SYNTHESIS OF NOVEL 5-(ALK-3-ENYL)-HYDANTOINS

Biljana Šmit* and Radoslav Z. Pavlović

Faculty of Science, University of Kragujevac, Radoja Domanovića 12 P.O. Box 60, 34000 Kragujevac, Serbia, biljam@kg.ac.rs

Abstract: In the multicomponent reaction under Bucherer-Bergs conditions, construction of 5-(alk-3-enyl)-hydantoin starting from unsaturated carbonyl compounds, such as aldehydes, ketones and β-ketoesters, was made in good yields. Some of them were acetylated at N(1) position with acetyanhydride. When α-allyl-β-ketoesters were used as substrate in the Bucherer-Bergs reaction an unexpected decarboxylation was observed. Decarboxylation was not observed only when 2-allyl-ethylacetoacetate was used for synthesis of hydantoin while in other cases fully decarboxylated products were obtained.

Keywords: Bucherer-Bergs reaction, hydantoins, acetylation, decarboxylation.

INTRODUCTION

Hydantoins (imidazolidine-2,4-diones) are important structural moiety found in several natural products and pharmacologically important compounds1. Hydantoins have a wide range of biological activities, such as anticonvulsant2, antitumor3, antiarrhythmic4 and antiandrogenic5. Activity of hydantoin derivatives depends on the nature of substitution of hydantoin ring6. In spite of the different examples of biological actions, 5,5-disubstituted hydantoins are mainly considered as anticonvulsant agents7, the most notably being 5,5-diphenylhydantoin (Dilantin, Phenyoitn). This compound was introduced in 1938, and despite significant toxic and teratological effects, is still a broadly used anticonvulsant for treatment of epilepsy. 5,5-Dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl]hydantoin8 is a pure antiandrogen that inhibits the testicular steroidogenic pathway, apparently acting by forming complexes with the cytoplasmic hormone receptors that are unable to undergo translocation into nuclei, thus blocking most of the biological response of the target cell to androgens9. It has been proposed for a combined treatment with a potent LHRH (luteinizing hormone – releasing hormone) agonist to block androgen formation, as the hormonal therapy of choice in prostatic carcinoma10.

Hydantoins are important precursors in organic synthesis of natural and nonnatural amino acids, via acid-, base- or enzyme-catalyzed hydrolysis. The most commonly used reaction for the synthesis of hydantoins is Bucherer-Bergs synthesis11 starting from aldehydes or ketones. This multicomponent reaction is not stereoselective resulting in formation of racemic mixture of hydantoins, if the prochiral ketone was used as a substrate.

Other methods for preparation of hydantoins include reaction of amino amides with triphosgene12, carbodiimides with α,β-unsaturated carboxylic acids13 and treatment of nitriles with organometallic reagents followed by addition of potassium cyanide and ammonium carbonate14,15.
Considering that 5-substituted hydantoins exhibit significant biological activities, in this paper we present the synthesis of novel 5-alkenyl hydantoins which also could be suitable for further functionalization.

RESULTS AND DISCUSSION

In the multicomponent reaction under Bucherer-Bergs conditions, construction of 5-(alk-3-enyl)-hydantoins, starting from unsaturated aldehydes, ketones and α-allyl-β-ketoesters, was made in good yields (Scheme 1).

\[
\begin{align*}
1a & : R_1=R_2=R_4=H, R_3=Me \\
1b & : R_1=R_3=R_4=Me, R_2=H \\
1c & : R_1=Me, R_2=COOEt, R_3=R_4=H \\
1d & : R_1=Et, R_2=COOEt, R_3=R_4=H \\
1e & : R_1=n-Pr, R_2=COOEt, R_3=R_4=H \\
2a & : R_1=R_2=R_4=H, R_3=Me \\
2b & : R_1=R_2=R_3=Me, R_4=H \\
2c & : R_1=Me, R_2=COOEt, R_3=R_4=H \\
2d & : R_1=Et, R_2=R_3=R_4=H \\
2e & : R_1=n-Pr, R_2=R_3=R_4=H
\end{align*}
\]

Scheme 1. Bucherer-Bergs synthesis of 5-alkenyl hydantoins

This reaction with trans-4-hexenal results in formation of hydantoin 2a with retention of double bond configuration. Unsaturated ketone 1b was converted to already known hydantoin 2b which was acetylated by reflux reaction in acetyanhydride into corresponding N(1)-acetyl derivative 3 in good yield (Scheme 2).

\[
\begin{align*}
2b & \text{ (81%)}
\end{align*}
\]

Scheme 2. N(1)-Acetylation of 5-alkenyl hydantoin 2b

Synthesis of 5-alkenyl hydantoins from β-ketoesters was performed in two steps. First step was α-alkylation of β-ketoesters with allyl chloride in anhydrous ethanol, in the presence of sodium ethoxide as a base. In the next step α-allyl-β-ketoesters were used as the substrates in Bucherer-Bergs reaction. Forming of 2-(4-alkyl-2,5-dioxo-imidazolidin-4-yl)-pent-4-enoic acid ethyl esters 2c (Scheme 1) as the resulting products was expected. However, only in the case of 2-allyl-ethylacetoacetate this product was obtained. In the cases where 1d and 1e were used as substrates unexpected fully decarboxylated products were observed (Scheme 3). Obviously, decarboxylation occurs after addition of HCl during the work up process.
Scheme 3. Synthesis of 5-alkenyl hydantoins from β-ketoesters

These alkenyl-hydantoins could serve as useful precursor for further modification, especially for the synthesis of bicyclic hydantoins. Moreover, substituted hydantoins are important building blocks for the synthesis of nonnatural amino acids.

EXPERIMENTAL

The β-ketoesters, allyl chloride, 6-methyl-5-hepten-2-one and trans-4-hexen-1-ol were obtained from Fluka. α-Allyl-β-ketoesters were sintetized by the reaction of allyl chloride with β-ketoesters in the presence of EtONa in ethanol as a solvent. Aldehyde trans-4-hexenal was obtained by the oxidation reaction of trans-4-hexen-1-ol with pyridinium chlorochromate in CH2Cl2 as a solvent. All liquid substances were purified by fractional distillation (semimicro and micro Vigreux columns). All alkenyl hydantoins were characterized by FTIR, 1H and 13C NMR spectroscopy. Hydantoins 2b16 and 2e17 are already known compounds.

IR spectra were recorded on the Perkin-Elmer FT-IR spectrometer model Spectrum One. The 1H and 13C NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 200 MHz in CDCl3 solution using TMS as internal standard.

Bucherer-Bergs synthesis of hydantoins (2a-e)

To a 100 cm3 round bottom flask equipped with reflux condenser 10 mmol substrate (1a-e), 0.98 g NaCN (20 mmol) and 3.84 g (40 mmol) (NH4)2CO3 were added to the solution of 50 cm3 of 50% aqueous EtOH. The reaction mixture was stirred and heated to reflux at 50-65 °C for 8-24 h. The reaction mixture was then cooled to ambient temperature and filtered. The pH was adjusted to ~2 by carefully adding conc. HCl. The filtrate was placed in a refrigerator for better crystallization of the products. In some cases filtrates were first evaporated under reduced pressure and after that returned to the refrigerator to crystallize. The crude material was recrystallized from appropriate solvent.

5-Pent-3-enyl-imidazolidine-2,4-dione (2a). White needles; IR (KBr, ν cm−1): 3436 (NH), 3205 (NH), 2926 (CH), 1778 (C=O), 1637 (C=C), 1422 (δ CH3), 1401 (δ CH2). 1H NMR (CDCl3, ppm): 1.63 (d, J=6.6 Hz), 1.91 (m 2H), 2.23 (q, J=7.2 Hz, 2H), 4.10 (dd, J=4.2, 7.8 Hz, 1H), 5.39 (m 1H), 5.55 (m 1H), 6.07 (bs NH), 8.40 (bs NH). 13C NMR (CDCl3, ppm): 12.72, 22.62, 31.39, 58.52, 126.15, 128.03, 137.80, 140.92, 157.59, 174.80. Yield: 1.377 g (82%).

5-But-3-enyl-5-ethyl-imidazolidine-2,4-dione (2d). White needles; IR (KBr, ν cm−1): 3448 (NH), 3170 (NH), 3068 (CH olefinic), 2975 (CH aliphatic), 1753 (C=O), 1716 (C=O), 1642 (C=C), 1454 (δ CH3), 1406 (δ CH2). 1H NMR (CDCl3, ppm): 0.93 (t, J=7.2 Hz, 3H), 1.60-2.22 (m 6H), 5.02 (m 2H), 5.77 (m...
1H), 6.41 (bs NH), 9.02 (bs NH). $^{13}$C NMR (CDCl$_3$, ppm): 7.55, 27.82, 30.00, 35.64, 67.49, 115.68, 136.79, 157.44, 177.03. Yield: 1.330 g (73%).

5-But-3-enyl-5-propyl-imidazolidine-2,4-dione (2e). White needles; IR (KBr, cm$^{-1}$): 3391 (NH), 3216 (NH), 3051 (CH olefinic), 2960 (CH aliphatic), 1764 (C=O), 1712 (C=O), 1644 (C=C), 1466 ($\delta$ CH$_2$), 1435 ($\delta$ CH$_3$). $^1$H NMR (CDCl$_3$, ppm): 0.92 ($\delta$, J=7.4 Hz, 3H), 1.22 (sex, J=7.4 Hz, 2H), 1.38-2.22 (m 6H), 5.01 (m 2H), 5.76 (m 1H), 6.88 (bs NH), 9.47 (bs NH). $^{13}$C NMR (CDCl$_3$, ppm): 13.86, 16.62, 27.73, 35.89, 39.08, 67.06, 115.56, 136.79, 157.83, 177.33. Yield: 1.352 g (69%).

N(1)-acetylation of hydantoin 2b (3)
To a 50 cm$^3$ round bottom flask equipped with reflux condenser 333.3 mg (1.7 mmol) 2b was added to the fresh distilled acetonhydride (5 cm$^3$) and heated to reflux for 3 h. Reaction mixture was then poured into water and placed in a refrigerator to crystallize. The crystalline product was filtered off, washed with distilled water and dried in a desiccator over anhydrous CaCl$_2$.

1-Acetyl-5-methyl-5-(4-methyl-pent-3-enyl)-imidazolidine-2,4-dione (3). White needle-like crystals. IR (KBr, cm$^{-1}$): 3205 (NH), 3042 (CH olefinic), 2924 (CH aliphatic), 1764 (C=O), 1712 (C=O), 1644 (C=C), 1466 ($\delta$ CH$_2$), 1435 ($\delta$ CH$_3$). $^1$H NMR (CDCl$_3$, ppm): 1.54 ($d$, J=1.4 Hz, 3H), 1.65 ($d$, J=1.4 Hz, 3H), 1.66 ($s$ 3H), 1.95 ($m$ 3H), 2.47 ($m$ 1H), 2.55 ($s$ 3H), 4.98 ($t$sep, J=7.4 Hz, 1.4 Hz, 1H). $^{13}$C NMR (CDCl$_3$, ppm): 17.53, 22.70, 23.12, 25.59, 26.12, 34.18, 68.72, 122.07, 133.31, 153.11, 169.65. Yield: 327.4 mg (81%).

CONCLUSION

In summary, synthesis of series 5-(alk-3-enyl)-hydantoins with unsaturated aldehydes, ketones and $\alpha$-allyl-$\beta$-ketoesters Bucherer-Bergs reaction conditions were described. Some of hydantoins were N(1)-acetylated in good yield, by using acetonhydride. Bucherer-Bergs reaction with $\alpha$-allyl-$\beta$-ketoesters (not only with $\alpha$-allyl-$\beta$-ethylacetoacetate) results in formation of unexpected fully decarboxylated products. These compounds are potential biologically active compounds. They can also be used in the synthesis of bicyclic hydantoins and nonnatural $\alpha$-amino acids.

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