Short communication

Two Methods for Spirothiohydantoin Synthesis

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Abstract

Two methods for spirothiohydantoin synthesis are presented. The title compounds were prepared with reaction of the corresponding 1-aminocycloalkanecarboxylic acids and thiourea. These compounds were also prepared by a hydrolysis of the relevant spirodithiohydantoins with barium hydroxide. The structures of the compounds obtained were verified by comparison of ^{1}H, and ^{13}C NMR, IR and MS spectral data.

Keywords: Spirothiohydantoins, spirodithiohydantoins, 1-aminocycloalkanecarboxylic acids, thiourea.

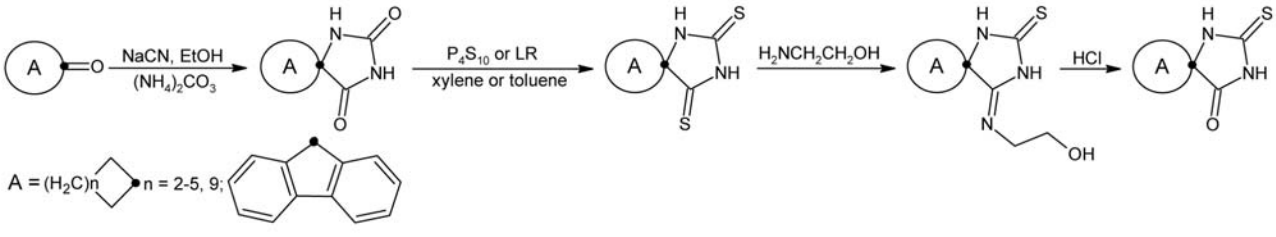
1. Introduction

The thiohydantoins are thioanalogues of hydantoins in which one or both carbonyl groups are substituted by thiocarbonyl groups. These organic compounds have been known for a long time. However, there is a little information of spirothiohydantoin derivatives as recently obtained compounds.[1]

The interest in these substances is determined by the wide range of applications that they possess. Some of these compounds express a pronounced biological activity in the form of antiepileptic,[2] antiarrhythmic,[3] anticancer,[4,5] antibacterial and antiviral (HSV and HIV)[6,7] agents. Others are used as pesticides,[8] dyes in the textile industry[9] or in the polymer catalysis.[10]

Different methods for the synthesis of 2-tiohydantoins have been developed. These compounds can be obtained by an interaction of 1-aminocarboxylic acids with ammonium thiocyanate in a medium of acetic anhydride.[11] These can also be obtained by a treatment of 1-aminocarboxylic acids with isocyanate.[12] 5,5-Disubstituted 2-thiohydantoins are prepared by condensation of benzyl with thiourea, monomethyl thiourea, dimethyl thiourea and diethyl thiourea.[13] In contrast, spiro-2-thiohydantoins are obtained by a rather lengthy synthetic procedure (Scheme 1), involving thionation of the initial spirohydantoins (using P_4S_{10} or Lawesson's reagent, LR) to the corresponding thioanalogues, treatment of the latter with 2-aminoethanol and subsequent hydrolysis with hydrochloric acid.[1,14,15]

The purpose of this paper is to present two methods for synthesis of spiro-2-thiohydantoins. The first one is an adaptation of a method published by Wang et al. in 2006,[16] and the second one is developed by our team as described in this paper. The methods described here are significantly shorter in terms of stages as compared to the procedure depicted in Scheme 1 and products are obtained in higher yield.



Scheme 1. Synthesis of spiro-5-(2-thiohydantoins) from the corresponding cyclic ketones.

2. Experimental

2. 1. Instrumentation and Methods

All used chemicals were purchased from Merck and Sigma-Aldrich. Melting points of compounds **3a-3e** were determined by a SMP-10 digital melting point apparatus as its scope is up to 300 °C. On the other hand, melting point temperatures of compounds **2a-2e** were determined by a Koffler apparatus as their melting points are greater than 300 °C. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. All products analyzed gave results within ± 0.2% of the calculated values. The purity of the compounds was checked by TLC on Kieselgel 60 F_{254}, 0.2 mm Merck plates. IR spectra were taken on Bruker-113 spectrometer in KBr discs. Mass spectra were recorded using LCQ-DUO $LCMS^2$ system with electrospray interface on CH-5 Varian MAT spectrometer at 70 eV. NMR spectra were taken on a Bruker DRX-250 spectrometer, operating at 250.13 and 62.90 MHz for ^1H and ^{13}C, respectively, using standard Bruker software. Chemical shifts were referenced to tetramethylsilane (TMS). Measurements in DMSO-d_6, $CDCl_3$ and D_2O solutions were carried out at ambient temperature (300 K). Typical conditions for ^1H NMR spectra were: pulse width 30°, 1 s relaxation delay, 16K time domain points, zero-filled to 64K, hard pulse with 90° pulse width of 11.8 μs; ^{13}C NMR spectra: pulse width 30°, 1 s relaxation delay, 16K time domain points, zero-filled to 32K, hard pulse with 90° pulse width of 6.4 μs at a power level of 3 dB below the maximum output.

The initial cycloalkanespiro-5-hydantoins **1a-1e** were synthesized via the Bucherer-Lieb method.[17] When we treated these compounds with LR the relevant spiro-2,4-dithiohydantoins **4a-4e** were obtained.[1] (9'-Fluorene)-spiro-5-(2,4-dithiohydantoin) **4f** was obtained by a method developed and published by us.[15]

2. 2. Synthesis of 1-aminocycloalkanecarboxylic Acids 2a-2e (Scheme 2)

A suspension of 0.01 mol of the corresponding cycloalkanespiro-5-hydantoin **1a-1e** and 0.019 mol of $Ba(OH)_2.8H_2O$ in 40 ml water was heated at 160 °C in an autoclave in a salt bath (50% KNO_3 + 50% $NaNO_2$) for two hours. After heating completion, the reaction mixture was cooled to room temperature, filtered and filtrate was treated with 0.021 mol of $(NH_4)_2CO_3$. The resulting solution was filtered, concentrated and the corresponding cyclic amino acid **2a-2e** crystallized after cooling. These compounds were recrystallized from methanol.

Under the conditions described in this procedure, the hydrolysis of (9'-fluorene)-spiro-5-hydantoin with barium hydroxide did not lead to the corresponding fluorenyl amino acid. It actually led to (9H-fluorene-9-yl)urea.[18,19]

1-aminocyclopentanecarboxylic acid (**2a**, n = 2). Yield 70%; m.p. > 300 °C; IR (KBr) ν 3478, 3212 (NH_2), 3049 (NH_3^+), 2962–2885 (CH_2), 2540, 2070 (NH_3^+), 1674 (COOH), 1623 (C-N), 1575 (COO^-), 1402–1331 (CH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.63–1.87 (m, 8H, CH_2), 8.17 (s, 2H, NH_2), 10.49 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6 + D_2O) δ 25.1 (C^3, C^4), 36.4 (C^2, C^5), 69.9 (C^1), 177.8 (C=O).

1-aminocyclohexanecarboxylic acid (**2b**, n = 3). Yield 75%; m.p. > 300 °C; IR (KBr) ν 3021 (NH_3^+), 2941–2855 (CH_2), 2568, 2076 (NH_3^+), 1622 (C-N), 1613 (COO^-), 1465–1329 (CH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.46–1.79 (m, 10H, CH_2), 8.23 (s, 2H, NH_2), 10.42 (s, 1H, COOH) ppm; ^{13}C NMR ($CDCl_3$) δ 22.1 (C^3, C^5), 28.8 (C^4), 36.9 (C^2, C^6), 64.6 (C^1), 156.3 (C=O, ax.), 179.7 (C=O, eq.).

1-aminocycloheptanecarboxylic acid (**2c**, n = 4). Yield 78%; m.p. > 300 °C; IR (KBr) ν 3023 (NH_3^+), 2945–2863 (CH_2), 2569, 2075 (NH_3^+), 1621 (C-N), 1612 (COO^-), 1464–1333 (CH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22–1.61 (m, 12H, CH_2), 8.38 (s, 2H, NH_2), 10.46 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 20.9 (C^3, C^6), 24.5 (C^4, C^5), 33.2 (C^2, C^7), 62.0 (C^1), 156.4 (C=O, ax.), 178.6 (C=O, eq.).

1-aminocyclooctanecarboxylic acid (**2d**, n = 5). Yield 82%; m.p. > 300 °C; IR (KBr) ν 3025 (NH_3^+), 2947–2861 (CH_2), 2568, 2073 (NH_3^+), 1620 (C-N), 1612 (COO^-), 1466–1336 (CH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20–1.63 (m, 14H, CH_2), 8.41 (s, 2H, NH_2), 10.48 (s, 1H, COOH).

1-aminocyclododecanecarboxylic acid (**2e**, n = 9). Yield 74%; m.p. > 300 °C; IR (KBr) ν 3026 (NH_3^+), 2946–2865 (CH_2), 2567, 2075 (NH_3^+), 1620 (C-N), 1614 (COO^-), 1465–1334 (CH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18–1.65 (m, 22H, CH_2), 8.43 (s, 2H, NH_2), 10.49 (s, 1H, COOH).

2. 3. Synthesis of Cycloalkanespiro-5-(2-thiohyidantoins)

2. 3. 1. Method A (an adaptation of a method published by Wang et al.,[16] Scheme 3)

The corresponding acid **2a-2e** and thiourea in the mole ratio 1 : 3 were placed in a flask and heated in a salt bath. When the salt bath temperature reached 220 °C the mixture began to melt. After about 5 minutes, when the temperature reached 225–230 °C, the homogeneous liquid started steaming (evaporating). The steaming stopped in 10 minutes and the mixture was refluxed at this temperature for 40 min. The reaction completion was monitored by TLC. The mixture was cooled down and 20 ml of water was added. Then the refluxing was continued until there was a complete dissolution. After cooling down to room temperature, the mixture was placed in a refrigerator for 3 hours. The crystals formed were separated by a

filtration and an additional product quantity was obtained by extraction of the maternal liquor with ethyl acetate. The ethyl acetate extract was purified by a column chromatography (Al_2O_3, type II Brockman activity). The eluent system used was ethyl acetate : petroleum ether (1 : 2).

Cyclopentanespiro-5-(2-thiohydantoin) (2-thioxo-1,3-diazaspiro[4.4]nonan-4-one, **3a**, n = 2**).** Yield 96%; m.p. 196–197 °C; IR (KBr) ν 3331 (N^3-H), 3126 (N^1-H), 3002–2861 (CH_2), 1750 (C=O), 1539, 1073 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.67–1.90 (m, 8H, CH_2), 10.28 (s, 1H, N^3-H), 11.59 (s, 1H, N^1-H); ^{13}C NMR ($CDCl_3$) δ 24.8 (C^7, C^8), 40.2 (C^6, C^9), 71.2 (C^5), 179.7 (C^2), 180.5 (C^4); DEPT135 ($CDCl_3$) δ 24.8 (C^7, C^8), 40.2 (C^6, C^9); MS (m/z) 170 (M^+).

Cyclohexanespiro-5-(2-thiohydantoin) (2-thioxo-1,3-diazaspiro[4.5]decan-4-one, **3b**, n = 3**).** Yield 95%; m.p. 200–201 °C; IR (KBr) ν 3520 (N^3-H), 3142 (N^1-H), 2934–2855 (CH_2), 1746 (C=O), 1538, 1076 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.23–1.62 (m, 10H, CH_2), 10.46 (s, 1H, N^3-H), 11.54 (s, 1H, N^1-H); ^{13}C NMR ($CDCl_3$) δ 21.7 (C^7, C^9), 25.2 (C^8), 32.1 (C^6, C^{10}), 65.7 (C^5), 179.0 (C^2), 180.9 (C^4); DEPT135 ($CDCl_3$) δ 21.7 (C^7, C^9), 25.2 (C^8), 32.1 (C^6, C^{10}); MS (m/z) 184 (M^+).

Cycloheptanespiro-5-(2-thiohydantoin) (2-thioxo-1,3-diazaspiro[4.6]undecan-4-one, **3c**, n = 4**).** Yield 98%; m.p. 210–211 °C; IR (KBr) ν 3448 (N^3-H), 3162 (N^1-H), 2936–2855 (CH_2), 1740 (C=O), 1535, 1036 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.56–1.79 (m, 12H, CH_2), 10.38 (s, 1H, N^3-H), 11.55 (s, 1H, N^1-H); ^{13}C NMR ($CDCl_3$) δ 21.8 (C^7, C^{10}), 29.0 (C^8, C^{10}), 36.3 (C^6, C^{11}), 67.8 (C^5), 180.1 (C^2), 180.6 (C^4); DEPT135 ($CDCl_3$) δ 21.8 (C^7, C^{10}), 29.0 (C^8, C^{10}), 36.3 (C^6, C^{11}); MS (m/z) 198 (M^+).

Cyclooctanespiro-5-(2-thiohydantoin) (2-thioxo-1,3-diazaspiro[4.7]dodecan-4-one, **3d**, n = 5**).** Yield 95%; m.p. 203–204 °C; IR (KBr) ν 3434 (N^3-H), 3169 (N^1-H), 2925–2853 (CH_2), 1738 (C=O), 1537, 1071 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.48–1.84 (m, 14H, CH_2), 10.32 (s, 1H, N^3-H), 11.53 (s, 1H, N^1-H); ^{13}C NMR ($CDCl_3$) δ 21.0 (C^7, C^{11}), 24.2 (C^9), 27.6 (C^8, C^{10}), 31.1 (C^6, C^{12}), 67.4 (C^5), 179.5 (C^2), 180.6 (C^4); DEPT135 ($CDCl_3$) δ 21.0 (C^7, C^{11}), 24.2 (C^9), 27.6 (C^8, C^{10}), 31.1 (C^6, C^{12}); MS (m/z) 212 (M^+).

Cyclododecanespiro-5-(2-thiohydantoin) (2-thioxo-1,3-diazaspiro[4.11]hexadecan-4-one, **3e**, n = 9**).** Yield 98%; m.p. 257–258 °C; IR (KBr) ν 3145 (N^3-H), 3108 (N^1-H), 2947–2865 (CH_2), 1740 (C=O), 1560, 1069 (C=S) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.32–1.60 (m, 22H, CH_2), 10.14 (s, 1H, N^3-H), 11.58 (s, 1H, N^1-H); ^{13}C NMR ($CDCl_3$) δ 18.6–30.2 (CH_2), 67.2 (C^5), 178.5 (C^2), 180.7 (C^4); MS (m/z) 268 (M^+).

2. 3. 2. Method B (Scheme 5)

1 g of the respective dithiospirohydantion **4a-4e** or **4f**, 3 g of barium hydroxide, 20 ml of water and 10 ml of ethanol were refluxed for 3 hours. After cooling, barium carbonate precipitate was filtered off and 1.5 g of ammonium carbonate was added to the filtrate in order to remove the excess barium ions. The corresponding monothiospirohydantoin crystallized when the filtered solution was concentrated. The final products **3a-3e** and **3f** were recrystallized from water.

The physicochemical parameters and the spectral data of the monothiospirohydantoins **3a-3e** obtained by Method B (with 90–95% yields as listed in Table 2 in the Results and Discussion Section) are identical with those synthesized by Method A.

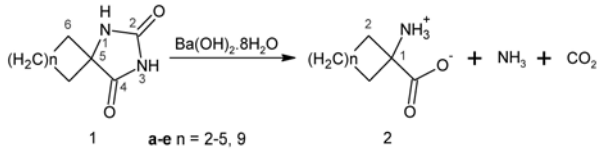
(9'-fluorene)-spiro-5-(2-thiohydantoin) (3f). Yield 98%; m.p. 302–303 °C; IR (KBr) ν 3656 (N^3-H), 3170 (N^1-H), 2970–2910 (CH, arom.), 1740 (C=O), 1652 (C=S), 1081 (C=S), 764, 741 (arom.) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.38–7.94 (m, 8H), 10.59 (s, 1H), 12.33 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 74.7 (C^5), 120.9 (arom.), 123.7 (arom.), 128.5 (arom.), 130.2 (arom.), 140.7 (arom.), 141.3 (arom.), 174.7 (C^2), 183.5 (C^4); MS (m/z) 266 (M^+).

3. Results and Discussion

The hydrolysis of hydantoins and spirohydantoins is among the most widely used method for synthesis of non-protein amino acids. The hydantoin ring is degraded by hydrolysis, resulting in a formation of $C^{\alpha,\alpha}$- symmetrically and asymmetrically disubstituted glycines.[20]

The main method for hydantoins and spirohydantoins synthesis is the Bucherer-Lieb method[17] based on the interaction between the corresponding ketone (in our case we used cyclic ketones with five, six, seven, eight and eleven membered ring), sodium or potassium cyanide, ammonium carbonate and ethanol. As a result of the references identified and on the basis of our repeated experiments, we concluded that the most effective method for hydrolysis of spirohydantoins derivatives is by using barium hydroxide.

The cycloalkanespiro-5-hydantoins **1a-1e** synthesized by the Bucherer-Lieb method were subjected to alkaline hydrolysis by barium hydroxide. As a result of

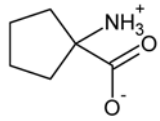
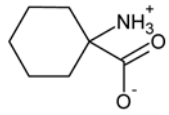
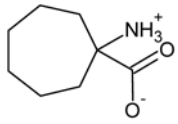
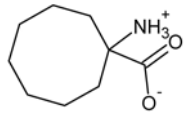
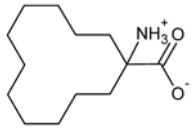


1 **a-e** n = 2-5, 9 2

Scheme 2. Synthesis of 1-aminocycloalkanecarboxylic acids **2a-2e**.

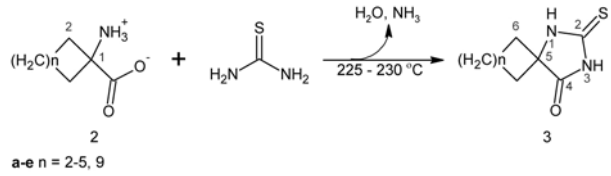
hydrolytic degradation of the hydantoin ring, the relevant 1-aminocycloalkanecarboxylic acids **2a-2e** were isolated (Scheme 2). The obtained physicochemical parameters of the acids are listed in Table 1.

Table 1. Physicochemical parameters of compounds **2a-2e**.

No[a]	Structure	M.p., °C	Yield,%	Rf[b]
2a		> 300	70	0.28
2b		> 300	75	0.32
2c		> 300	78	0.31
2d		> 300	82	0.32
2e		> 300	74	0.34

[a] Compounds numbering is in accordance with Scheme 2.
[b] Eluent system (vol. ratio): pyridine : n-butanol : acetic acid : water = 10 : 15 : 3 : 12.

As a result of condensation between 1-aminocycloalkanecarboxylic acids and thiourea, the relevant cycloalkanespiro-5-(2-thiohydantoins) **3a-3e** were synthesized (Scheme 3). This reaction was applied for the first time to non-protein amino acids, according to a modification of the method of Wang et al.[16]



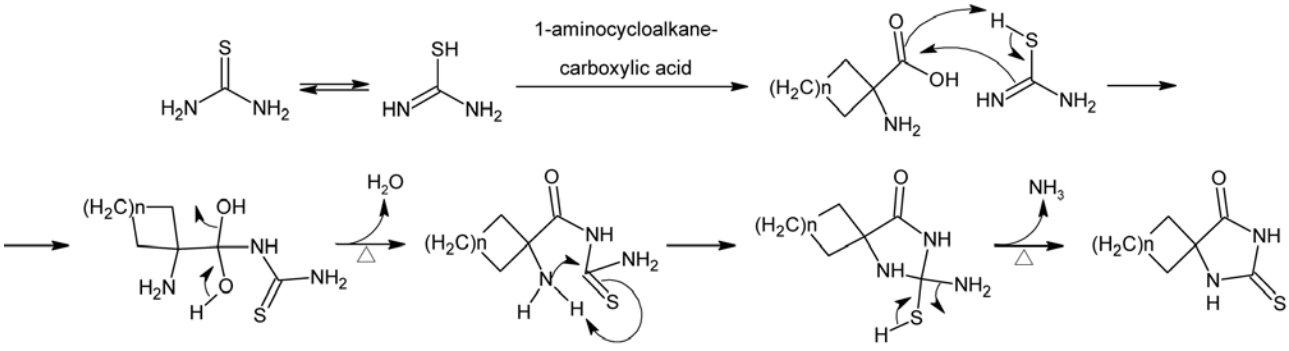
Scheme 3. Synthesis of cycloakanespiro-5-(2-thiohydantoins) **3a-3e** from the corresponding 1-aminocycloalkanecarboxylic acids **2a-2e**.

The obtained product yield of **3a-3e** was the highest, when the mole ratio between the initial compounds (1-aminocycloalkanecarboxylic acid and thiourea) was 1 : 3. A decrease in the product yield was observed in both cases when the reactants mole ratio was 1 : 2 (60–70%) and 1 : 1 (below 50%). The varying of the reaction temperature below 220 °C led to extremely poor yields (between 25 and 37%). Contrary, the product yield reached 40–45% by increasing the reaction time over 2 hours. When the reaction mixture is heated above 230 °C, the isolation of the final products was much more complicated. Reaction conditions introduced by our method led to extremely pure crystalline substances.

The probable reaction mechanism, in accordance to those proposed by Wang et al.,[16] is illustrated in Scheme 4.

The spectral data and the physicochemical parameters of the synthesized compounds **3a-3e** correspond to those obtained by us before using the other method[1], as the yields quoted now are slightly better. Furthermore, it is important to note that the number of steps for the synthesis of the cycloalkanespiro-5-(2-thiohydantoins) **3a-3e** are reduced by two, compared to the method already known[1].

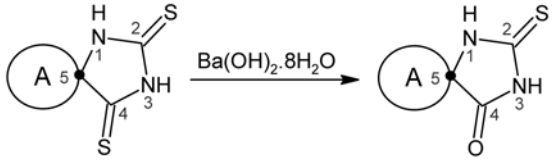
Bucherer and Lieb made unsuccessful attempts to synthesize 2,4-dithiospirohydantoins, and Henze and Smit[21] synthesized different spiriodithiohidantoin derivatives by using P_4S_6 in tetralin as solvent. Only Carrington[22] was able to obtain the corresponding derivatives of dithiospirohdantoins with low yields by a modified Bucherer method using CS_2 as reagent. Considering results reached by other groups, we optimized the synthesis by using a Lawesson's reagent.[1]

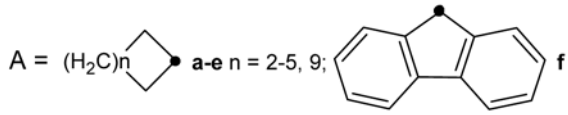


Scheme 4. Probable mechanism for the synthesis of cycloalkanespiro-5-(2-thiohydantoins) from 1-aminocycloalkanecarboxylic acids.

By our assumption a degradation of four-atom ring of LR occurs in a solution, with the formation of a bipolar ion that enable nucleophilic attack on the more accessible carbonyl group in the second position of the hydantoin ring. Consequently, the corresponding spiro-5-(2-thiohydantoin) is formed and it is likely to form a six-atomic cyclic trimer containing phosphorus as a byproduct of the reaction. The conversion of carbonyl group at the fourth position in the hydantoin ring is performed by the same way, which leads to the final formation of the corresponding 2,4-dithioderivative.

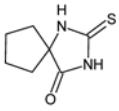
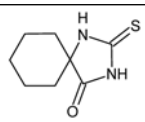
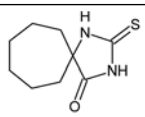
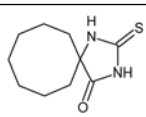
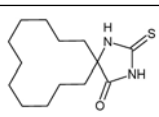
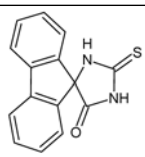
We found no data in the literature for similar studies of dithioderivative hydrolysis. First, we conducted the hydrolysis by treatment of the dithiospirohydantoins with barium hydroxide at 160 °C in an autoclave. As a result, we have founded that unlike the spirohydantoins, which give a corresponding amino acid, the alkaline hydrolysis of dithiospirohydantins results in a mixture of products. When changing the reaction conditions, mainly by changing the solvent (i.e., ethanol), and heating at 100 °C, the corresponding monothiospirohydantoins were obtained (Scheme 5, Table 2). The best results were obtained when the water : ethanol solvent ratio was 2 : 1 and heated at 100 °C for 3 hours. In that case the yields were between 90–98%. When the water : ethanol solvent ratio was changed to 1 : 1 or 1 : 2, the yields fell below 80%, and below 65%, respectively, regardless of the heating time.





Scheme 5. Synthesis of spiro-2-thiohydantoins **3a-3e, 3f** from the corresponding spiro-2,4-dithiohydantoins **4a-4e, 4f**

Table 2. Physicochemical parameters of compounds **3a-3e, 3f**.

No[a]	Structure	M.p., °C	Yield, % Method A[b]	Method B[c]	Rf[d]
3a		196–197	96	91	0.53
3b		200–201	95	90	0.59
3c		210–211	98	95	0.64
3d		203–204	95	91	0.71
3e		257–258	98	95	0.79
3f		302–303	–[e]	98	0.71

[a] Compounds numbering is in accordance with Schemes 3 and 5.
[b] Experimental procedure 2.3.1.
[c] Experimental procedure 2.3.2.
[d] Eluent system (vol. ratio): benzene : ethanol = 5 : 1.
[e] Under the conditions specified in method 2.1, the relevant fluorenyl amino acid did not form.[18,19]

The elemental analysis and the spectral data of compounds **3a-3e** and **3f** showed a complete match with our earlier results.[1,23]

4. Conclusions

Two effective methods for synthesis of different spiro-2-thiohydantoins have been introduced. The first method is an adaptation of a method published by Wang[16] (Method A), and the second one (Method B) is developed by our group. These methods are based on the reaction between 1-aminocycloalkanecarboxylic acid and thiourea, as well as on the treatment of spirodithiohydantoins with barium hydroxide. The described methods are shorter, compared to already known techniques, and gave products with high yields (90–98%). The compounds were characterized by IR, NMR and mass spectral data, which confirmed the suggested structures.

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6. References

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Povzetek

V prispevku sta predstavljeni dve metodi za pripravo spirotiohidantoinov. Spojine so bile pripravljene z reakcijo ustreznih 1-aminocikloalkilkarboksilnih kislin in tiouree. Iste spojine so bile pripravljene tudi s hidrolizo ustreznih spiroditiohidantoinov z barijevim hidroksidom. Strukture pripravljenih spojin so bile preverjene s primerjalno analizo ^{1}H in ^{13}C NMR, IR ter MS podatkov