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

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Abstract: In the multicomponent reaction under Bucherer-Bergs conditions, construction of 5-(alk-3-enyl)-hydantoins 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 acetanhydride. 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 compounds[1]. Hydantoins have a wide range of biological activities, such as anticonvulsant[2], antitumor[3], antiarrhytmic[4] and antiandrogenic[5]. Activity of hydantoin derivatives depends on the nature of substitution of hydantoin ring[6]. In spite of the different examples of biological actions, 5,5-disubstituted hydantoins are mainly considered as anticonvulsant agents[7], the most notably being 5,5-diphenylhydantoin (Dilantin, Phenytoin). 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]hydantoin[8] 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 androgens[9]. 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 carcinoma[10].

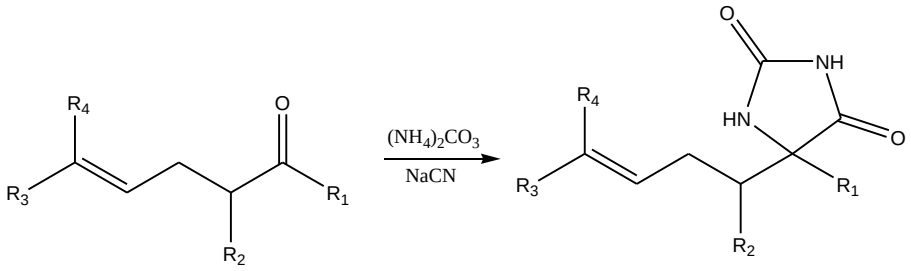
Hydantoins are important precursors in organic synthesis of natural and nonnatural amino acids, via acid-, base- or enzyme-catalyzed hydrolysis. The most commonly used reaction for the synthesis of hydantoins is Bucherer-Bergs synthesis[11] starting from aldehydes or ketones. This multicomponent reaction 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 triphosgene[12], carbodiimides with α,β-unsaturated carboxylic acids[13] and treatment of nitriles with organometallic reagents followed by addition of potassium cyanide and ammonium carbonate[14,15].

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).



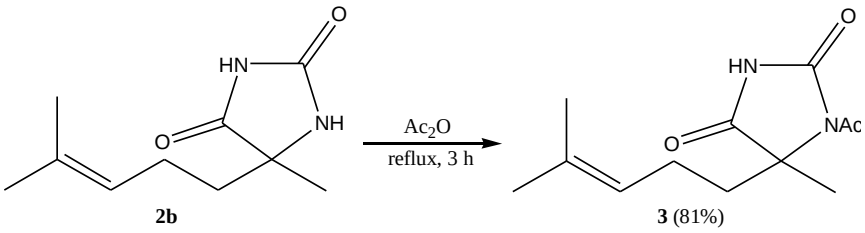
1a-e **2a-e**

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_3=R_4=Me, R_2=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

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

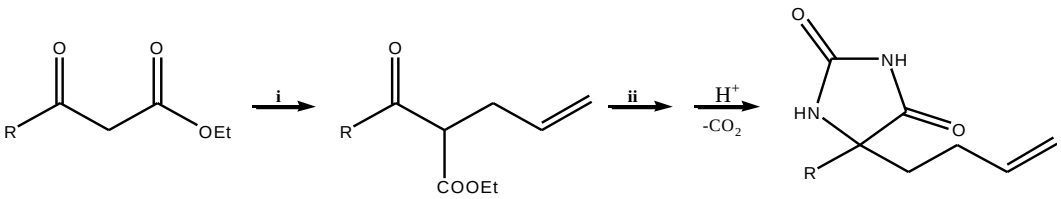
This reaction with *trans*-4-hexenal results in formation of hydantoin **2a** with retention of double bond configuration. Unsaturated ketone **1b** was converted to already known hydantoin **2b** which was acetylated by reflux reaction in acetanhydride into corresponding N(1)-acetyl derivative **3**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



2b **3** (81%)

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** (Scheme1) 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.



R=Et, n-Pr
i: allyl chloryde, EtONa, EtOH
ii: $(NH_2)CO_3$, NaCN, EtOH/H_2O

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 CH_2Cl_2 as a solvent. All liquid substances were purified by fractional distillation (semimicro and micro Vigreux columns). All alkenyl hydantoins were characterized by FTIR, ^{1}H and ^{13}C NMR spectroscopy. Hydantoins **2b**[16] and **2c**[17] are already known compounds.

IR spectra were recorded on the Perkin-Elmer FT-IR spectrometer model Spectrum One. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 200 MHz in $CDCl_3$ solution using TMS as internal standard.

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

To a 100 cm^3 round bottom flask equipped with reflux condenser 10 mmol substrate (**1a-e**), 0.98 g NaCN (20 mmol) and 3.84 g (40 mmol) $(NH_4)_2CO_3$ were added to the solution of 50 cm^3 of 50% aqueous EtOH. The reaction mixture was stirred and heated to reflux at 50-65 ^{o}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 CH_3), 1401 (δ CH_2). **^{1}H NMR** ($CDCl_3$, 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). **^{13}C NMR** ($CDCl_3$, ppm): 12.72, 22.62, 31.39, 58.52, 126.15, 128.03, 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 CH_3), 1406 (δ CH_2). **^{1}H NMR** ($CDCl_3$, 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, ν cm^{-1}): 3391 (NH), 3216 (NH), 3051 (CH olefinic), 2960 (CH aliphatic), 1764 (C=O), 1712 (C=O), 1644 (C=C), 1466 (δ CH_3), 1435 (δ CH_2). **^{1}H NMR** ($CDCl_3$, ppm): 0.92 (*t*, 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 condeser 333.3 mg (1.7 mmol) **2b** was added to the fresh distilled acetanhydride (5 cm^3) and heated to reflux for 3 h. Reaction mixture was than 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, ν cm^{-1}): 3205 (NH), 3042 (CH olefinic), 2924 (CH aliphatic), 1798 (C=O), 1746 (C=O), 1678 (C=C). **^{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 (*tsep*, 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 α-allyl-β-ketoesters Bucherer-Bergs reaction conditions were described. Some of hydantoins were N(1)-acetylated in good yield, by using acetanhydride. Bucherer-Bergs reaction with α-allyl-β-ketoesters (not only with α-allyl-β-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 α-amino acids.

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REFERENCES

1. G. Baccolini, C. Boga, C. Delpivo, G. Micheletti, *Tetrahedron Lett.* **2011**, *52*, 1713.
2. (a) M. M. El- Kerdawy, A. S. Tantawy, A. A. Abououf, *Egypt. J. Chem.* **1974**, *17*, 845; (b) B. Dziedzic, A. Szadowska, A. Kaminska, *Acta Pol. Pharm.* **1978**, *35*, 423.
3. T. R. Rodgers, M. P. Lamontagne, A. Markovac, A. B. Ash, *J. Med. Chem.* **1977**, *20*, 591.
4. M. L. Brown, G. B. Brown, W. J. Brouillette, *J. Med. Chem.* **1997**, *40*, 602.
5. M. Sanudo, M. Garcia-Valverde, S. Marcaccini, T. Torroba, *Tetrahedron* **2012**, *68*, 2621.
6. L. Hroch, M. Hruskova, J. Schmitz, G. Schnakenburg, M. Gutschow, *Synthesis* **2012**, *44*, 1907.
7. A. Spinks, W. S. Waring, *Progr. Med. Chem.* **1963**, *3*, 313.
8. T. Ojasoo, J. P. Raynand, *Prog. Cancer Res. Ther.* **1983**, *25*, 11.

9. J. G. Tezon, M. H. Vazquez, J. A. Blaquier, *Endocrinology* **1982**, *111*, 2039.
10. F. A. Lefebvre, C. Seguin, A. Belanger, S. Caron, M. R. Sariamand, F. Labrie, *Prostate* **1982**, *3*, 569.
11. E. Were, *Chem. Rev.* **1950**, *46*, 403.
12. D. Zhang, X. C. Xing, G. D. Cuny, *J. Org. Chem.* **2006**, *71*, 1750.
13. A. Volonterio, M. Zanda, *Lett. Org. Chem.* **2005**, *2*, 44.
14. C. Montagne, M. Shipman, *Synlett* **2006**, 2203.
15. C. Montagne, J. J. Shiers, M. Shipman, *Tetrahedron Lett.* **2006**, *47*, 9207.
16. J. Weichet, J. Hodrova, L. Blaha, *Coll. Czech. Chem. Commun.* **1966**, *31*, 1323.
17. J. Giroux, R. Granger, I. S. Beaulaton, J. Lanet, *Therapie* **1959**, *14*, 42.