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Short Note

5-Ethoxy-1-(4-methoxyphenyl)-5-methyl-3-phenylimidazolidine-2,4-dione

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Abstract: The title compound is a hydantoin derivative that has been synthesized through a three-component reaction of ethyl pyruvate, *p*-anisidine and phenyl isocyanate. This paper provides a comprehensive spectral dataset for the title compound, including ^{1}H and ^{13}C{^{1}H} NMR, IR, HRMS, and X-ray crystallography analyses. A tentative mechanism comprising two complementary pathways is provided based on additional experiments with the preformed intermediates.

Keywords: multicomponent reactions; hydantoins; heterocycles

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1. Introduction

Hydantoins are important nitrogen heterocyclic compounds that have been known for more than a century, since their discovery by Adolf von Baeyer in 1861 [1]. Structurally related to barbiturates, hydantoins are efficient calcium channel blockers, and for this reason they are mainly used in medicine as anticonvulsant drugs, such as in the case of phenytoin, phosphenytoin or ethotoin (Figure 1) [2–4]. In addition, numerous hydantoin derivatives show assorted biological activities such as antidiabetic [5], antiulceric [6], antiarrhythmic [7], antimicrobial [8], antiviral [9] or antitumoral [10] ones and are also used in agrochemistry as herbicidal and antifungal agents [11–13].

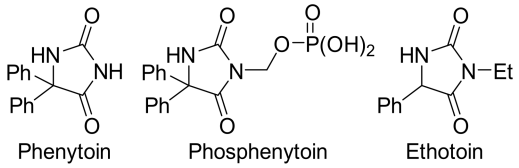
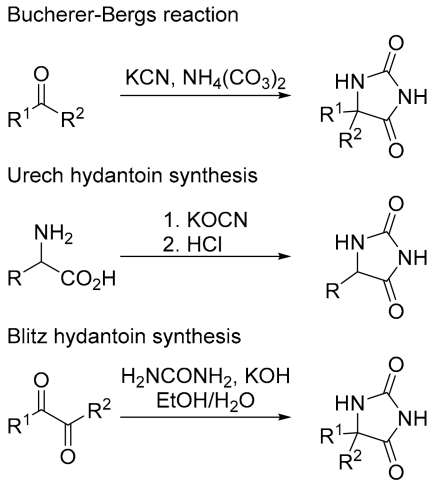


Figure 1. Structure of anticonvulsant hydantoins.

Traditionally, Bucherer–Bergs [14], Urech [15] and Biltz [16] reactions are used for the formation of the hydantoin skeleton, starting from ketones or aldehydes, aminoacid derivatives or dicarbonylic compounds, respectively (Scheme 1), but in the last century a wide number of alternative methods for the construction of the hydantoin scaffold have been reported [17–20]. In particular, much attention has been paid to to the development of multicomponent protocols to access the hydantoin heterocycle [21–24]. These multicomponent approaches have many benefits in comparison with stepwise reactions, including their step efficiency, atom economy, high exploratory power and convergence, and, in addition, they are ideally suited for an environmentally friendly synthesis [25,26].

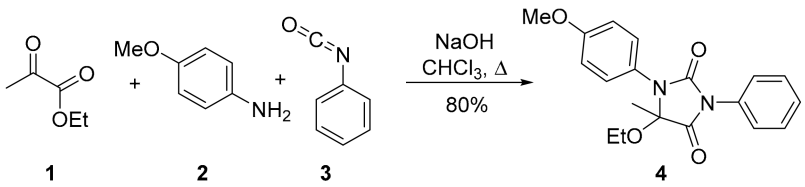


Scheme 1. Traditional synthesis of hydantoins.

In this context, a few years ago, we described a Brönsted acid-catalyzed multicomponent synthesis of dihydropyrrolones starting from amines, aldehydes and pyruvate derivatives [27]. More recently, we have reported the enantioselective version of such a reaction, using chiral phosphoric acids [28], and next we have extended the reaction to the use of acetylene carboxylates instead of pyruvate derivatives [29]. Moreover, the scope of the reaction has been expanded to the synthesis of the phosphorus and fluorine substituted substrates [30]. Continuing with our interest in the applications of multicomponent reactions for the synthesis of heterocyclic substrates, herein we report a pyruvate-based three-component reaction for the synthesis of a hydantoin derivative holding a tetrasubstituted stereocenter.

2. Results and Discussion

The overnight reaction of ethyl pyruvate **1**, *p*-anisidine **2** and phenyl isocyanate **3** in the presence of sodium hydroxide in refluxing chloroform affords hydantoin derivative **4** in a good yield after purification by column chromatography and crystallization from diethyl ether (Scheme 2).



Scheme 2. Three-component synthesis of hydantoin **4**.

Hydantoin derivative **4** was fully characterized on the basis of its ^{1}H and ^{13}C{^{1}H} NMR, DEPT and IR spectra and HRMS (see ESI). One of the most characteristic signals for substrate **4** in the ^{1}H NMR spectrum (CD_3OD) is the ethoxy group, which is seen as two representative double quartets at δ_H = 3.53 ppm ($^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.0 Hz) and δ_H = 3.85 ppm ($^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.0 Hz), typical for a diastereotopic methylene group in an ethyl moiety. The methyl substituent at the 5-membered heterocycle appears as a singlet at δ_H = 1.52 ppm, in the typical range for a methyl group of a quaternary carbon.

Likewise, in the ^{13}C NMR spectrum of hydantoin **4**, the quaternary stereogenic carbon presents a chemical shift at δ_C = 86.1 ppm, and its ethoxy and methyl substituents can be detected by the chemical shifts at δ_C = 11.1 and 55.8 ppm and δ_C = 17.8 ppm, respectively. The urea and amide type carbonyl groups are in this case seen at δ_C = 149.5 and 166.3 ppm. The substitution of the carbon atoms was verified by Distortionless Enhancement by Polarization Transfer (DEPT) experiments.

The IR spectrum of hydantoin **4** shows several absorptions in the interval ν = 3054–2911 cm^{-1} corresponding to the stretching vibration of aromatic and aliphatic C–H bonds, and the overtones of the aromatic rings in the area at ν = 2356–2302 cm^{-1}. The most relevant absorption observed in the IR spectrum corresponds to the stretching of amide and urea C=O bonds at ν =1728 cm^{-1}. The vibration of aromatic C–C bonds results in a strong absorption at ν = 1511 cm^{-1}, and the stretching vibration of the C–N bond is manifested as an absorption at ν = 1406 cm^{-1}. Due to the presence of the ethoxy group, the IR spectrum shows a doublet and a multiplet for the asymmetric and symmetric stretching bonds of the C–O–C bonds at ν = 1252 and 1049 cm^{-1}, respectively.

Moreover, the high-resolution mass spectrometry experiment shows a single peak corresponding to a molecular ion with an exact mass of 341.1504 amu that fits with the predicted mass of the calculated molecular formula far within the standard tolerated deviation.

In order to unequivocally determine the identity of hydantoin **4**, a monocrystal was isolated from a mixture of CH_2Cl_2/hexanes, and then an X-ray diffraction analysis was performed to clearly confirm the structure of substrate **4** (Figure 2). Key features of the crystal structure of hydantoin **4** are the planar arrangement of the 5-membered heterocycle, as expected by the presence of two carbonyl sp^2 carbons, which are conjugated with the two nitrogen atoms, and the twisted conformation of both aromatic substituents in order to minimize the steric interactions with the carbonyl and the ethoxy and methy groups.

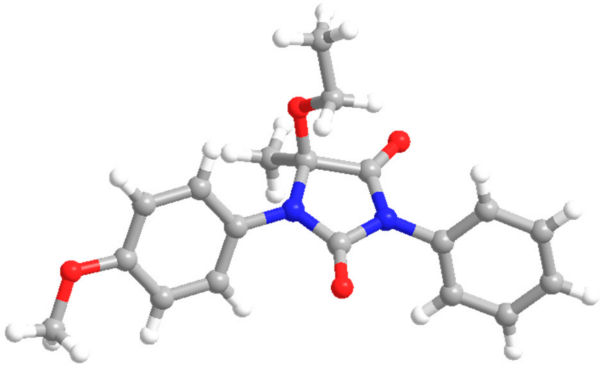
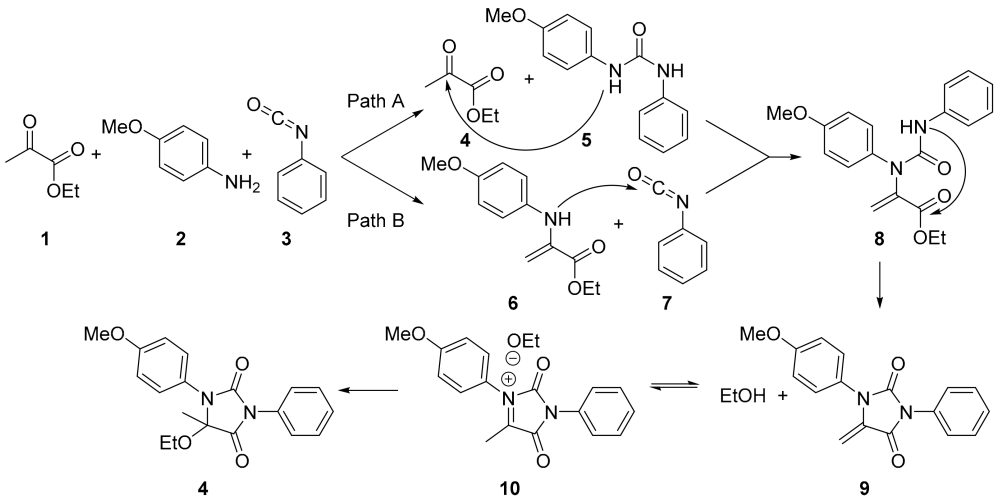


Figure 2. X-ray structure of hydantoin **4** (*S* enantiomer shown).

Based on the determined structure of hydantoin substrate **4**, we propose two complementary mechanisms for the three-component process (Scheme 3). In the first of our proposals, *p*-anisidine **2** and phenyl isocyanate **3** are combined to form urea derivative **5**, which, by means of a condensation reaction between the most nucleophilic nitrogen of the urea substrate and the ketone functionality of ethyl pyruvate **4**, leads to the formation of α-enaminoester **8**. Next, a nucleophilic addition of the second nitrogen of the urea to the ester moiety would afford methylene-hydantoin species **9** with the loss of ethanol. Then, the acid-base isomerization of the enamine functional group in **9** leads to iminium species **10**, which is stabilized by the presence of an ethoxide anion, whose formation is favored by the presence of sodium hydroxide. Finally, the ethoxide nucleophile anion undergoes a nucleophilic addition to the iminium moiety to afford hydantoin substrate **4**. In the second proposal, enamine intermediate **8** arises from an initial amine-carbonyl condensation of ethyl pyruvate **1** and *p*-anisidine **3**, leading to enamine **6**, followed by a subsequent nucleophilic addition of the enamine nucleophile to phenyl isocyanate **3**. In view of the fact that if the reaction is carried out with the preformation of the intermediate urea **5** or enamine **6**, hydantoin substrate **4** is equally obtained, we conclude that both mechanisms are indeed implied in this transformation.



Scheme 3. Proposed pathway for the formation of hydantoin **4**.

3. Materials and Methods

3.1. General Experimental Information

Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light. ^{1}H, and ^{13}C-NMR spectra were recorded on a Varian Unity Plus (Varian Inc., NMR Systems, Palo Alto, Santa Clara, CA, USA) (at 300 MHz, 75 MHz, 120 MHz and 282 MHz, respectively) and on a Bruker Avance 400 (Bruker BioSpin GmbH, Rheinstetten, Germany) (at 400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual $CHCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C NMR). Coupling constants (*J*) are reported in Hertz. Data for ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, coupling constant, integration. Multiplicity abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR peak assignments were supported by distortionless enhanced polarization transfer (DEPT). High resolution mass spectra (HRMS) were obtained by positive-ion electrospray ionization (ESI). Data are reported in the form *m*/*z* (intensity relative to base = 100). Infrared spectra (IR) were taken in a Nicolet iS10 Thermo Scientific spectrometer (Thermo Scientific Inc., Waltham, MA, USA) as neat solids. Peaks are reported in cm^{-1}.

*3.2. Experimental Procedures and Characterization Data for Hydantoin **4***

A solution of ethyl pyruvate (116 mg, 111 μL, 1 mmol), *p*-anisidine (123 mg, 1 mmol) and phenyl isocyanate (119 mg, 109 μL, 1 mmol) in $CHCl_3$ (3 mL) was stirred under reflux overnight in the presence of NaOH (80 mg, 2 mmol). The reaction was washed with water (2 × 5 mL), and the organic layer was dried over $MgSO_4$ and concentrated under vacuum. The resulting crude residue was purified by column chromatography (AcOEt/Hexanes 5:95) followed by crystallization from Et_2O, affording 271 mg of hydantoin **4** (79%) as a white solid. M.p.: 140–142 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53–7.44 (m, 5H, 5 × CH_{Ar}, Ph), 7.36 (d, $^{3}J_{HH}$ = 9.1 Hz, 2H, 2 × CH_{Ar}, *p*-$CH_3OC_6H_4$), 7.02 (d, $^{3}J_{HH}$ = 9.1 Hz, 2H, 2 × CH_{Ar}, *p*-$CH_3OC_6H_4$), 3.85 (dq, $^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.0 Hz, 1H, CH_2, OEt), 3.84 (s, 3H, CH_3O), 3.53 (dq, $^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.0 Hz, 1H, CH_2, OEt), 1.52 (s, 3H, CH_3), 1.31 (dd, $^{3}J_{HH}$ = 7.0 Hz, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3, OEt) ppm. ^{13}C-NMR {^{1}H} (101 MHz, $CDCl_3$) δ 166.3 (NC=O), 155.0 ($C_{quat}O$, *p*-$CH_3OC_6H_4$), 149.5 (NC=ON), 127.4 ($C_{quat}N$, Ph), 125.4 (2 × CH_{Ar}, Ph), 124.7 (CH_{Ar}, Ph), 123.4 (2 × CH_{Ar}, Ph),122.8 ($C_{quat}N$, *p*-$CH_3OC_6H_4$), 122.4 (2 × CH_{Ar}, *p*-$CH_3OC_6H_4$), 110.8 (2 × CH_{Ar}, *p*-$CH_3OC_6H_4$), 55.8 (OCH_2, OEt), 51.8 (OCH_3, *p*-$CH_3OC_6H_4$), 17.8 (CH_3), 11.1 (CH_3, OEt) ppm. FTIR (neat) ν_{max}: 3054 (Ar-H

st), 2980–2911 (Alk-H st), 2356–2302 (ar comb), 1728 (C=O st), 1511 (ar C–C), 1406 (C–N st), 1252 (d, C–O–C st, as), 1049 (m, C–O–C st, sy), 737 (=C–H δ oop), 701 (d, CH_2 γ) cm^{-1}. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{48}N_2O_9$ 341.1501, Found 341.1504. Crystal Data for $C_{19}H_{20}N_2O_4$ (M = 340.37 g/mol): monoclinic, space group P21/c (no. 14), a = 12.55957(12) Å, b = 10.65990(12) Å, c = 13.02617(14) Å, a = 90.0°, β = 99.1587(10)°, g = 90.0°, V = 1721.76(3) Å3, Z = 4, T = 150.00(10) K, μ(CuKα) = 0.763 mm^{-1}, r_{calc} = 1.313 g/cm^3, 30,974 reflections measured (7.13° ≤ 2Θ ≤ 137.908°), 3188 unique (Rint = 0.0355, Rsigma = 0.0146) which were used in all calculations. The final R1 was 0.0470 (I > 2σ(I)) and wR2 was 0.1155 (all data). CCDC Deposition number: 2080208.

4. Conclusions

The synthesis of hydantoin derivative **4** is accomplished by a three-component reaction of ethyl pyruvate, *p*-anisidine and phenyl isocyanate. ^1H and $^{13}C\{^1H\}$ NMR, IR, HRMS and X-ray crystallography analyses unequivocally confirm the identity of the title compound. Moreover, two complementary pathways for the mechanism of the formation of hydantoin **4** are provided on the basis of additional experiments starting from the preformed intermediates.

Supplementary Materials: ^1H and ^{13}C-NMR, IR and HRMS spectra, ortep drawing, cif file and mol file of compound **4**.

Author Contributions: Conceptualization, A.L.-F., X.d.C., E.M.d.M., F.P. and J.V.; methodology, A.L.-F. and X.d.C.; software, A.L.-F. and X.d.C.; validation, E.M.d.M. and J.V.; formal analysis, A.L.-F. and X.d.C.; investigation, A.L.-F. and X.d.C.; resources, E.M.d.M., F.P. and J.V.; data curation, A.L.-F. and X.d.C.; writing—original draft preparation, J.V.; writing—review and editing, A.L.-F., X.d.C., E.M.d.M., F.P. and J.V.; visualization, E.M.d.M., F.P. and J.V.; supervision, E.M.d.M. and J.V.; project administration, E.M.d.M. and J.V.; funding acquisition, E.M.d.M., F.P. and J.V. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available in the supplementary materials file or on request from the corresponding author (^1H and ^{13}C-NMR, IR and HRMS spectra, ortep drawing and cif file).

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the corresponding author.

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