Synthesis of spiro-annelated γ-lactams by isocyanide-based multicomponent reactions involving *gem*-disubstituted bifunctional reagents

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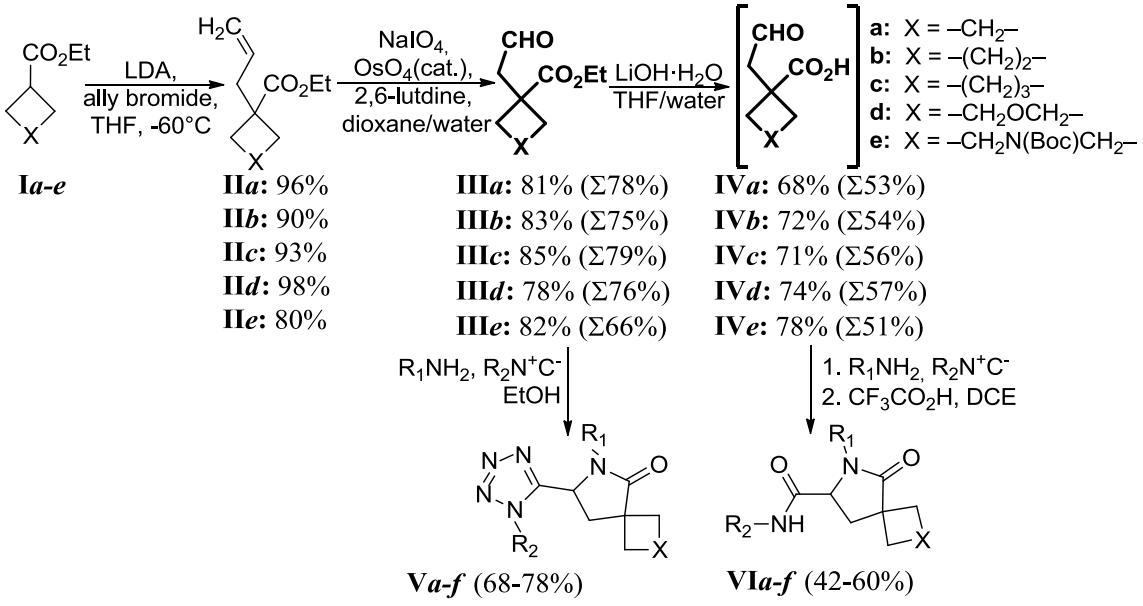
The new bifunctional *gem*-disubstituted alicyclic compounds **III*a-e*** and **IV*a-e*** were synthesized in several steps involving alkylation with allyl bromide and oxidative cleavage of resulting alkene. *Gem*-disubstituted oxo-esters **III*a-e*** were introduced into *azido*-Ugi reaction followed by one-pot intramolecular bond formation to afford 3-(tetrazol-5-yl)-2-azaspiro[4.*n*]alkan-1-ones **V**. The three component Ugi reaction with isocyanides, primary amines and 1-(2-oxoethyl)cycloalkanecarboxylic acids **IV*a-e*** affords spirocyclic *N*-substituted pyroglutamides **VI**.

Spirocyclic fragments are presented in various low-molecular biologically active compounds. In particular, γ-lactame moiety is the common structural unit for "racetames" – the large class of nootropic agents. Therefore, substances containing 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 (IMCR), especially their subsequent cyclization is one of the most employed synthetic way leading to such structures in the current medicinal chemistry. Combination of these two steps allows to obtain various heterocyclic products with high molecular diversity [1–6]. The goal of research was to work out a strategy for design and synthesis of unique bifunctional reagents bearing such specific molecular topology that allows to produce in IMCR spiro-annelated products. ω-oxoesters were chosen as bifunctional reagents for *azido*-IMCR followed by intramolecular amide bond formation giving 5-tetrazole substituted spirocyclic γ-lactams.

In our original method[7] at first cyclic esters **I*a-e*** were alkylated with allyl bromide in THF at -65°C in the presence of LDA. Allylic derivatives **II*a-e*** were oxidized by sodium periodate in presence of catalytic amounts of OsO_4. The obtained ethyl esters of cyclic ω-oxoacids **III*a-e*** were introduced into *azido*-Ugi reaction followed by intramolecular amide bond formation (Scheme 1).



I*a-e* **II*a*:** 96% **II*b*:** 90% **II*c*:** 93% **II*d*:** 98% **II*e*:** 80%

III*a*: 81% (Σ78%) **III*b*:** 83% (Σ75%) **III*c*:** 85% (Σ79%) **III*d*:** 78% (Σ76%) **III*e*:** 82% (Σ66%)

IV*a*: 68% (Σ53%) **IV*b*:** 72% (Σ54%) **IV*c*:** 71% (Σ56%) **IV*d*:** 74% (Σ57%) **IV*e*:** 78% (Σ51%)

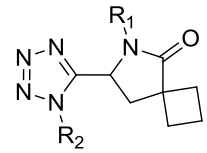
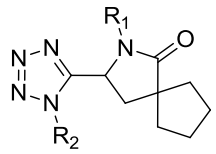
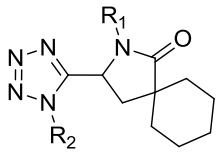
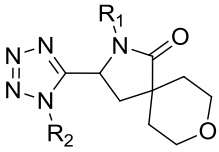
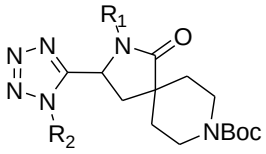
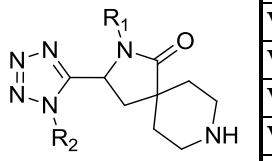
V*a-f* (68-78%) **VI*a-f*** (42-60%)

Scheme 1.

The first step of this *one-pot* procedure (*azido*-Ugi reaction) was performed in absolute ethanol with equimolar amounts of primary amines and isocyanides (8-12h, TLC control). Solvent was removed *in vacuo*, the residue was dissolved (or suspended) in 10% TFA solution in DCE and heated at 80-85°C for 16-20h. Reactions were cooled down to the room temperature, TFA was neutralized by 10% aqueous Na_2CO_3. Yields of the target compounds were 59-72%.

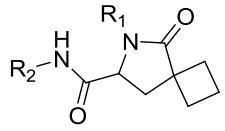
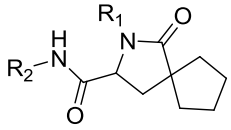
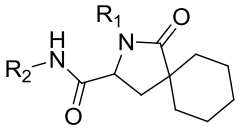
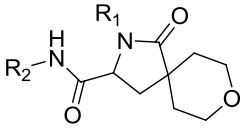
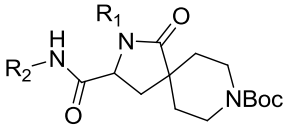
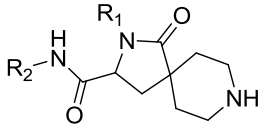
According to this procedure the diverse set of novel spirocyclic compounds (see table 1) was synthesized and characterized by 1H-NMR spectra and LC/MS.

Table 1.

	№	R_1	R_2	Yiled (%)
	**V*a*{1}**	cyclopropyl	(2-methoxy)ethyl	59
	V*a*{2}	*p*-chlorophenyl	(2-methoxy)ethyl	56
	V*a*{3}	3,4-dimethylbenzyl	(2-methoxy)ethyl	77
	V*a*{4}	cyclopropyl	phenyl	64
	V*a*{5}	*p*-methylphenyl	phenyl	72
	**V*b*{1}**	isobutyl	*tert*-butyl	62
	V*b*{2}	*n*-methylsulphanylbenzyl	*tert*-butyl	69
	V*b*{3}	2-(*o*-methoxyphenyloxy)-ethyl	*tert*-butyl	60
	V*b*{4}	isobutyl	*p*-fluorobenzyl	63
	V*b*{5}	*p*-methylsulphanylbenzyl	*p*-fluorobenzyl	67
	V*b*{6}	2-(*o*-methoxyphenyloxy)-ethyl	*p*-fluorobenzyl	53
	V*b*{7}	isobutyl	*p*-fluorobenzyl	51
	V*b*{8}	isobutyl	phenyl	58
	**V*c*{1}**	*p*-fluorophenyl	*tert*-butyl	72
	V*c*{2}	*p*-methylbenzyl	*tert*-butyl	67
	V*c*{3}	(thiophene-2-yl)methyl	*tert*-butyl	51
	V*c*{4}	*p*-fluorophenyl	(2-methoxy)ethyl	62
	V*c*{5}	*p*-methylbenzyl	(2-methoxy)ethyl	64
	V*c*{6}	(thiophene-2-yl)methyl	(2-methoxy)ethyl	63
	V*c*{7}	*p*-methylbenzyl	*m*-methoxylbenzyl	67
	V*c*{8}	2-(pyridine-4-yl)ethyl	*m*-methoxylbenzyl	64
	**V*d*{1}**	cyclopropylmethyl	*m*-fluorobenzyl	78
	V*d*{2}	4-bromo-3-methylphenyl	*m*-fluorobenzyl	69
	V*d*{3}	2-(1*H*-imidazole-4-yl)ethyl	*m*-fluorobenzyl	55
	V*d*{4}	4-bromo-3-methylphenyl	*o*-methoxylbenzyl	65
	V*d*{5}	2-(1*H*-imidazole-4-yl)ethyl	*o*-methoxylbenzyl	60
	V*d*{6}	3,4-dichlorobenzyl	*o*-methoxylbenzyl	79
	**V*e*{1}**	2,2,2-trifluoroethyl	(2-methoxy)ethyl	58
	V*e*{2}	*m*-chlorophenyl	(2-methoxy)ethyl	62
	V*e*{3}	indane-5-yl	(2-methoxy)ethyl	64
	V*e*{4}	*p*-methylbenzyl	*p*-fluorobenzyl	71
	V*e*{5}	(thiophene-2-yl)methyl	*p*-fluorobenzyl	69
	V*e*{6}	cyclopropyl	*p*-chlorophenyl	73
	**V*f*{1}**	2,2,2-trifluoroethyl	(2-methoxy)ethyl	54
	V*f*{2}	*m*-chlorophenyl	(2-methoxy)ethyl	48
	V*f*{3}	indane-5-yl	(2-methoxy)ethyl	52
	V*f*{4}	*p*-methylbenzyl	*p*-fluorobenzyl	55
	V*f*{5}	(thiophene-2-yl)methyl	*p*-fluorobenzyl	50
	V*f*{6}	cyclopropyl	*p*-chlorophenyl	58

The obtained ethyl esters of cyclic *ω*-oxoacids **III*a-e*** were hydrolyzed in mild conditions using $LiOH \cdot H_2O$ in aqueous THF media. Due to their instability, isolated *ω*-oxoacids **VI*a-e*** were immediately introduced into Ugi reaction with equimolar amounts of primary amines and isocyanides (12-20h, TLC control). Yields of the target spiro-annelated γ-lactams were 59-92%[8]. According to this method various novel spirocyclic compounds with amide fragment (see Table 2) were synthesized and characterized by ^{1}H-NMR spectra and LC/MS.

Table 2.

	№	R_1	R_2	Yield (%)
	**V*a*{1}**	*i*-propyl	*tert*-butyl	67
	V*a*{2}	2-methoxyethyl	*tert*-butyl	70
	V*a*{3}	2-methoxyethyl	2,6-dimethylphenyl	73
	V*a*{4}	cyclopropylmethyl	*p*-chlorophenyl	72
	V*a*{5}	isobutyl	*p*-chlorophenyl	83
	**V*b*{1}**	piperonyl	*tert*-butyl	68
	V*b*{2}	2,4-dimethylbenzyl	*tert*-butyl	71
	V*b*{3}	4-chloro 3-methyl-phenyl	isoamyl	69
	V*b*{4}	isobutyl	*p*-fluorobenzyl	72
	V*b*{5}	*m*-chlorophenyl	*p*-fluorobenzyl	82
	**V*c*{1}**	2,4-dimethylbenzyl	*tert*-butyl	82
	V*c*{2}	3,4-difluorophenyl	*tert*-butyl	92
	V*c*{3}	2,6-dimethylphenyl	2,6-dimethylphenyl	87
	**V*d*{1}**	*p*-(methylthio)benzyl	*tert*-butyl	68
	V*d*{2}	3-chloro-4-fluorobenzyl	*tert*-butyl	82
	V*d*{3}	*p*-methoxyphenyl	isoamyl	78
	V*d*{4}	cyclopropylmethyl	*m*-methylbenzyl	67
	**V*e*{1}**	2-methoxyethyl	*tert*-butyl	59
	V*e*{2}	(pyridine-3-yl)methyl	*tert*-butyl	73
	V*e*{3}	phenyl	*tert*-butyl	69
	V*e*{4}	2-methoxyethyl	2,6-dimethylphenyl	78
	V*e*{5}	(pyridine-3-yl)methyl	2,6-dimethylphenyl	89
	V*e*{6}	phenyl	2,6-dimethylphenyl	75
	V*e*{7}	cyclopropyl	*p*-chlorophenyl	72
	**V*f*{1}**	2-methoxyethyl	*tert*-butyl	34
	V*f*{2}	(pyridine-3-yl)methyl	*tert*-butyl	36
	V*f*{3}	phenyl	*tert*-butyl	48
	V*f*{4}	2-methoxyethyl	2,6-dimethylphenyl	39
	V*f*{5}	(pyridine-3-yl)methyl	2,6-dimethylphenyl	31
	V*f*{6}	phenyl	2,6-dimethylphenyl	42
	V*f*{7}	cyclopropyl	*p*-chlorophenyl	51

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