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ORIGINAL PAPER

Synthesis of 2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamides from 2-acetylcyclohexanone via palladium-catalysed aminocarbonylation

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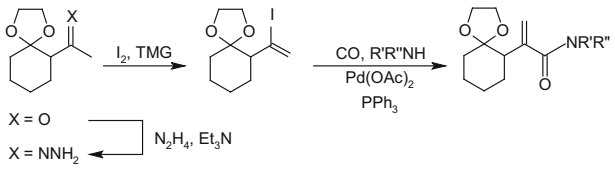
Abstract 6-(1-Iodovinyl)-1,4-dioxaspiro[4.5]decane, an iodoalkene obtained from 2-acetylcyclohexanone via ethylene ketal formation, hydrazone formation and iodination, was aminocarbonylated in the presence of a palladium-phosphine precatalyst. Systematic investigations revealed that 2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamides can be obtained in high yields via palladium-catalysed aminocarbonylation. The influence of the amine nucleophiles and of the reaction conditions on the isolated yields was investigated.

Graphical abstract



Keywords Carbonylation · Carbon monoxide · Amine nucleophile · Palladium catalyst · Iodoalkene

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Introduction

Since the early discovery of palladium-catalysed alkoxy- and aminocarbonylation of aryl halides [1], hundreds of aryl esters and amides were synthesised. The great variety of primary and secondary amines used as *N*-nucleophiles allowed for the synthesis of a countless variety of carboxylic acid derivatives. The synthetic potential of these carbonylation reactions was illustrated using several aryl halides and their synthetic surrogates, aryl triflates. Simple model compounds and substrates of practical importance were investigated [2–6]. Its industrial importance and application have been recently reviewed [7, 8]. Moreover, the intramolecular alkoxy- and aminocarbonylations resulted in the formation of lactones and lactames, respectively [9].

As analogues of aryl halides, iodo- and bromo-alkenes were also synthesised and widely used as substrates [5, 6]. Besides the substrates of direct practical (biological, pharmacological) importance, simple (basic) structures were also investigated with the aim of clearing-up the reaction mechanism and of synthesising new and useful building blocks [10].

As a part of our ongoing research interests on the carbonylation of iodoalkenes, the synthesis of various building blocks was carried out [11–13]. Recently, we turned our attention towards the synthesis of compounds with substituted cyclohexanone backbone.

2-Acetylcyclohexanone is one of the key representatives of β-diketones. Its Schiff base derivatives obtained with diaminoalkanes [14], 2-benzoyl-3-hydroxy-2*H*-indazol obtained with benzohydrazide [15], enolate alkylation [16] and nitrosation [17] products were published. The electrochemically induced Michael reactions of *o*-benzoquinones with 2-acetylcyclohexanone led to the

formation of the corresponding catechols [18]. The double Mannich reaction of 2-acetylcyclohexanone proved to be the key step to the synthesis of pyrazole- and oxazol-fused azatricyclic ring systems [19]. The regioselective reaction of cyanothioacetamide with 2-acetylcyclohexanone resulted in pyridine-2(1*H*)-thione derivatives.

Due to its facile tautomerization [20, 21], 2-acetylcyclohexanone forms enolate complexes with various metals such as Fe(II), Co(II), Ni(II), Cu(II), Cu(I), Zn(II), V(III), V(IV), Cr(III), U(VI) [22–29]. Some of them proved to be active catalyst in C-N and C-O bond formation [23, 25, 26] and Ziegler–Natta polymerisation [27].

In the present study, the synthesis of 2-(1,4-dioxaspiro-[4.5]decan-6-yl)acrylamides from 2-acetylcyclohexanone is reported. To the best of our knowledge, the selective functionalisation of 2-acetylcyclohexanone (or that of compounds with similar structure) in the side chain is unprecedented. Starting from 2-acetylcyclohexanone a high-yielding palladium-catalysed aminocarbonylation of the corresponding iodoalkene was used as a key reaction.

Results and discussion

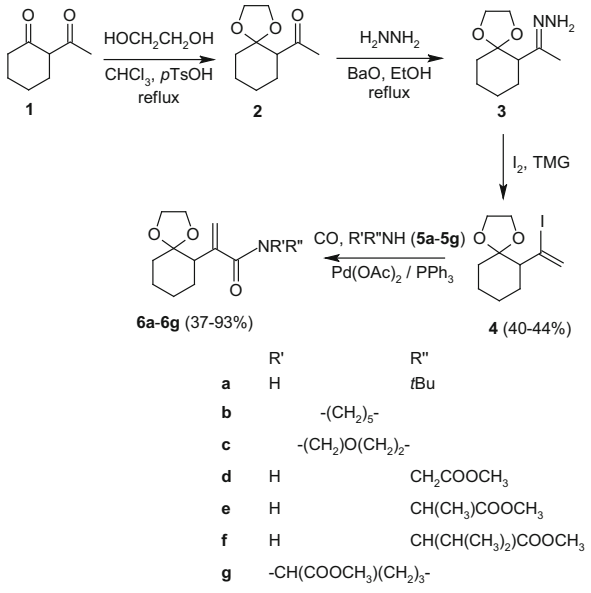
Synthesis of the iodoalkene substrate, 6-(1-iodovinyl)-1,4-dioxaspiro[4.5]decane (4)

2-Acetylcyclohexanone (**1**) was protected at the ring keto functionality as ethylene ketal with the aim to reduce unwanted side reactions in the subsequent reaction with hydrazine (Scheme 1). The reaction was performed with ethylene glycol, in chloroform at reflux and in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst. The target monoketal **2** was isolated from the reaction mixture by column chromatography. However, the formation of **2** (Table 1) was accompanied by the formation of several side products, such as the regioisomeric ketal **2x**, diketal **2y** and surprisingly cyclohexanone ketal **2z** besides an open-chain diketal **2w**. It has to be added that the target compound **2** was isolated and fully characterised, **2x**–**2w** were identified by MS only. Some representative experiments carried out during the optimisation are shown in Table 1.

It can be stated that (1) long reaction times (up to 4 days) are necessary to obtain reasonable conversion; (2) the product ratio is sensitive to the molar ratio of **1** to PTSA (entries 3–5); (3) the highest chemoselectivity towards **2** is 77 % (entries 4, 6); (4) the reaction is scalable to 0.1 mol without decreasing chemoselectivity (entry 6); and (5) the target compound monoketal **2** can be isolated in 40–44 % yields.

The 1,4-dioxaspiro[4.5]decane derivative **2** was then transformed into the corresponding hydrazone **3** in the presence of hydrazine hydrate and barium oxide in ethanol at reflux. Crude **3** was then treated with iodine in the presence of a strong base, TMG (*N*,*N*,*N*′,*N*′-tetramethylguanidine) (Scheme 1). The iodoalkenyl derivative **4** was obtained in 62 % yield (based on **2**). Although the general methodology for the preparation of iodoalkenes from ketones has been known for a long time [30, 31], the optimised reported procedure shows several marked differences with respect to reported ones, such as differences in reaction temperature (hydrazone formation), in using BaO (hydrazone formation), in the amount of base (TMG). Therefore, a complete description of the preparation of **4** is given in the "Experimental" section.

Scheme 1

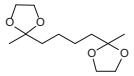


Palladium-catalysed aminocarbonylation of 4

The iodoalkene substrate **4** was aminocarbonylated in the presence of a palladium catalyst formed in situ by the reaction of palladium(II) acetate and two molar equivalents of triphenylphosphine. The reactions were performed in DMF, in the presence of triethylamine as base, at 50 °C, under a balloon of carbon monoxide. The *N*-nucleophiles **5a**–**5g** were used in excess as given in the "Experimental" section (Scheme 1).

It is worth mentioning that the above $Pd(OAc)_2$/2 PR_3-type 'precatalyst' is widely used in various cross-coupling and carbonylation reactions. It serves as a precursor of 'in situ' formed palladium(0)-tertiary phosphine systems. It has been proved by cyclic voltammetry and NMR measurements that palladium(II) is reduced to palladium(0),

Table 1 Product distribution obtained in the ethylene ketal formation from **1**

Entr.	**1** /mmol	PTSA /mmol	Time /h	Conv. /% [a]	Composition of the product mixture /% (isolated yields)[a]				
					 **2**	 **2x**	 **2y**	 **2z**	 **2w**
1	21	0.1	96	82	36 (27)	4	17	16	9
2	21	0.5	96	>99	69 (40)	5	7	12	7
3	35	0.05	40	77	37 (25)	5	28	3	4
4	35	0.6	90	>99	77 (44)	1	9	7	6
5	35	0.8	90	95	65 (40)	3	15	7	5
6 [b]	107	1.3	96	95	75 (42)	3	6	8	3

Reaction conditions: **1**/ethylene glycol = 1/1, chloroform (reflux)

[a] Determined by GC and GC–MS

[b] Described in the "Experimental" section

Table 2 Aminocarbonylation of **4** in the presence of palladium-PPh_3 in situ catalysts

Entr.	*N*	Time/h	Conv.[a]/ %	Isolated yield of **6**
1	**a**	18	>98	51 (**6a**)
2[b]	**a**	10	>98	93 (**6a**)
3	**a**	2	95	80 (**6a**)
4	**b**[c]	21	>98	64 (**6b**)
5[b]	**b**[c]	72	85	67 (**6b**)
6	**c**[c]	72	90	56 (**6c**)
7[b]	**c**[c]	72	85	53 (**6c**)
8	**d**[d]	24	78	47 (**6d**)
9	**e**[d]	25	>98	43 (**6e**)
10	**f**[d]	144	93	41 (**6f**)
11	**g**[d]	144	65	37 (**6g**)

Reaction conditions (unless otherwise stated): 1 mmol of substrate **4**; 0.025 mmol of $Pd(OAc)_2$; 0.05 mmol of PPh_3; 3 mmol of **a**; 0.5 cm^3 of triethylamine; solvent: 10 cm^3 of DMF, reaction temperature: 50 °C; 1 bar CO, n.d.: not determined

[a] Determined by GC and GC–MS (naphthalene as internal standard)

[b] 3 mmol of **4**

[c] Substrate **4**/amine ratio = 1/1.5

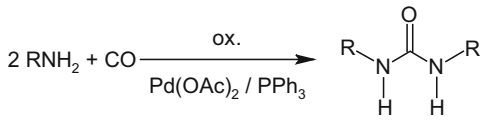
[d] Substrate **4**/amine ratio = 1/1.1, i.e. 1.1 mmol of **d**, **e**, **f** and **g** (as a hydrochloride salt) were used

while one of the two equivalents of phosphine ligands is oxidised [32–34]. In our case, the formation of coordinatively highly unsaturated $Pd(PPh_3)(S)_n$ (S stands for a coordinating solvent (DMF)) complex is supposed, while the 'second' equivalent of PPh_3 is oxidised to triphenylphosphine oxide. Under the aminocarbonylation conditions used, the action of other compounds (amine, carbon monoxide) as reducing agents cannot be excluded.

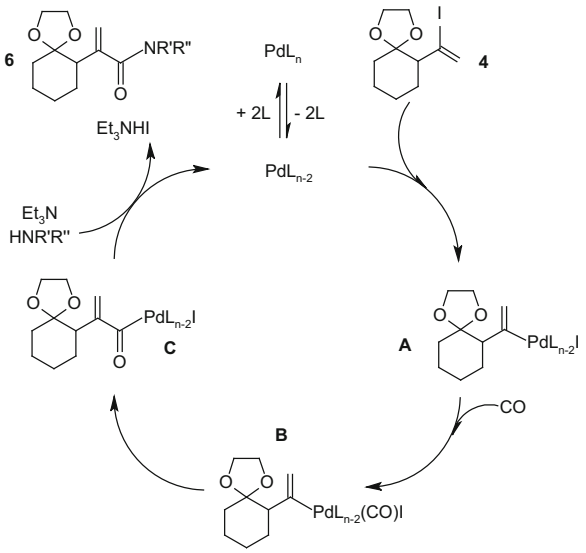
A highly chemoselective reaction was observed in the presence of all *N*-nucleophiles **5a**–**5g** resulting in the formation of the corresponding carboxamide derivative **6a**–**6g** in moderate to high yields. Although the highest conversions were obtained with primary amine **5a** (Table 2, entries 1, 3) and cyclic secondary amines (**5b**, **5c**) (entries 4, 6), all of the amines tested, including amino acid methyl esters (**5d**–**5g**) (entries 8–11), gave satisfactory results. The aminocarbonylations with sterically more bulky *N*-nucleophiles (**5f**, **5g**) needed longer reaction times (entries 10, 11).

Interestingly, the isolated yields increased when practically full conversion was achieved but the reaction time

Scheme 2



Scheme 3



was limited to 2 h (entries 1 and 3). Similarly, scaling-up the reaction resulted in higher isolated yields (entries 1, 2). Thus, when the amount of the substrate **4** to be converted was increased (from the generally used 1 to 3 mmol), higher isolated yields were obtained even if isolation was done at lower conversion (entries 4, 5). These results can be explained taking into account the competitive aminocarbonylation reactions of the reacting nucleophiles giving rise to *N*,*N*′-disubstituted ureas [35, 36] as undesired side products (Scheme 2). Since the nucleophiles are present in excess, prolonged reaction times resulted in the formation of large amount of by-products which made the chromatographic purification of the crude reaction products more difficult.

For comparison, the reactivity of substrates bearing 1-iodovinyl functionalities such as α-iodo-styrene [37, 38] and α-iodoethenyl-naphthalene isomers [39] was related to that of **4** in carbonylation reactions. It can be stated that the reactivity of the above aryl-iodoalkenes, synthesised and used as substrates in our laboratory [35–39], proved to be definitely higher than that of **4**. However, the tolerance towards dioxolane ring makes this reaction valuable since otherwise unobtainable building blocks such as 2-substituted cyclohexanones, chiral propionic amides with cyclohexyl moieties, can be synthesised.

The aminocarbonylation of **4** can be rationalised as follows. Compound **4** undergoes facile oxidative addition to palladium(0) resulting in the palladium(II)-alkenyl intermediate (**A**) (Scheme 3). It has to be noted that the iodo-carbon bond has higher polarizability than the corresponding C(sp^2)-X bonds in its structural analogues such as chloro- and bromo-alkenes. In general, in line with the decreasing carbon-halide bond energy, the rate of the oxidative addition to palladium(0) and consequently the efficiency of carbonylations decrease in the order C-I > C(OTf) ≥ C–Br > C–Cl > C-F [2, 9]. The formation of the complex containing terminal carbonyl ligand (**B**) is followed by carbon monoxide insertion into palladium(II)-alkenyl bond. The highly reactive acyl intermediate (**C**) gives the target carboxamide (**5**) in the product forming (reductive elimination) step, while the coordinatively unsaturated Pd(0) intermediate is re-formed.

Conclusions

The aminocarbonylation of 6-(1-iodovinyl)-1,4-dioxaspiro[4.5]decane **4** provides an easy access to synthetically useful building blocks possessing α,β-unsaturated carboxamide moieties. The target compounds were synthesised via mono(ethyleneketal)-hydrazone-iodoalkene-carboxamide sequence and 2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamides **6a**–**6g** were isolated in yields of practical interest.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with an Agilent Technologies 6890 N gas chromatograph fitted with an HP-1MS capillary column [injector temp. 250 °C; oven: starting temp. 50 °C (hold-time 1 min), heating rate 15 °C min^{-1}, final temp. 320 °C; detector temp. 150 °C; carrier gas: helium (rate: 1.5 cm^3 min^{-1})]. The FT-IR spectra were taken in KBr pellets using an IMPACT 400 spectrometer (Nicolet) applying a DTGS detector in the region of 400–4000 cm^{-1}, the resolution was 4 cm^{-1}. The amount of the samples was ca. 0.5 mg.

The iodoalkene substrate (**4**) was synthesised by the modified Barton procedure [30, 31]. The amine

nucleophiles were purchased from Sigma-Aldrich and were used without further purification.

*1-(1,4-Dioxaspiro[4.5]decan-6-yl)ethanone (**2**)*

In a typical experiment, a mixture of 15.0 g 2-acetylcyclohexanone (107 mmol), 6.64 g, ethylene glycol (107 mmol) and 0.22 g *p*-toluenesulfonic acid (1.3 mmol) in 200 cm^3 chloroform was heated under reflux for 68 h in a Dean-Stark apparatus. The reaction mixture was cooled and then neutralised and washed with 0.3 M aqueous sodium hydroxide (3 × 60 cm^3). The combined organic solution was dried on sodium sulfate and evaporated to dryness. The crude compound was subjected to column chromatography [silicagel 60 (Fluka), 0.035–0.070 mm], acetone/hexane (15/85). Yield: 8.72 g (44 %). The spectral data of **2** are in good agreement with those published previously [40].

*6-(1-Iodovinyl)-1,4-dioxaspiro[4.5]decane (**4**)*

Step 1 8.72 g compound **2** (47.4 mmol), 3.41 g freshly distilled hydrazine hydrate (98 %, 68.2 mmol) and 2.4 g barium oxide (15.6 mmol) were heated in 80 cm^3 refluxing ethanol for 21 h. After completion of the reaction, the mixture was poured onto water and extracted with dichloromethane (3 × 50 cm^3). Then the combined organic phase was washed with water (3 × 100 cm^3) and 50 cm^3 brine, and dried over sodium sulfate. After the evaporation of the solvent, the crude hydrazone derivative **3** was obtained and used in the next step without further purification.

Step 2 to a stirred solution of 20.5 g iodine (80.8 mmol) in 70 cm^3 ether 12.97 g *N*,*N*,*N*′,*N*′-tetramethylguanidine (112.6 mmol) was added at ice bath cooling. To this solution, the etheral solution (50 cm^3) of 7.59 g **3** (38.3 mmol) was added drop-wise at room temperature. The reaction mixture was stirred for 1 h and the precipitated salt was filtered. The solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto 240 cm^3 iced water and extracted with dichloromethane (3 × 50 cm^3). The combined organic layer was washed with 1 N aqueous hydrochloric acid (3 × 50 cm^3), 50 cm^3 water, 5 % aqueous sodium hydrogen carbonate (2 × 50 cm^3), then with 50 cm^3 water, 10 cm^3 saturated aqueous sodium thiosulphate, and water (3 × 50 cm^3) again. The dichloromethane solution was dried on sodium sulfate and evaporated. The highly pure product **4** was used as obtained. In order to avoid its oxidative and photochemical decomposition, **4** has to be kept under argon in refrigerator. Using it in carbonylation reactions, reproducible results can be obtained even after 2 months. No changes in its colour and analytical characteristics were observed within this time interval.

Yield: 10.2 g brownish yellow, viscous oil (62 % based on **2**); $R_f = 0.72$ (15 % acetone/hexane, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): $\delta = 6.25$ (1H, s, =CH), 5.97 (1H, s, =CH), 3.79–4.07 (4H, m, OCH_2), 2.29–2.44 (1H, m, CH), 1.22–1.80 (8H, m, CH_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 129.3$, 110.0, 109.4, 65.1, 65.0, 56.7, 36.8, 32.3, 24.8, 23.6 ppm; IR (KBr): $\bar{\nu} = 1609$ (C=C) cm^{-1}; MS: *m/z* (%) = 294 (M^+), 167 (100), 125 (8), 99 (11), 95 (15), 67 (16).

*Aminocarbonylation of 6-(1-iodovinyl)-1,4-dioxaspiro[4.5]-decane (**4**) in the presence of N-nucleophiles under atmospheric carbon monoxide pressure*

In a typical experiment, 5.6 mg $Pd(OAc)_2$ (0.025 mmol), 13.2 mg triphenylphosphine (0.05 mmol), 294 mg 6-(1-iodovinyl)-1,4-dioxaspiro[4.5]decane (**4**, 1 mmol), amine nucleophile (3 mmol of **5a**/1.5 mmol of **5b** or **5c**/1.1 mmol of **5d**–**5g**) and 0.5 cm^3 triethylamine were dissolved in 10 cm^3 DMF under argon in a 100 cm^3 three-necked flask equipped with a gas inlet, reflux condenser with a balloon (filled with argon) at the top. The atmosphere was changed to carbon monoxide. The reaction was conducted for the given reaction time upon stirring at 50 °C and analysed by GC–MS. The mixture was then concentrated and evaporated to dryness. The residue was dissolved in 20 cm^3 chloroform and washed with water (3 × 20 cm^3). The organic phase was dried over sodium sulfate, filtered, and evaporated to give a crystalline material or a waxy residue. All compounds were subjected to column chromatography (silicagel 60 (Merck), 0.063–0.200 mm), EtOAc/$CHCl_3$ (solvent ratios are specified, vide infra).

N-(tert-Butyl)-2-(1,4-dioxaspiro[4.5]decan-6-yl)-acrylamide (**6a**, $C_{15}H_{25}NO_3$)

Yield: 307 mg (93 %); white solid; m.p.: 123–124 °C; $R_f = 0.44$ (6 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): $\delta = 6.68$ (1H, bs, NH), 5.84 (1H, s, =CH), 5.33 (1H, s, =CH), 3.83–3.97 (4H, m, OCH_2), 2.65–2.73 (1H, m, CH), 1.64–1.83 (6H, m, CH_2), 1.43–1.53 (2H, m, CCH_2), 1.32 (9H, s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.5$, 146.6, 121.4, 110.3, 65.1, 64.4, 50.7, 50.3, 46.9, 36.2, 30.3, 29.4, 28.7, 25.4, 23.7 ppm; IR (KBr): $\bar{\nu} = 3334$ (NH), 1648 (CON), 1620 (C=C) cm^{-1}; MS: *m/z* (%) = 267 (5, M^+), 252 (2), 195 (24), 167 (54), 153 (27), 99 (100), 86 (52).

1-(Piperidin-1-yl)-2-(1,4-dioxaspiro[4.5]decan-6-yl)-prop-2-en-1-one (**6b**, $C_{16}H_{25}NO_3$)

Yield: 560 mg (67 %); yellow viscous oil; $R_f = 0.49$ (50 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): $\delta = 5.29$ (1H, s, =CH), 5.16 (1H, s, =CH), 3.87 (4H, s, OCH_2), 3.18–3.72 (4H, m, NCH_2), 2.80 (1H, dd, $J = 11.2$, 3.9 Hz, CH), 1.38–1.85 (12H, m, CH_2), 1.26–1.37 (2H, m, CCH_2) ppm;

^{13}C NMR ($CDCl_3$): δ = 171.6, 144.6, 116.3, 110.2, 64.2, 63.8, 48.1, 46.5, 42.5, 34.4, 29.5, 26.2, 25.5, 24.9, 24.7, 23.5 ppm; IR (KBr): $\bar{\nu}$ = 1636 (CON), 1616 (C=C) cm^{-1}; MS: *m/z* (%) = 279 (22, M^+), 234 (67), 167 (40), 138 (22), 112 (39), 99 (100), 86 (75), 84 (63).

1-Morpholino-2-(1,4-dioxaspiro[4.5]decan-6-yl)prop-2-en-1-one (**6c**, $C_{15}H_{23}NO_4$)
Yield: 280 mg (53 %); jonquil/yellowish white solid; m.p.: 88–89 °C; R_f = 0.33 (50 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): δ = 5.40 (1H, s, =CH), 5.21 (1H, s, =CH), 3.81–3.99 (4H, m, OCH_2), 3.38–3.72 (8H, m, $N(CH_2)_2O$), 2.86 (1H, dd, J = 11.0, 4.1 Hz, CH), 1.42–1.89 (6H, m, CH_2), 1.35 (2H, td, J = 12.5, 4.0 Hz, CCH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 171.9, 143.9, 117.5, 110.2, 66.8, 64.2, 63.9, 47.8, 46.4, 42.0, 34.2, 29.4, 24.9, 23.6 ppm; IR (KBr): $\bar{\nu}$ = 1644 (CON), 1620 (C=C) cm^{-1}; MS: *m/z* (%) = 281 (12, M^+), 236 (16), 209 (22), 195 (10), 167 (36), 139 (22), 99 (100), 86 (60).

Methyl 2-[2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamido]-acetate (**6d**, $C_{14}H_{21}NO_5$)
Yield: 160 mg (47 %); yellowish brown oil; R_f = 0.17 (10 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): δ = 7.47 (1H, bs, NH), 5.98 (1H, s, =CH), 5.45 (1H, s, =CH), 3.94–4.19 (2H, m, $NHCH_2$), 3.75–3.94 (4H, m, OCH_2), 3.72 (3H, s, OCH_3), 2.73–2.78 (1H, m, CH), 1.53–1.89 (6H, m, CH_2), 1.31–1.53 (2H, m, CCH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 170.7, 170.3, 144.6, 123.4, 110.1, 65.2, 64.6, 52.1, 46.8, 41.3, 36.2, 30.2, 25.4, 23.7 ppm; IR (KBr): $\bar{\nu}$ = 3339 (NH), 1755 (COO), 1659 (CON), 1622 (C=C) cm^{-1}; MS: *m/z* (%) = 283 (3, M^+), 268 (1), 252 (2), 224 (1), 167 (28), 99 (100), 86 (43).

Methyl 2-[2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamido]-propanoate (**6e**, $C_{15}H_{23}NO_5$, 1/1 mixture of two diastereomers)
Yield: 150 mg (43 %); white solid; m.p.: 57–58 °C; R_f = 0.40 (20 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): δ = 7.64–7.71/7.43–7.50 (1H, m, NH), 6.03/5.95 (1H, d, J = 1.2 Hz, =CH), 5.48/5.45 (1H, s, =CH), 4.66 (1H, q, J = 7.2 Hz, *CH*CH_3), 3.86–3.97 (4H, m, OCH_2), 3.72/3.77 (3H, s, OCH_3), 2.82 (1H, dd, J = 11.9, 4.5 Hz, CCH)/2.72 (1H, dd, J = 12.3, 4.0 Hz, CCH), 1.86–1.48 (8H, m, CH_2), 1.44/1.38 (3H, d, J = 7.2, CH*CH*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 173.8, 169.8/169.3, 144.9/144.7, 123.5/122.9, 110.2, 65.3/65.1, 64.6/64.5, 52.3, 48.1/48.0, 46.9/46.7, 36.3/36.1, 30.4/29.9, 25.5/25.4, 23.7, 18.5/18.4 ppm; IR (KBr): $\bar{\nu}$ = 3273 (NH), 1751 (COO), 1652 (CON), 1619 (C=C) cm^{-1}; MS: *m/z* (%) = 297 (3, M^+), 282 (1), 266 (2), 238 (3), 195 (16), 167 (34), 99 (100), 86 (48).

Methyl 2-[2-(1,4-dioxaspiro[4.5]decan-6-yl)acrylamido]-3-methylbutanoate (**6f**, $C_{17}H_{27}NO_5$, 1/1 mixture of two diastereomers)
Yield: 180 mg (41 %); yellowish brown viscous oil; R_f = 0.70 (49 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): δ = 7.71/7.32 (1H, d, J = 8.4 Hz, NH), 6.01/5.94 (1H, s, =CH), 5.46/5.42 (1H, s, =CH), 4.49-4.64 (1H, m, NH*CH*), 3.81-4.00 (4H, m, OCH_2), 3.71/3.70 (3H, s, OCH_3), 2.79/2.67 (1H, dd, J = 12.4, 3.8 Hz, CCH), 2.12–2.26 (1H, m, *CH*$(CH_3)_2$), 1.41–1.87 (8H, m, CH_2), 0.90 (3H, d, J = 6.8 Hz, CH*CH*$_3$), 0.84 (3H, d, J = 6.8 Hz, CH*CH*$_3$) ppm; ^{13}C NMR ($CDCl_3$): δ = 173.8, 169.8, 145.0/144.9, 123.7/123.1, 110.1, 65.4/65.0, 64.6/64.5, 57.2/57.1, 51.9, 47.2/47.0, 36.5/36.0, 31.2/31.0, 30.5/30.0, 25.5/25.4, 23.7, 18.9, 17.7 ppm; IR (KBr): $\bar{\nu}$ = 3359 (NH), 1744 (COO), 1653 (CON), 1620 (C=C) cm^{-1}; MS: *m/z* (%) = 325 (4, M^+), 310 (4), 294 (2), 266 (22), 195 (25), 167 (45), 130 (6), 99 (100), 86 (43).

Methyl 1-[2-(1,4-dioxaspiro[4.5]decan-6-yl)acryloyl]-pyrrolidine-2-carboxylate (**6g**, $C_{17}H_{25}NO_5$, 1/1 mixture of two diastereomers)
Yield: 160 mg (37 %); yellowish brown viscous oil; R_f = 0.44 (49 % EtOAc/$CHCl_3$, this mixture was used also for chromatography); ^{1}H NMR ($CDCl_3$): δ = 5.47/5.45 (1H, s, =CH), 5.41/5.37 (1H, s, =CH), 4.37–4.59 (1H, m, NCH), 3.82–4.03 (4H, m, OCH_2), 3.71 (3H, s, OCH_3), 3.44–3.82 (2H, m, NCH_2), 2.94–3.04/2.77–2.91 (1H, m, CCH), 1.26–2.38 (10H, m, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 173.0/172.8, 171.3/170.9, 145.5/144.9, 118.2/116.8, 110.3/110.0, 64.5, 64.1/63.9, 58.5, 52.0, 49.3/48.8, 46.7/45.4, 34.7/34.1, 29.6/29.2, 29.3, 25.7/25.2, 24.9, 23.6 ppm; IR (KBr): $\bar{\nu}$ = 1747 (COO), 1643 (CON), 1616 (C=C) cm^{-1}; MS: *m/z* (%) = 323 (11, M^+), 308 (2), 292 (3), 264 (15), 195 (55), 167 (44), 128 (31), 99 (100), 86 (46), 70 (45).

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