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Synthesis of Spiro Compounds Based on Bicyclo[3.3.1]nonane

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Abstract: **Organic compounds with bicyclic structure are important because of their stereochemical features and biological activity. The studies of synthesis of spiro compounds bearing bicyclo[3.3.1]nonane framework were based on bicyclo[3.3.1]nonan-2,6-dione and bicyclo[3.3.1]nonan-2-one. These starting compounds were converted to corresponding α-haloketones and treated with 2-aminoethanethiol using microwave irradiation to give new heterocyclic compounds - spiro[bicyclo[3.3.1]nonan-3-ono-2,2'-thiazolidine] and spiro[bicyclo[3.3.1]nonan-3,7-diono-2,2':6,2'-dithiazolidine]. The efficient method for 3-bromobicyclo[3.3.1]nonan-2,6-dione synthesis was offered.**

Keywords: **bicyclo[3.3.1]nonane, spiro-compounds, microwave synthesis, thiazolidine, α-haloketones**

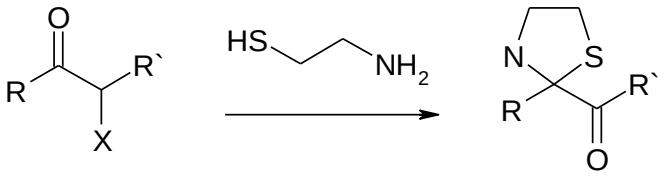
I. Introduction

Organic compounds with bicyclic structure are interesting because of their stereochemical features and biological activity. Such compounds can be often found both in natural products and in synthetic drugs [1, 2]. Presence of condensed [3, 4] or spiro [5-7] heterocyclic ring(s) is also important for biological activity. The aim of the presented work was the study of synthesis of spiro compounds based on bicyclo[3.3.1]nonane framework.

II. Results and discussion

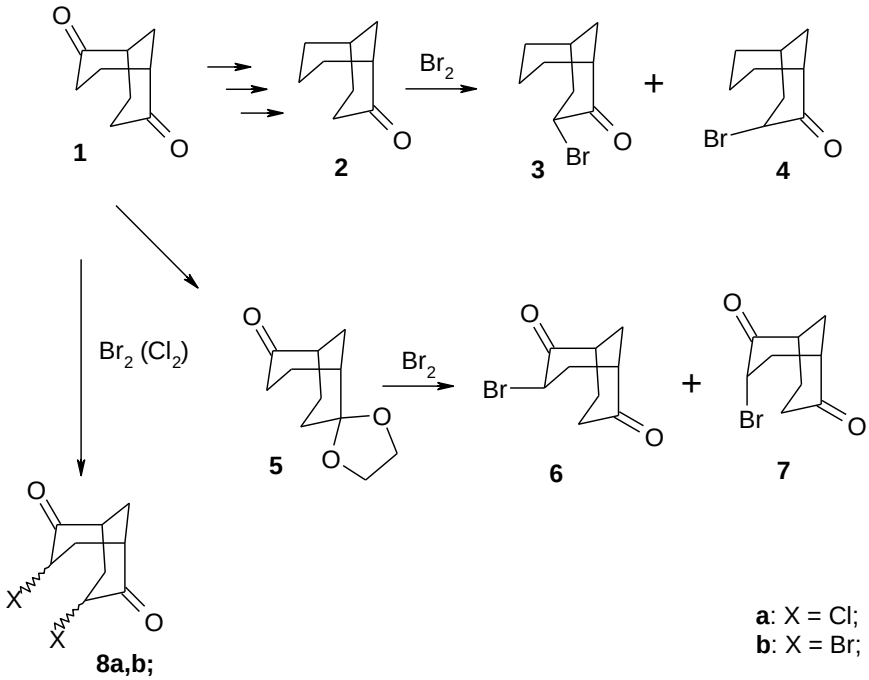
It is known that α-haloketones can react with 2-aminoethanethiol to give spirothiazolidine derivatives. After oxidation by air and further rearrangements carbonyl group in such cases moves to the position of halogen [8] (Scheme 1). Reaction time can sometimes be shortened by using microwave irradiation [9, 10].

Scheme 1



Our usual starting material bicyclo[3.3.1]nonan-2,6-dione (**1**) was synthesized according to [11] and converted to bicyclo[3.3.1]nonan-2-one (**2**) by known methods [12] (Scheme 2).

Scheme 2



Compound **5** [13] was synthesized from compound **1** by protection of one of the carbonyl groups. Ketones **2** and **5** were treated with bromine in acetic acid or $CHCl_3$ to give a mixtures of α-bromoketones **3** and **4** [14] or **6** and **7** [15], respectively. Predominantly *ekzo* isomers (**3**) were formed. Both carbonyl groups of compounds **6** and **7** were found to be unprotected because of evolution of hydrobromic acid. Previously compounds **6** and **7** were synthesized by direct bromination of diketone **1** and identified in a mixture of by-products by MS without isolation of individual compounds [16]. Our way of synthesis allowed getting these compounds free from unreacted **1** and dibromo derivatives **8b**. Di-α-haloketones **8a**,**b** [17, 18] were synthesized by chlorination or bromination of diketone **1** with chlorine or bromine, respectively. α-Haloketones **3**, **4**, **6**, **7** and **8a**,**b** were allowed to react with 2-aminoethanethiol to form heterocyclic spiro compounds **9** and **11** (Scheme 3).

Sharp peaks of N-H groups in IR spectra of compounds **9** and **11** in $CHCl_3$ (3290 and 3287 cm^{-1}, respectively) do not change form and frequency of dilution. Vibration frequency of C=O groups (1699 and 1703 cm^{-1}, respectively) indicates the presence of intramolecular hydrogen bond as well. Values of chemical shift (208.0 and 203.7 ppm, III**.** respectively) of C=O carbon in ^{13}C NMR spectra confirm this conclusion. Formation of isomeric compounds with opposite orientation of heterocyclic ring was not observed. Obviously a formation of intramolecular hydrogen bond between N-H and C=O groups was important for the formation of spiro ring. Unfortunately compound **10** couldn't be found in the reaction mixture. The amount of resinous by-products was unexpectedly high in this case. Possibly the conformation of compounds **6** and **7** was more beneficial for intermolecular condensation reactions.

The ratio of α-haloketones **3** and **4** and 2-aminoethanethiol were changed from 1:1.2 to 1:10. The highest yields of compound **9** were achieved at 1:6. The reaction of **3** and **4** and 2-aminoethanethiol (1:6) in benzene at room temperature for 72 hours resulted in 12% yield of compound **9**, reflux for 4 hours in 15%. The irradiation of dry **3** and **4** and 2-aminoethanethiol in microwave oven for 30 min (4 x 6 min) gave 15% of **9** and resinous by-products. Addition of water has enhanced the yield of **9** to 28%. The prolongation of reaction time to 6 x 6 min enhanced the yield of compound **9** to 54%. 3,7-Dichlorbicyclo[3.3.1]nonan-2,6-dione (**8a**) in the synthesis of compound **11** reacted faster and gave less by-products thant its dibromo analogue **8b**.

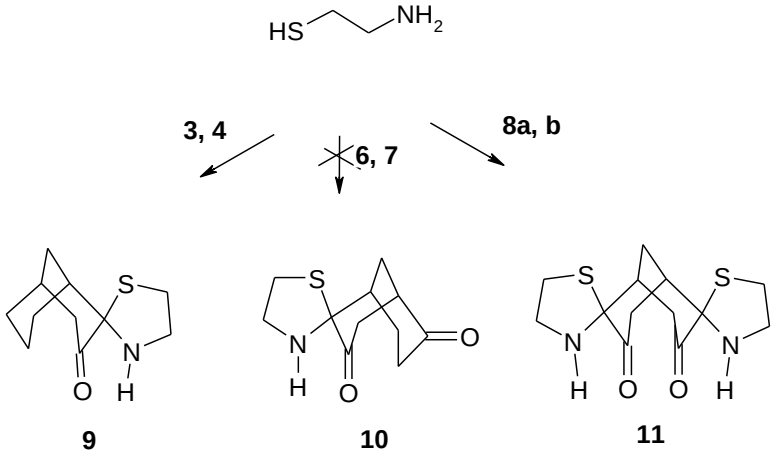
III. EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer spectrophotometer model FT-IR Spectrum BX II. ^1H-NMR spectra were recorded on Varian Unity Inova (300 MHz). The purity of compounds was checked on silica gel 60 F_{254} plates (Merck). Visualisation was achieved by UV irradiation or by treating with 4-methoxybenzaldehyde or ninhydrine solutions. Domestic microwave oven was used for MW irradiation (100 W)..

Spiro[bicyclo[3.3.1]nonan-3-ono-2,2'-thiazolidine] (9)

Isomeric 3-bromobicyclo[3.3.1]nonan-2-ones **3** and **4** 0.27 g (1.24 mmol), 10 ml H_2O and 0.57 g (7.4 mmol) 2-aminoethanethiol were heated in microwave oven for 36 min (6 periods of 6 min). 2-Aminoethanethiol was added in 6 portions. The reaction was completed when no traces of **3** and **4** in TLC were left. Obtained product was purified by flash chromatography on silica gel (dichloromethane-methanol 200:1) to give 0.14 g (54%) **9** as yellow oil. IR (cm^{-1}): 3290 (N-H), 1699 (C=O). ^1H NMR ($CDCl_3$): 1.20-1.56 (4H, m, CH_2), 1.60-1.75 (2H, m, CH_2), 1.82-1.91 (1H, m, CH), 2.10-2.25 (3H, m, SCH_2, CH), 2.30-2.39 (2H, m, NCH_2), 2.45-2.55 (1H, m, CH), 2.70-2.79 (2H, m, CH_2), 2.94-3.12 (3H, m, CH_2, CH), 3.70-3.78 (1H, m, NH). ^{13}C NMR ($CDCl_3$): 17.9; 29.0; 30.9; 32,2; 32.3; 37.6; 43.2; 44.7; 53.2 (C-S); 86.5 (C-S-N); 208.0 (C=O). Anal. Calcd. for $C_{11}H_{17}NOS$: C 62.52%; H 8.11%; N 6.63%; S 15.17%. Found: C 62.90 %; H 7.99%.

Scheme 3



3-Bromobicyclo[3.3.1]nonan-2,6-dione (**6** and **7**)

To a stirred solution of 6,6-ethylendioxy-bicyclo[3.3.1]nonan-2-dione **5** [13] 0.67g (3.42 mmol) in 25 ml $CHCl_3$ 0.55g (3.42 mmol) bromine in 25 ml $CHCl_3$ was added, kept for 20 min, washed with 5% $NaHCO_3$, dried on anhydrous Na_2SO_4, evaporated and purified by flash chromatography on silica gel (hexane and ethyl acetate 4:1) to give 0.33 g (42 %) **6** and **7** as crystalline powder; m. p. 105 - 108 ºC. IR (cm $^{-1}$): 1680, 1665 (C=O). ^{1}H NMR ($CDCl_3$): 1.94-2.10 (2H, m, CH_2), 2.21-2.48 (4H, m, CH_2), 2.63-2.84 (3H, m CH, CH_2), 3.11-3.18 (1H, m, CH), 4.66-4.72 (1H, dd, J = 16 and 6 Hz, CH). Anal. Calcd. for $C_9H_{11}BrO_2$: C 46.78%, H 4.80%, Br 34.58%. Found: C 49.03%, H 5.57%, Br 32.49%.

Spiro[bicyclo[3.3.1]nonan-3,7-dione-2,2':6,2‘-dithiazolidine] (11)

Isomeric 3,7-dichlorbicyclo[3.3.1]nonan-2,6-diones **8a**, 0.22 g (1 mmol), 10 ml H_2O and 0.77 g (11 mmol) 2-aminoethanethiol was heated in microwave oven for 36 min (6 periods of 6 min). 2-Aminoethanethiol was added in 6 portions. Reaction was monitored by TLC. The obtained product was purified by flash chromatography on silica gel (dichloromethane) to give 0.11 g (37%) **11** as yellow oil. IR (cm $^{-1}$): 3287 (N-H), 1703 (C=O). ^{1}H NMR ($CDCl_3$): 2.45-2.50 (2H, m, CH_2), 2.65-2.76 (4H, m, CH_2), 3.78-3.39 (10H, m, CH_2), 3.72 (2H, dd, J = 12 and 5 Hz, NH). ^{13}C NMR ($CDCl_3$): 28.9, 38.2, 44.1, 42.3, 52.8, 86.2 (N-C-S), 203.7 (C=O). Anal. Calcd. for $C_{13}H_{18}N_2O_2S_2$: C 52.32%; H 6.08%; N 9.39%; S 21.49%. Found: C 52.39; H 5.98%.

IV. Conclusions

1. New heterocyclic compounds - spiro[bicyclo[3.3.1]nonan-3-ono-2,2'-thiazolidine] and spiro[bicyclo[3.3.1]nonan-3,7-diono-2,2':6,2‘-dithiazolidine] were synthesized using microwave irradiation.
2. The structure of spiro[bicyclo[3.3.1]nonan-3-ono-2,2'-tiazolidine] and spiro[bicyclo[3.3.1]nonan-3,7-diono-2,2':6,2‘-ditiazolidine] was postulated by the presence of intramolecular hydrogen bonds.
3. The efficient method for 3-bromobicyclo[3.3.1]nonan-2,6-dione synthesis was offered.

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Linas Labanauskas, Albinas Žilinskas, Sigita Višņakova, Gintaras Urbelis, Olga Gedrimaite, Ričardas Rozenbergas, Andrejs Podgurskis. Spiro savienojumu sintēze uz biciklo[3.3.1]nonāna bāzes

Spiro vai bicikliskas struktūras organiskie savienojumi izraisa interesi kā no stereoķīmijas, tā bioloģiskās aktivitātes viedokļa. Minētie savienojumu fragmenti, tai skaitā kondensēti vai spirosaistīti ar heterocikliskiem gredzeniem, ir bieži sastopami dabasvielu un ārstniecības līdzekļu struktūrās. Spiro savienojumi ar biciklo[3.3.1]nonāna struktūru sintezēti no biciklo[3.3.1]nonān-2,6-diona vai biciklo[3.3.1]nonān-2-

ona. Minētie savienojumi tika pārvērsti attiecīgos mono- un di-α-halogenketonos, kuri, reaģējot ar 2-aminoetantiolu, veidoja jaunus heterocikliskos savienojumus – spiro[biciklo[3.3.1]nonān-3-on-2,2'-tiazolidīnu] un spiro[biciklo[3.3.1]nonān-3,7-dion-2,2':6,2'-ditiazolidīnu]. Pētīta galaproduktu sintēzes optimizācija un iznākumu palielināšanas iespēja. Izstrādāta jauna, uz mikroviļņu starojuma balstīta, spiro[biciklo[3.3.1] nonān-3-on-2,2'-tiazolidīna] un spiro[biciklo[3.3.1]nonān-3,7-dion-2,2':6,2'-ditiazolidīna] sintēzes metode. Savienojumu struktūras ir noteiktas balstoties uz iekšmolekulāro ūdeņraža saišu klātbūtni. Pretējas konfigurācijas heterocikla izomēru veidošanās nav novērota. Izstrādāta vienkārša 3-brombiciklo[3.3.1]nonān-2,6-diona sintēzes metode, kura balstīta uz vienas karbonilgrupas aizsardzību ar etilēnglikolu. Atšķirībā no agrāk izmantotās neaizsargātas karbonilgrupas tiešās bromēšanas vai hlorēšanas metodes [16], izstrādātā metode ļauj izdalīt no reakcijas maisījuma brombiciklo[3.3.1]nonān-2,6-dionu tīrā veidā. Diemžēl šī savienojuma reakcijā ar 2-aminoetāntiolu veidojas nevis sagaidāmais spirosavienojums, bet gan tikai sveķveidīgi produkti.

Линас Лабанаускас, Албинас Жилинскас, Сигита Вишнякова, Гинтарас Урбелис, Олга Гедримайте, Ричардас Розенбергас, Андрей Подгурский. Синтез спиросоединений на основе бицикло [3.3.1] нонана

Органические соединения спиро- или бициклической структуры изучаются по причине их интересной стереохимии и проявлющейся биологической активности. Упомянутые фрагменты, в том числе конденсированные или спиро-связанные с гетероциклическими кольцами, часто встречаются в структурах природных соединений и синтетических лекарственных средств. Синтез спиро-соединений, имеющих в своей структуре каркас бицикло[3.3.1]нонана, был основан на модификации бицикло[3.3.1]нонан-2,6-диона и бицикло[3.3.1]нонан-2-она. Упомянутые исходные соединения превращены в соответствующие моно- и ди-α-галогенкетоны, которые реагировали с 2-аминоэтантиолом в разных условиях и образовали новые гетероциклические соединения - спиро[бицикло[3.3.1]нонан-3-оно-2,2'-тиазолидин] и спиро[бицикло[3.3.1]нонан-3,7-дионо-2,2':6,2'-дитиазолидин]. Были изучены возможности оптимизации реакции циклообразования и повышения выхода целевых спиропроизводных. Предложен новый метод синтеза спиро[бицикло[3.3.1]нонан-3-он-2,2'-тиазолидина] и спиро[бицикло[3.3.1]нонан-3,7-дион-2,2':6,2'-дитиазолидина], основанный на использовании микроволнового облучения. Определение их структуры опирается на наличии внутримолекулярных водородных связей. Образование изомеров с противоположной ориентацией гетерокольца не замечено. Разработан более эффективный метод синтеза 3-бромбицикло[3.3.1]нонан-2,6-диона, основанный на предварительной защите одной карбонильной группы циклизацией ее с этиленгликолем. В отличие от ранее использоваемого прямого бромирования или хлорирования незащищенного дикетона [16], предложенный метод позволил выделить чистый бромбицикло[3.3.1]нонан-2,6-дион. Но при взаимодействии этого соединения с 2-аминоэтантиолом, образовалось не ожидаемое спиросоединение, а лишь смолянистые продукты.