOH·H_2O$, THF, water; iv, R^1NH_2, $R^2N^+{\equiv}C^-$, EtOH, 60 °C.

Table 1 Yields of products **21**–**25**.

Compound	R^1	R^2	Yield (%)
21a	Pr^i	Bu^t	67
21b	$MeO(CH_2)_2$	Bu^t	70
21c	$MeO(CH_2)_2$	2,6-$Me_2C_6H_3$	73
21d	cyclopropylmethyl	4-ClC_6H_4	72
21e	Bu^i	4-ClC_6H_4	83
22a	(benzo[*d*][1,3]dioxol-5-yl)methyl	Bu^t	68
22b	3,4-$Me_2C_6H_3CH_2$	Bu^t	71
22c	4-Cl-3-MeC_6H_3	$Me_2CH(CH_2)_2$	69
22d	Bu^i	4-$FC_6H_4CH_2$	72
22e	3-ClC_6H_4	4-$FC_6H_4CH_2$	82
23a	3,4-$Me_2C_6H_3CH_2$	Bu^t	82
23b	3,4-$F_2C_6H_4$	Bu^t	92
23c	3,4-$F_2C_6H_4$	2,6-$Me_2C_6H_3$	87
24a	4-$MeSC_6H_4CH_2$	Bu^t	68
24b	4-Cl-3-$FC_6H_3CH_2$	Bu^t	82
24c	4-$MeOC_6H_4$	$Me_2CH(CH_2)_2$	78
24d	cyclopropylmethyl	3-$MeC_6H_4CH_2$	67
25a	$MeO(CH_2)_2$	Bu^t	59
25b	(3-pyridyl)methyl	Bu^t	73
25c	Ph	Bu^t	69
25d	$MeO(CH_2)_2$	2,6-$Me_2C_6H_3$	78
25e	(3-pyridyl)methyl	2,6-$Me_2C_6H_3$	89
25f	Ph	2,6-$Me_2C_6H_3$	75

Synthesis of compounds **6**–**10** and **11**–**15** was described earlier.[17] Ethyl esters **11**–**15** were hydrolyzed under mild conditions, using $LiOH·H_2O$ in aqueous THF media. Due to their instability, oxo acids **16**–**20** were immediately introduced into the Ugi reaction with primary amines and isocyanides (12–20 h, TLC control).[†] Yields of the target products **21**–**25** were 59–92% (Table 1).

[†] *General procedure*. Oxo ester **11**–**15** (10 mmol) was dissolved in THF (50 ml). Solution of $LiOH·H_2O$ (15 mmol) in 20 ml of water was added dropwise at 5–10 °C. After stirring at room temperature (3–8 h, TLC control) the mixture was concentrated to approximately quarter of volume, diluted with 50 ml of water and washed with Et_2O (3×30 ml). The water layer was acidified with 5% H_2SO_4 to pH 5, the product was extracted with Et_2O (3×30 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oxo acids were unstable and were immediately processed further. Primary amine (0.55 mmol) and oxo acid (0.50 mmol) were dissolved in EtOH (3.0 ml). Isocyanide (0.55 mmol) was added and the reaction mixture was stirred at 60–65 °C for 12 h, then evaporated *in vacuo*. The residue was dissolved in EtOAc (3 ml) and treated with 5 ml of saturated aqueous $NaHCO_3$, the organic layer was separated, the aqueous one was extracted with EtOAc (2×2 ml). The combined organic extracts were washed with water (2×5 ml), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was treated with 10% EtOAc in Et_2O (to cause crystallization of the product), or purified by chromatography (silica gel, EtOAc–hexane, 1 : 20 → 1 : 10). For characteristics of the products, see Online Supplementary Materials.

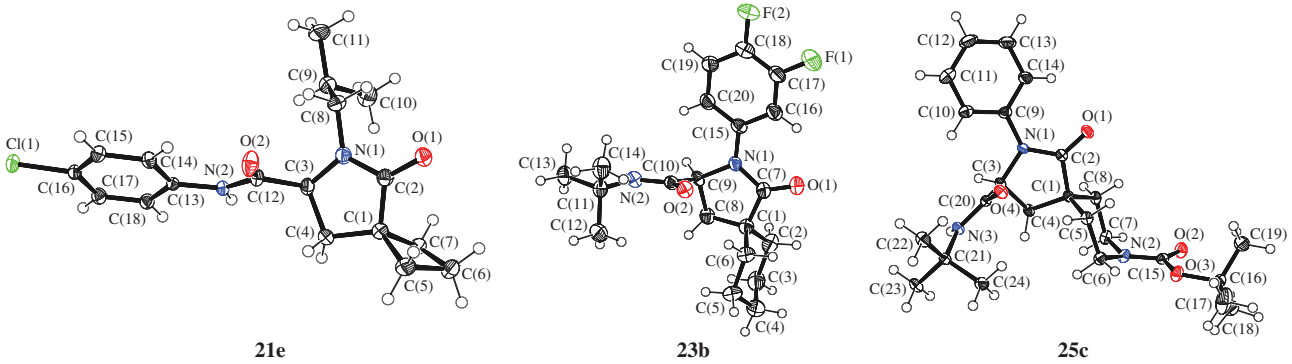


Figure 1 General view of the molecules **21e**, **23b** and **25c**.

After crystallization of compounds **21e**, **23b** and **25c**‡ from acetonitrile, the crystals of a suitable shape were obtained. The results of X-ray diffraction analysis proving the supposed structures of the target products are presented in Figure 1.§

Thus, three component Ugi reaction employing the γ-oxoacids, amines and isocyanides led to a series of previously undescribed spirocyclic N-substituted γ-lactams **21**–**25** in good yields.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.020.

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‡ N-*(4-Chlorophenyl)-6-isobutyl-5-oxo-6-azaspiro[3.4]octane-7-carboxamide* **21e**. Yield 83%, beige solid, mp 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.54 (d, 2H, *J* 8.8 Hz), 7.30 (d, 2H, *J* 8.8 Hz), 4.12 (dd, 1H, *J* 4.0 and 8.0 Hz), 3.62 (dd, 1H, *J* 13.6 and 8.8 Hz), 2.76 (dd, 1H, *J* 13.6 and 5.6 Hz), 2.57 (dd, 1H, *J* 13.6 and 8.8 Hz), 2.49 (m, 2H), 2.32 (dd, 1H, *J* 13.6 and 6.8 Hz), 2.00 (m, 5H), 0.92 (d, 3H, *J* 6.8 Hz), 0.83 (d, 3H, *J* 6.8 Hz). MS (ESI), *m/z*: 335.8 $[M+H]^+$.

N-*(*tert*-Butyl)-2-(3,4-difluorophenyl)-1-oxo-2-azaspiro[4.5]decane-3-carboxamide* **23b**. Yield 92%, white solid, mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (m, 1H), 7.15 (m, 2H), 5.35 (s, 1H), 4.39 (dd, 1H, *J* 8.8 and 6.4 Hz), 2.52 (dd, 1H, *J* 13.6 and 8.8 Hz), 2.01 (dd, 1H, *J* 13.6 and 6.4 Hz), 1.70 (m, 6H), 1.49 (m, 1H), 1.36 (m, 3H), 1.22 (s, 9H). MS (ESI), *m/z*: 365.6 $[M+H]^+$.

tert-*Butyl 3-(*N-tert-*butylcarbamoyl)-1-oxo-2-phenyl-2,8-diazaspiro[4.5]decane-8-carboxylate* **25c**. Yield 62%, beige solid, mp > 200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 2H, *J* 8.0 Hz), 7.40 (t, 2H, *J* 8.4 Hz), 7.22 (t, 1H, *J* 7.2 Hz), 5.38 (s, 1H), 4.53 (m, 1H), 4.04 (m, 2H), 3.03 (m, 2H), 2.52 (m, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.89 (m, 1H), 1.65 (m, 2H), 1.58 (m, 1H), 1.48 (s, 9H), 1.16 (s, 1H). MS (ESI), *m/z*: 430.8 $[M+H]^+$.

§ All measurements were performed on a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71073 Å]. All calculations were performed using SHELXTL 5.1.[18]

Crystal data for **21e**. Crystals ($C_{18}H_{23}ClN_2O_2$, *M* = 334.83) are monoclinic, space group $P2_1/c$, at 100(2) K: *a* = 14.0887(9), *b* = 11.3599(7) and *c* = 10.9088(7) Å, β = 101.4250(10)°, *V* = 1711.32(19) Å^3, *Z* = 4, d_{calc} = 1.300 g cm^{-3}, μ(MoKα) = 0.235 cm^{-1}, *F*(000) = 712. 14336 reflections were measured ($2\theta < 58°$), from which 4558 are independent (R_{int} = = 0.0286), wR_2 = 0.1820 and GOF = 1.056 for all independent reflections [R_1 = 0.0642 for observed reflections with $I > 2\sigma(I)$].

Crystal data for **23b**. Crystals ($C_{20}H_{26}F_2N_2O_2$, *M* = 364.43) are monoclinic, space group $P2_1$, at 100(2) K: *a* = 9.4469(6), *b* = 17.1418(10) and *c* = 11.7537(7) Å, β = 92.0030(10)°, *V* = 1902.2(2) Å^3, *Z* = 4, d_{calc} = = 1.273 g cm^{-3}, μ(MoKα) = 0.095 cm^{-1}, *F*(000) = 776. 15009 reflections were measured ($2\theta < 52°$), from which 3852 are independent (R_{int} = = 0.0365), wR_2 = 0.2233 and GOF = 1.003 for all independent reflections [R_1 = 0.0755 for observed reflections with $I > 2\sigma(I)$].

Crystal data for **25c**. Crystals ($C_{24}H_{35}N_3O_4$, *M* = 429.55) are monoclinic, space group $P2_1/c$, at 100(2) K: *a* = 19.8264(11), *b* = 11.4163(7) and *c* = 10.5796(6) Å, β = 97.9730(10)°, *V* = 2371.5(2) Å^3, *Z* = 4, d_{calc} = = 1.203 g cm^{-3}, μ(MoKα) = 0.082 cm^{-1}, *F*(000) = 928. 19023 reflections were measured ($2\theta < 58°$), from which 6288 are independent (R_{int} = = 0.0281), wR_2 = 0.1101 and GOF = 1.015 for all independent reflections [R_1 = 0.0408 for observed reflections with $I > 2\sigma(I)$].

CCDC 918243–918245 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.