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Synthesis of tetrazole-substituted spirocyclic γ-lactams by one-pot azido-Ugi reaction–cyclization

Vasiliy Yu. Stolyarenko,* Anatoliy A. Evdokimov and Vladimir I. Shishkin

Moscow State University of Radioelectronics, Engineering and Automation, 119454 Moscow, Russian Federation. Fax: +7 495 433 4688; e-mail: vstolyarenko@gmail.com

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1-Ethoxycarbonyl-1-(2-oxoethyl)cycloalkanes in the azido-Ugi reaction with primary amines, isocyanides and TMS-N_3 afford 3-(tetrazol-5-yl)-2-azaspiro[4.*n*]alkan-1-ones.

Spirocyclic fragments are present in various low-molecular biologically active compounds. In particular, γ-lactam moiety is the common structural unit for 'racetames' – the large class of nootropic compounds. Therefore, compounds containing such spirocyclic N-substituted γ-lactams are of a great interest due to their potential biological activity.

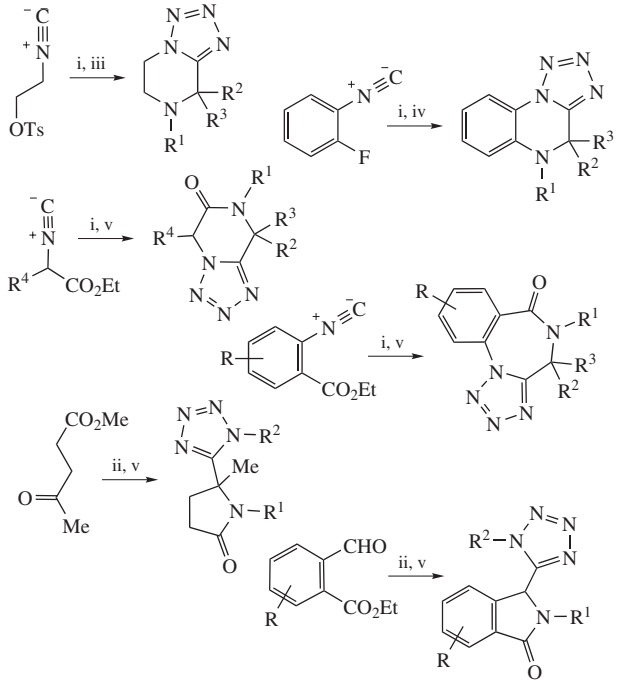
Chemical modification of products of isocyanide-based multicomponent reactions (including reactions involving chiral auxilarities[1]), especially their subsequent cyclization is one of the most employed synthetic ways to such structures in the current medicinal chemistry.[2] Combination of these two steps allows obtaining various heterocyclic products with high molecular diversity.[3–8] In particular, using hydrazoic acid instead of carboxylic acid in the classic Ugi reaction (usually generated *in situ* from TMS-azide and corresponding alcohol) gives 1,5-disubstituted tetrazoles[9,10] that are conformational mimetics of *cis*-amide group.[11,12]

The azido-Ugi reaction with the usage of bifunctional reactants provides synthetic approaches to various classes of heterocyclic compounds: piperazinone–tetrazoles,[10] azepine–tetrazoles,[13,14] benzdiazepine–tetrazoles,[15] quinoxaline–tetrazoles[16] and tetrazole-substituted γ-lactams[17] (Scheme 1). However, to our knowledge there are no literature examples describing synthesis of tetrazole-substituted spirocyclic γ-lactams.

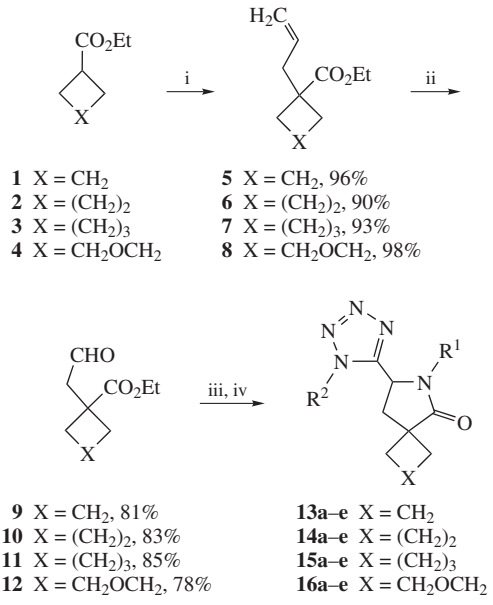
This work describes an extension of such a trend towards a special family of bifunctional reactants (Scheme 2). γ-Oxo esters **9**–**12** having geminal CO_2Et and CH_2CHO fragments at saturated cycle were readily accessed from (oxa)cycloalkanecarboxylates **1**–**4**. Subjection of oxo esters **9**–**12** to the azido-Ugi reaction followed by intramolecular amide bond formation gave 5-tetrazole substituted spirocyclic γ-lactams **13**–**16**. This transformation was based on the recent example describing subsequent steps which were performed as a one-pot procedure employing methyl levulinate.[17]

Synthesis of the target compounds **13**–**16** was performed according to Scheme 2 (R^1 and R^2 are specified in Table 1).

In a typical experiment, cyclic esters **1**–**4** were alkylated with allyl bromide.† Allylic derivatives **5**–**8** were oxidized with sodium periodate in the presence of catalytic amounts of OsO_4.‡ The obtained γ-oxo esters **9**–**12** were introduced into azido-Ugi reaction with equimolar amounts of primary amines and isocyanides (8–12 h, TLC control), followed by intramolecular amide bond formation.§ Yields of the target compounds were 50–72% (Table 1).



Scheme 1 Various examples of azido-Ugi–cyclization employing bifunctional reagents. *Reagents and conditions*: i, R^1NH_2, $R^2C(O)R^3$, TMS-N_3, MeOH; ii, R^1NH_2, $R^2N^+{\equiv}C^-$, TMS-N_3, MeOH; iii, S_N2; iv, S_NAr; v, cyclization.



1 X = CH_2
2 X = $(CH_2)_2$
3 X = $(CH_2)_3$
4 X = CH_2OCH_2

5 X = CH_2, 96%
6 X = $(CH_2)_2$, 90%
7 X = $(CH_2)_3$, 93%
8 X = CH_2OCH_2, 98%

9 X = CH_2, 81%
10 X = $(CH_2)_2$, 83%
11 X = $(CH_2)_3$, 85%
12 X = CH_2OCH_2, 78%

13a–e X = CH_2
14a–e X = $(CH_2)_2$
15a–e X = $(CH_2)_3$
16a–e X = CH_2OCH_2

Scheme 2 *Reagents and conditions*: i, LDA, allyl bromide, THF, –60 °C; ii, $NaIO_4$, OsO_4 (cat.), 2,6-lutidine, dioxane, water, room temperature; iii, R^1NH_2, $R^2N^+{\equiv}C^-$, TMS-N_3, EtOH; iv, 10% TFA in DCE, 70–75 °C.

Table 1 Compounds **13–16**.

Compound	R^1	R^2	Yield (%)
13a	Cyclopropyl	2-Methoxyethyl	52
13b	4-Chlorophenyl	2-Methoxyethyl	55
13c	3,4-Dimethylbenzyl	2-Methoxyethyl	59
13d	Cyclopropyl	Ph	65
13e	*p*-Tolyl	Ph	67
14a	Bu^i	Bu^t	56
14b	4-Methylsulfanylbenzyl	Bu^t	72
14c	2-(2-Methoxyphenoxy)ethyl	4-Fluorobenzyl	56
14d	Bu^i	4-Fluorobenzyl	51
14e	4-Methylsulfanylbenzyl	4-Fluorobenzyl	65
15a	4-Fluorophenyl	Bu^t	52
15b	2-(2-Pyridyl)ethyl	Bu^t	58
15c	4-Fluorophenyl	2-Methoxyethyl	50
15d	4-Methylbenzyl	2-Methoxyethyl	58
15e	2-(2-Pyridyl)ethyl	3-Methoxybenzyl	50
16a	Cyclopropylmethyl	3-Fluorobenzyl	55
16b	4-Bromo-3-methylphenyl	3-Fluorobenzyl	64
16c	2-(1*H*-imidazol-4-yl)ethyl	3-Fluorobenzyl	63
16d	4-Bromo-3-methylphenyl	2-Methoxybenzyl	59
16e	2-(1*H*-imidazol-4-yl)ethyl	2-Methoxybenzyl	62

After crystallization of compounds **13e** and **16d** from acetonitrile, the crystals of a suitable shape were obtained; the results of X-ray diffraction analysis are presented in Figure 1.¶

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.03.020.

† *Allylation of cyclic esters* **1–4** *(general procedure)*. To a solution of LDA (freshly prepared from 130 mmol of diisopropylamine and 130 mmol of 2.5 M BuLi) in 90 ml of absolute THF at –60 °C, 100 mmol of ester **1** was slowly added. The resulted solution was stirred at –60 °C for 30 min, then 130 mmol of allyl bromide was added dropwise keeping temperature below –55 °C. Stirring was continued at this temperature for 40 min, then the reaction mixture was allowed to reach room temperature within 4–6 h. Concentrated NH_4Cl solution (75 ml) was slowly added, the organic layer was separated and the water layer was extracted with EtOAc (3×50 ml); the combined organic extracts were washed with 50 ml 10% H_2SO_4, water (2×20 ml), brine (2×20 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* at 60 °C, and the residue was purified on silica gel (hexane : EtOAc = 6 : 1). For characteristics of compounds **5–8**, see Online Supplementary Materials.

‡ *Oxidation of compounds* **5–8** *(general procedure)*. To a well-stirred solution of 100 mmol of allylic compound **5–8** and 200 mmol of 2,6-lutidine in 300 ml of dioxane and 30 ml of water, 0.5 mmol of OsO_4 (2.5% solution in absolute Bu^{t}OH) was added. After 15 min, 400 mmol of sodium periodate was added. The mixture was stirred for 8–10 h, then diluted with 500 ml of EtOAc. Inorganic precipitate was filtered off, the filtrate was washed with water (3×300 ml), 10% H_2SO_4 (2×50 ml), saturated aqueous $Na_2S_2O_3$ solution (4×50 ml) and dried with Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified on silica gel (hexane : EtOAc = = 4 : 1). For characteristics of compounds **9–12**, see Online Supplementary Materials.

§ *Azido-Ugi reaction–one-pot cyclization (general procedure)*. Primary amine (0.55 mmol), oxo ester **9–12** (0.50 mmol) and TMS-N_3 (0.55 mmol) were dissolved in EtOH (3.0 ml) in a vial. Isocyanide (0.60 mmol) was added and the mixture was stirred at room temperature for 12 h, then evaporated *in vacuo*. Subsequently, 10% TFA solution in DCE (3.0 ml) was added and the reaction mixture was heated at 70–75 °C for 8–10 h. The mixture was treated with saturated aqueous K_2CO_3, the organic layer was separated, the aqueous one was extracted with EtOAc (2×2ml). The combined organic extracts were washed with water (2×5 ml). The organic layer was dried over Na_2SO_4 and then concentrated *in vacuo*. The residue was treated with 10% EtOAc in Et_2O (to cause crystallization of the product) or purified on silica gel (EtOAc : hexane = 1 : 10 → 1 : 2). For characteristics of compounds **13–16**, see Online Supplementary Materials.

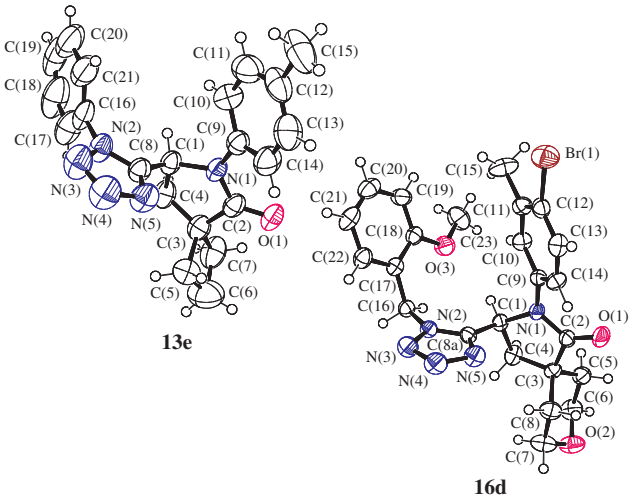


Figure 1 General view of the molecules of **13e** and **16d**.

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¶ 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 **13e**. Crystals ($C_{21}H_{21}N_5O$, M = 359.43) are monoclinic, space group $C2/c$, at 296(2) K: a = 22.007(2), b = 11.2333(13) and c = = 18.695(2) Å, β = 123.621(2)°, V = 3848.6(8) Å^3, Z = 8, d_{calc} = 1.241 g cm^{-3}, μ(MoKα) = 0.080 cm^{-1}, F(000) = 1520. 13 186 reflections were measured (2θ < 58°), from which 4197 are independent (R_{int} = 0.0817), wR_2 = = 0.1575 and GOF = 1.008 for all independent reflections [R_1 = 0.0509 for 2712 observed reflections with $I > 2\sigma(I)$].

Crystal data for **16d**. Crystals ($C_{24}H_{26}BrN_5O_3$, M = 512.41) are triclinic, space group $P\bar{1}$, at 293(2) K: a = 6.2629(9), b = 12.8858(17) and c = = 14.605(2) Å, α = 94.657(2)°, β = 91.384(2)°, γ = 90.916(2)°, V = = 1174.3(3) Å^3, Z = 2, d_{calc} = 1.449 g cm^{-3}, μ(MoKα) = 1.786 cm^{-1}, F(000) = 528. 12 724 reflections were measured (2θ < 58°), from which 5662 are independent (R_{int} = 0.0642), wR_2 = 0.1147 and GOF = 0.965 for all independent reflections [R_1 = 0.0464 for 2758 observed reflections with $I > 2\sigma(I)$].

CCDC 918594 and 918596 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.