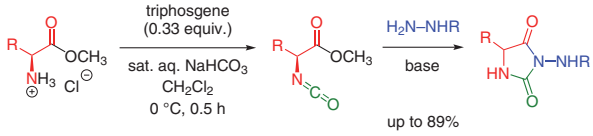
New Synthesis of 3-Aminohydantoins via Condensation of Hydrazines with Isocyanates Derived from α-Amino Esters

Houda Bouchnak[a]
Thierry Ollevier*[b]
Jamil Kraïem*[a]

[a] Laboratoire de Développement Chimique, Galénique et Pharmacologique des Médicaments LR12ES09, Faculté de Pharmacie, Université de Monastir, Monastir, Tunisia
jamil.kraiem@fphm.u-monastir.tn
[b] Département de Chimie, Université Laval, 1045 Avenue de la Médecine, Québec, QC, G1V 0A6, Canada
thierry.ollevier@chm.ulaval.ca



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Abstract A new, simple, and efficient method for the synthesis of 3-aminohydantoins was reported in two steps, starting from the corresponding *L*-amino esters. Commercially available α-amino esters were converted into the corresponding isocyanate derivatives, which were then subjected to the condensation reaction with hydrazine hydrate and arylhydrazines, in the presence of DMAP and DIPEA. This method provides the corresponding 3-aminohydantoins in moderate and good yields under a simple and practical protocol.

Key words 3-aminohydantoins, α-amino esters, hydrazines, isocyanates, cyclization

Hydantoins or 1,3-imidazolidin-2,4-diones are five-membered nitrogen heterocycles that display a wide range of biological activities, some of them being used as efficient drugs for various pathologies.[1–5] In particular, 3-aminohydantoin derivatives are very promising compounds in the field of medicinal chemistry.[6–9] Indeed, several molecules containing the aminohydantoin moiety are endowed with various biological activities and have proven to be effective in the treatment of a large array of diseases (Figure 1).[5–10] In a recent study, we reported the 3-amino-5-benzylimidazolidine-2,4-dione (3-aminohydantoin derived from phenyl alanine) as a promising scaffold in dopaminergic neuroprotection and neurorescue in the *in vivo* and *in vitro* 6-hydroxydopamine models of Parkinson's disease.[11] We believe that 3-aminohydantoins are still understudied in medicinal chemistry. This probably arises from the methods of preparation of these compounds, which are not sufficiently developed to make these molecules easily available.[1]

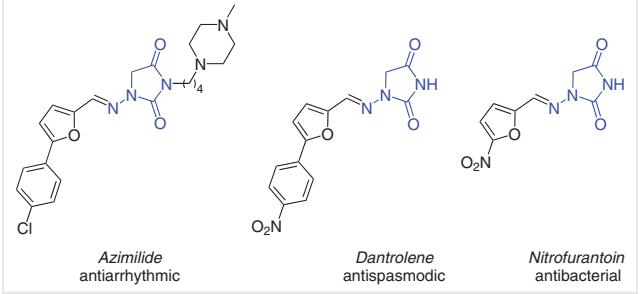


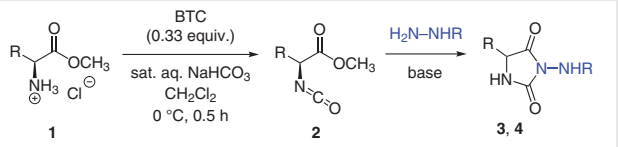
Figure 1 Examples of available 3-aminohydantoin-derived drugs

Despite the simplicity of the chemical structure of 3-aminohydantoins and their importance as promising scaffolds and bioactive molecules, only few methods describing their synthesis have been reported in the literature. In 1985, Lalezari *et al.* reported a one-step synthesis of 3-aminohydantoins via the condensation of α-aminoacids with *tert*-butyl hydrazinecarboxylate in the presence of quinoline as the solvent and base. This method requires heating at an elevated temperature (240 °C) during 3–10 h.[12,13] Yousong et *al.* described a seven-step synthesis of substituted 3-aminohydantoin derivatives, starting from an aldehyde and diethylmalonate. The synthesis involves an isocyanate as an intermediate, which is further reacted with an arylhydrazine. An intramolecular cyclization, in the presence of metallic sodium and ethanol affords the corresponding hydantoin.[14] Hamuro *et al.* disclosed a five-step solid-phase synthesis of 3-aminohydantoins from amino acids using Phoxime resin.[15] Janda *et al.* also described a six-step soluble-polymer-supported synthesis of 3-aminohydantoins from amino acids.[16] More recently, Beauchemin *et al.* developed a cascade synthesis of 3-aminohydantoins using α-amino esters and *N*-substituted isocyanates.[10] These methods have some drawbacks, such as harsh reaction conditions, in some cases low yields, multistep synthesis, and above all the nonavailability of the reagents used in these

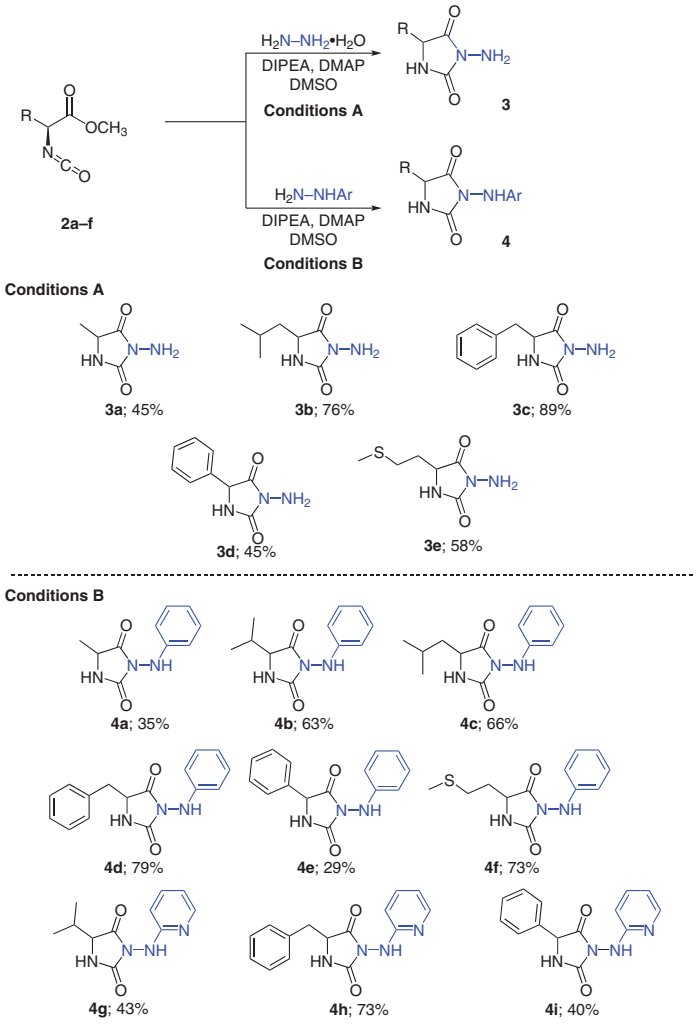
reactions especially for the last three methods.[10,15,16] We believe that more economical and practical methods, using more available and less expensive reagents, to easily access 3-aminohydantoins are still needed.

In this work, we developed a new method for the easy access to 3-aminohydantoins using available and inexpensive reagents under relatively mild conditions. This method involves firstly preparing isocyanate derivatives from L-amino esters, and, secondly, reacting these isocyanates with hydrazine hydrate and aromatic hydrazines in the presence of diisopropyl ethylamine (DIPEA, 3 equiv.) and dimethyl aminopyridine (DMAP, 0.2 equiv.) in dimethyl sulfoxide (DMSO) as the solvent to provide 3-aminohydantoin derivatives (Scheme 1).

Initially, commercially available α-amino esters **1a–f** were converted into the corresponding isocyanate derivatives **2a–f** according to a literature method (Scheme 1).[17,18] Triphosgene (bis(trichloromethyl)carbonate, BTC) reacted with the amine group of the α-amino ester in biphasic medium (50:50 CH_2Cl_2/sat. aq. $NaHCO_3$) to provide quantitatively the corresponding isocyanate, which was used in the next step without purification. All isocyanate derivatives **2a–f** prepared in this work are known compounds.[19–21] In the second step, isocyanates **2a–f** were reacted with (aryl)hydrazine to afford the corresponding 3-aminohydantoins (Scheme 2).[22]



Scheme 1 Two-step synthesis of 3-aminohydantoins from α-amino esters



Scheme 2 Scope of 3-aminohydantoins **3a–e** and **4a–i**.[22] *Reagents and conditions*: isocyanate **2a–f** (5 mmol), hydrazine (5 mmol), DIPEA (15 mmol), DMAP (1 mmol), 0 °C, 0.5 h; 100 °C, 0.5 h (conditions A)/120 °C, 8 h (conditions B).

Hydantoins **3** and **4** were prepared using different reaction conditions, i.e., temperature and reaction time (Scheme 2). This is probably due to the difference between the reactivity of hydrazine as the nucleophile and that of arylhydrazines. Indeed, it was found that the reaction of isocyanates with hydrazine hydrate requires heating up to 100 °C for 0.5 h to provide the corresponding 3-aminohydantoins **3** with moderate to good yields. However, the reaction of arylhydrazines requires a higher temperature (120 °C) and a longer reaction time (8 h) to provide the corresponding 3-aminohydantoins **4** with satisfactory yields. Notably, only a low yield of the product was obtained when 3-amino-5-benzylimidazolidine-2,4-dione was heated at 150 °C without using DMAP.[5] In this work, we prepared a series of fourteen 3-aminohydantoins. 3-Aminohydantoins **3a–e** possessing an NH_2 group linked to N-3 of the heterocycle were isolated in 45–89% yields, whereas substituted hydantoins **4a–i** on the N-3 atom of the cycle were obtained in 29–79% isolated yields. While L-amino esters were used as precursors, we found that all synthesized 3-aminohydantoins were obtained in the racemic form. This was confirmed by measuring their optical rotation ($[\alpha]_D$ = 0 in all cases). This result is somewhat expected, since Beauchemin *et al.* obtained the same result when they prepared 3-aminohydantoins following their procedure, which required heating to 100 °C.[10]

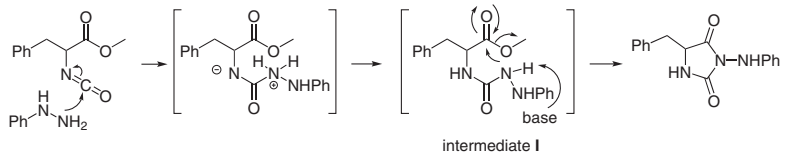
Firstly, the addition of the hydrazine on the isocyanate group leads to the noncyclic intermediate (Scheme 3). Subsequently, by heating the reaction mixture at the appropriate temperature, the cyclization occurred by attack of the nitrogen atom on the ester function. We found that the use of the DIPEA (3 equiv.)/DMAP (0.2 equiv.) system was necessary to ensure product formation. Without using this basic system, significantly lower yields of 3-aminohydantoins were obtained.[5] Apparently, the basic system facilitates the transfer of the proton linked to nitrogen which attacks the ester during the cyclization step. In order to confirm the proposed mechanism, we isolated the intermediate formed by the reaction between phenylhydrazine and isocyanate **2a** after stirring for 0.5 h at 0 °C and before subjecting the reaction mixture to heating. Both ^1H and ^{13}C NMR data of the obtained intermediate are in agreement with the proposed structure of the intermediate **I** highlighted in Scheme 3 (see the Supporting Information).

We believe that our method for the synthesis of 3-aminohydantoins, described in this work, has several advantages over those described in the literature for the following reasons. (i) Nakamura *et al.* described the synthesis of 3-aminohydantoins **3c** and **3d** as precursors to prepare new useful molecules for the treatment of Alzheimer's desease.[8] These authors used the method of Lalezari *et al.*,[12] which provided the 3-aminohydantoins in 10% and 23%, yields respectively. The same 3-aminohydantoins were prepared using our method under milder conditions and with higher yields (**3c**: 89%, **3d**: 45%; Scheme 2). (ii) Janda *et al.* prepared 3-aminohydantoins **3a**, **3b**, and **3c** in six steps starting from the corresponding amino esters.[16] The chemical yields obtained using their method are in the 60–67% yield range, whereas our method provided the same 3-aminohydantoins in steps with 46–89% yields (**3a**: 45%, **3b**: 76%, **3c**: 89%). (iii) Hamuro *et al.*[15] reported a five-step procedure to prepare 3-aminohydantoins **4a** and **4d** in 47% and 34% yields, respectively, starting from the corresponding amino acids. In this work, 3-aminohydantoins **4a** and **4d** were obtained in two steps with 35% and 79% yields, respectively. (iv) Our method does not require the use of specific reagents, such as Phoxime resin [15] or MeO-PEG-$CH_2CH_2NH_2$,[16] which are rather expensive polymers used as leaving groups to facilitate the cyclization step. Likewise, aminoisocyanates, used by Beauchemin et *al.*[10] as reagents to prepare 3-aminohydantoins, are not readily available.[23]

In summary, we have developed a new method for the synthesis of 3-aminohydantoins in two steps, relying on the use of available and low-cost reagents, such as α-amino esters, together with hydrazine hydrate or simple arylhydrazines. This method provides a variety of substituted and nonsubstituted 3-aminohydantoins in moderate to good yields and appears a simpler and more practical method than the previously disclosed ones. This method will allow easier access to 3-aminohydantoins in order to exploit them in the field of medicinal chemistry. Further work taking advantage of this method is under way and will be reported in due course.

Conflict of Interest

The authors declare no conflict of interest.



Scheme 3 Proposed reaction mechanism of the 3-aminohydantoin formation

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2217-6821.

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(18) **Typical Procedure for the Synthesis of Isocyanates 2a–f**
A mixture of phenylalanine methyl ester hydrochloride (**1a**, 4.30 g, 20 mmol) and triphosgene (BTC) (1.98 g, 6.66 mmol) in saturated aqueous sodium bicarbonate (100 mL) and dichloromethane (100 mL) was stirred in an ice bath for 0.5 h and then poured into a 500 mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to afford quantitatively the corresponding isocyanate **2a**. The isocyanate was used in the next step without further purification.
Methyl 2-Isocyanato-3-phenylpropanoate (2a)
The product was isolated as colorless oil (3.88 g, 19.0 mmol, 95%). IR (KBr): 2257, 1747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 3 H), 7.23 (dd, J^1 = 8.4 Hz, J^2 = 1.6 Hz, 2 H), 4.29 (dd, J^1 =7.6 Hz, J^2 = 4.4 Hz, 1 H), 3.80 (s, 3 H), 3.17 (dd, J^1 = 13.6 Hz, J^2 = 4.4 Hz, 2 H), 3.05 (dd, J^1 = 13.6 Hz, J^2 = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 135.6, 129.3, 128.6, 127.4, 126.5, 58.5, 53.1, 39.8.
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(22) **Experimental Procedure and Characterization Data**
Isocyanate **2** (5 mmol), hydrazine hydrate (0.25 mL, 5 mmol), DIPEA (2.55 mL, 15 mmol), and DMAP (0.122 g, 1 mmol) were dissolved in anhydrous dimethyl sulfoxide (2 mL). The mixture was stirred for 0.5 h at 0 °C and then heated for 0.5 h at 100 °C in a pressure tube. The progress of the reaction was monitored by TLC. After cooling the reaction mixture to room temperature, the product was precipitated by adding diethyl ether (5 mL). The precipitate was then filtered and purified by flash chromatography using CH_2Cl_2/MeOH (90:10) as the eluent.
5-[2-(Methylthio)ethyl]-3-(phenylamino)imidazolidine-2,4-dione (4f)
According to the general procedure, the product was isolated as white solid (0.966 g, 3.6 mmol, 73%); R_f = 0.44 (CH_2Cl_2/CH_3OH, 95:5); mp 164–166 °C. IR (KBr): 3359, 3108, 1778, 1732 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.52 (s, 1 H, Ph–NH), 8.34 (s, 1 H, NH–CO), 7.22–6.67 (m, 5 H, Ph), 4.37 (dd, J^1 = 6.8 Hz, J^2 = 5.0 Hz, 1 H, CH–CH_2), 2.62 (m, 2 H, S–CH_2), 2.07 (s, 3 H, CH_3–S), 1.90 (m, 2 H, CH_2–CH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.0, 155.6, 147.2, 129.3, 120.0, 112.5, 54.3, 31.6, 29.1, 15.0. HRMS: *m/z* calcd for $C_{12}H_{15}N_3O_2S$ [M^+]: 266.0959; found [M + H^+]: 266.0958.
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