Journal scientific and applied research, vol. 3, 2013
Association Scientific and Applied Research
International Journal

Original Contribution

ISSN 1314-6289

TWO METHODS FOR 3-AMINOCYCLOPENTANESPIRO-5-HYDANTOIN THIONATION

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Abstract: *This article presents two methods for 3-aminocyclopentanespiro-5-hydantoin thionation. These methods are based on the treatment of the titled compound with P_4S_{10} or Lawesson's reagent. The corresponding dithio-analogue was synthesized as a result of these interactions. The structure of the product obtained was verified by ^1H NMR, ^{13}C NMR and mass spectral data.*

Key words: *3-aminocyclopentanespiro-5-hydantoin, thionation*

I. Introduction

The interaction between cyclohexanespiro-5-(2-thiohydantoin) and hydrazine hydrate at different reaction conditions was studied and presented in a previous publication [1].

It was found that conducting the reaction at normal conditions resulted in formation of the corresponding 2-hydrazone of the initial compound [1].

Unlike the aforementioned case, the refluxing of cyclohexane-spiro-5-(2-thiohydantoin) and hydrazine hydrate led to obtaining of the relevant 3-amino derivative [1].

The thionation of 3-aminocyclohexanespiro-5-hydantoin by using P_4S_{10} and Lawesson's reagent (LR) as thionation reagents led to preparing of the corresponding dithioanalogue [1].

The aim of this paper is to present the application of the thionation techniques, described above, to 3-aminocyclopentane-spiro-5-hydantoin.

The interest in obtaining 3-aminocycloalkanespiro-5-(2,4-dithiohydantoins) is determined by their presumed biological activities and future studies planned thereon.

Available data published in the literature represent a further support to this suggestion.

It is well known, for example, that different 3-aminocycloalkane-spiro-5-hydantoins exert well pronounced, atropine-sensitive, contractile effects on guinea-pig ileum longitudinal muscle preparations [2].

II. Experimental

II.1. Materials and methods

All chemicals used were purchased from Merck and Sigma-Aldrich.

The cyclopentanespiro-5-hydantoin (compound **1**, Scheme 1) was synthesized *via* the Bucherer-Lieb method [3]. The 3-aminocyclopentanespiro-5-hydantoin (compound **2**, Scheme 1) was synthesized in accordance with Naydenova et. al. [2]. Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) was prepared in accordance with Ref. 4.

Melting point was determined with a digital melting point apparatus SMP 10. NMR spectra were taken on a Bruker DRX-250 spectrometer, operating at 250.13 and 62.90 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software. Chemical shifts were referenced to tetramethylsilane (TMS). Measurements were carried out at ambient temperature. Mass spectrum was recorded using LCQ-DUO LCMS2 System Electrospray Interface on CH-5 Varian MAT spectrometer at 70 eV. The purity of the compound was checked *via* thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent systems (vol/vol ratio):
(A) chloroform : acetone = 9 : 1;
(B) ethylacetate : petroleum ether = 1 : 5.

II.2. Synthesis of 3-aminocyclopentanespiro-5-(2,4-dithiohydantoin) (compound 3, Scheme 1)

II.2.1. Thionation of compound 2 with LR

A suspension of 1.69 g (0.01 mol) of 3-aminocyclopentanespiro-5-hydantoin (compound **2**, Scheme 1) and 8.08 g (0.02 mol) of LR in 40 ml toluene was refluxed for 6 hours. The solvent was decanted, then cooled down to room temperature and extracted with methylene chloride / water. The methylene chloride layer was dried over anhydrous sodium sulphate and then it was evaporated to dry. The product obtained was recrystallized from methylene chloride / petroleum ether.

Yield: 1.23 g (61 %);

M.p.: 174-175 ˚C;

$Rf_A = 0.75$; $Rf_B = 0.37$;

^{1}H NMR (δ, ppm, DMSO-d_6): 1.22-1.76 (m, 8H, CH_2), 7.34 (s, 2H, NH_2), 12.80 (s, 1H, N^1-H);

^{13}C NMR (δ, ppm, DMSO-d_6): 47.1 (C^7, C^8), 60.2 (C^6, C^9), 72.2 (C^5), 175.8 (C^2), 207.3 (C^4);

MS: m/z 201, calculated for $C_7H_{11}N_3S_2$ $(M)^+$ 201.

II.2.2. Thionation of compound 2 with P_4S_{10}

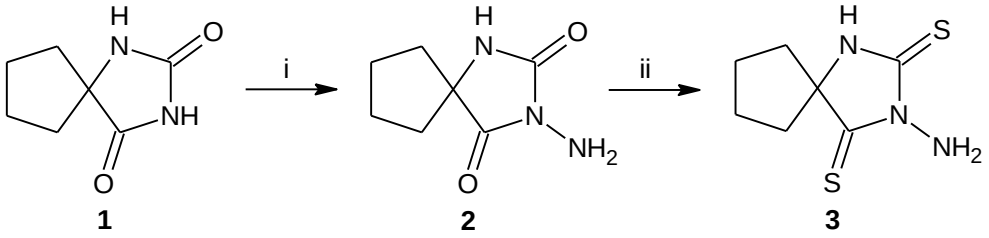
A suspension of 1.69 g (0.01 mol) of 3-aminocyclopentanespiro-5-hydantoin (compound **2**, Scheme 1) and 4.45 g (0.01 mol) of P_4S_{10} in 40 ml xylene was refluxed for 5 hours. The solvent was decanted, then cooled down to room temperature and extracted with methylene chloride / water. The methylene chloride layer was dried over anhydrous sodium sulphate and then it was evaporated to dry. The product obtained was recrystallized from methylene chloride / petroleum ether.

Yield: 38 %.

III. Results and discussion

The synthesis of 3-aminocyclopentanespiro-5-(2,4-di-thiohydantoin) (compound **3**) was carried out in accordance with Scheme 1. The reagents and conditions are listed below (see the experimental part for details).

The initial cyclopentanespiro-5-hydantoin (compound **1**, Scheme 1) was obtained through the application of the Bucherer-Lieb method [3] to cyclopentanone. The ketone was treated with sodium cyanide, ammonium carbonate and ethanol. Thus, the product obtained was subjected to an interaction with hydrazine hydrate in accordance with Naydenova et al. [2]. As a result of this procedure, the relevant 3-amino derivative (**2**) was obtained.



1 **2** **3**

Scheme 1. *Synthesis of 3-aminocyclopentanespiro-5-(2,4-dithiohydantoin). Reagents and conditions: (i) hydrazine hydrate, reflux [2]; (ii) P_4S_{10} or LR, xylene or toluene, reflux [1]*

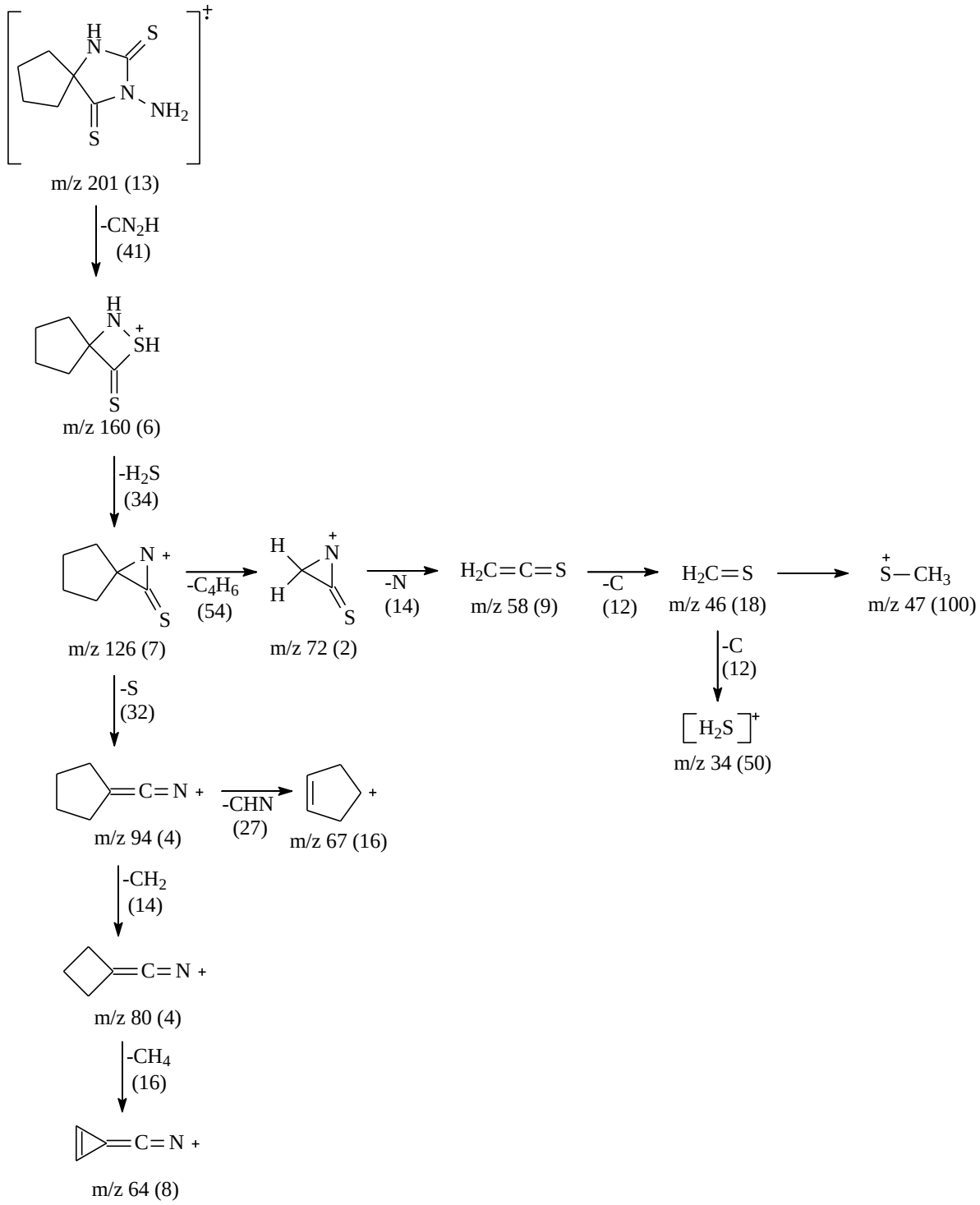
The next step of the study presented was the thionation of 3-aminocyclopentanespiro-5-hydantoin [also named 3-amino-1,3-diazaspiro[4.4]nonane-2,4-dione] (compound **2**, Scheme 1). Two thionation methods were applied to product **2** for this purpose. The first method was based on the interaction of compound **2** with LR in a medium of toluene (see method II.2.1., experimental part). The second technique was the treatment of compound **2** with P_4S_{10} in a medium of xylene (see method II.2.2., experimental part).

These two procedures were carried out in accordance with previously published data in the literature [1]. The structure of compound **3** obtained was confirmed *via* NMR and mass spectral data (see the experimental part). The fragmentation of 3-aminocyclo-pentanespiro-5-(2,4-dithiohydantoin) [also named 3-amino-1,3-diaza-spiro[4.4]nonane-2,4-dithione] (compound **3**) is presented in Scheme 2.

Acknowledgements

Financial support by the Agricultural University – Plovdiv, Bulgaria (Contract 06-12) is gratefully acknowledged.

The author is grateful also to Prof. N. Stoyanov, Razgrad, Prof. B. Aleksiev, Sofia and Mr. G. Marinov, Sofia for stimulating discussions.



Scheme 2. *Fragmentation of compound* ***3***

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