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A versatile method for the synthesis of substituted 1-aminohydantoin derivatives

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Abstract—An efficient and versatile method has been developed for the synthesis of 1-aminohydantoin derivatives which can be substituted at all the possible positions of the hydantoin ring. The starting materials are aldehydes, ketones, carboxylic acids and hydrazides as well as isocyanates readily available from commercial sources. The semicarbazide-type reaction product of an *N*-acyl-*N*′-(1-cyanoalkyl)hydrazine, obtained from the above materials by methods known from the literature, and an isocyanate is cyclized in the presence of a basic catalyst to yield 1-acylamino-4-imino-2-oxoimidazolidine derivatives whose acid catalyzed hydrolysis leads to 1-aminohydantoin derivatives in good to excellent yields. The last two steps are carried out in a single reaction medium.

Although the first 1-aminohydantoin derivatives (1-aminoimidazolidine-2,4-diones) were synthesized at the end of the 19th century[1] no general and versatile route has been developed for the synthesis of 1-aminohydantoins which can be substituted in any or all of the possible substituent positions. Many publications[2–5] and patents[6,7] describe the preparation of 1-aminohydantoins carrying substituents only in certain positions. Recently a paper has been published describing solid support synthesis of 1-aminohydantoins.[8]

The significance of the derivatives containing the 1-aminohydantoin core structure is exemplified by several commercially available drugs (Fig. 1), for example the antimicrobial Nitrofurantoin[9] and the sceletal muscle relaxant Dantrium.[10] The diversity in activity of hydantoins also bearing 1-methyleneamino groups is shown by two other compounds, Azimilide and BW68C whose activity is different from that of the previously mentioned two compounds. Azimilide is a candidate drug against arrhythmia,[11] while BW68C is a potent inhibitor of platelet aggregation acting as an agonist of the prostaglandin D-receptor.[12] The anthelmintic activity of 1-aminohydantoins bearing a cinnamoyl moiety on the amino function (Fig. 1) has also been reported.[13]

The goal of this work was to develop a simple, general route (Scheme 1) for the synthesis of 1-aminohydantoins **4** which can bear substituents at all the possible ring positions.

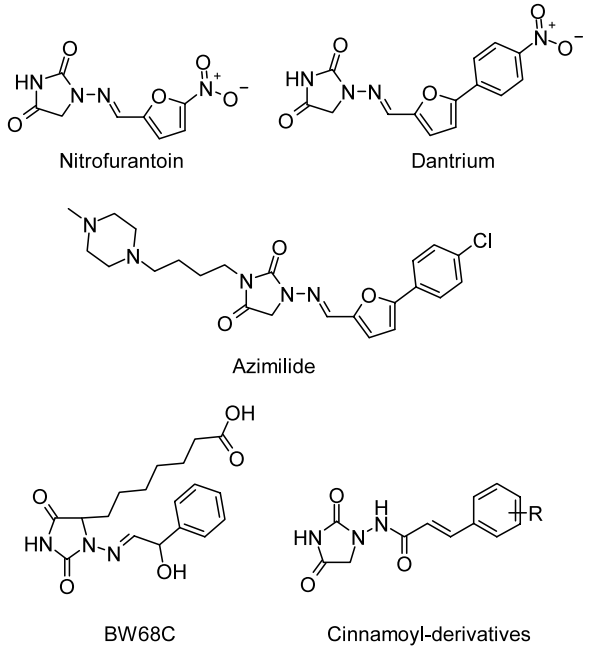

Figure 1.

Keywords: 1-aminohydantoin derivatives; intramolecular cyclization; versatile synthesis method.
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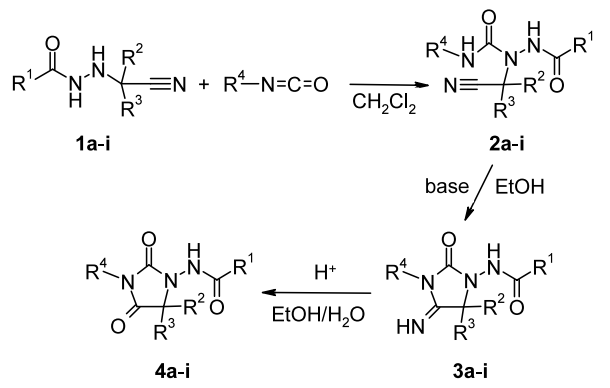


Scheme 1. General synthetic route for the preparation of 1-aminohydantoins.

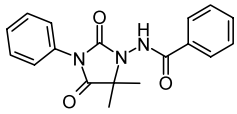
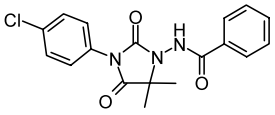
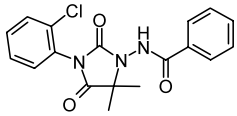
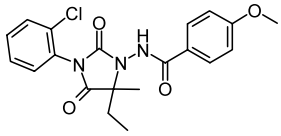
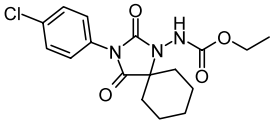
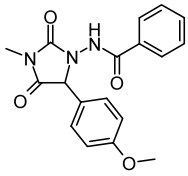
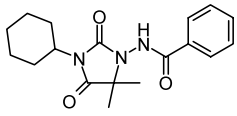
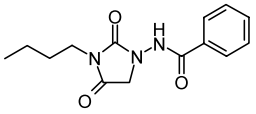
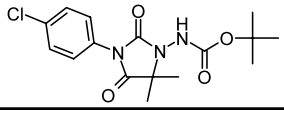
To obtain 1-aminohydantoins, firstly an isocyanate was reacted with the amino nitrogen of an *N*-acyl-*N*′-(1-cyanoalkyl)hydrazine **1** resulting in the intermediary 1-acyl-2-(1-cyanoalkyl)-4-substituted-semicarbazides **2**. Intramolecular cyclization via nucleophilic attack of the amide-nitrogen on the cyano carbon atom produced imino-compounds **3** the hydrolysis of which gave 1-aminohydantoins **4** (Table 1). The cyclization and subsequent hydrolysis were conducted in one pot.

Hydrazides of type **1** can be obtained through many known routes. Such methods include a Strecker-type reaction using a carboxylic acid hydrazide, a ketone or an aldehyde and sodium or potassium cyanide,[14,15] addition of hydrogen cyanide to *N*-substituted hydrazones,[16] acylation of α-cyanoalkyl-hydrazines,[17] and condensation of acid hydrazides with a cyanohydrin.[18,19] The introduction of a large number of different substituents is possible due to availability of a very large number of starting materials, i.e. aldehydes, ketones, carboxylic acids, hydrazides and isocyanates, which are required for the synthesis of **1**.

The addition of isocyanates to **1** was carried out in dichloromethane from which the intermediates **2** were precipitated. The formation of **3** in solution takes place by a slow spontaneous cyclization of **2**, however, in the presence of 5–10 mol% of base, cyclization was complete within a few hours. The reactions were carried out in EtOH where **2** was only partially soluble, but after the addition of 5 mol% NaOEt in EtOH **2** dissolved within 2–3 min which was followed by the reappearance of a precipitate after about 0.5 h. The cyclization resulting in the formation of **3h** ($R^1=Ph$, $R^2=R^3=H$, $R^4=n$Bu) occured within 10 min without addition of base. This is probably due to the lack of steric hindrance as the carbon atom next to the cyano function is not substituted (cf. **3a**–**g**, **3i**). The acid-catalyzed hydrolysis of **3** yielding **4** required a reaction time ranging from a few hours to 2 days.

The reaction procedure is as follows. To a suspension of **2** in EtOH was added 0.05 mol% of NaOEt in EtOH. Following cyclization, the reaction mixture was acidified by addition of aqueous 2 M HCl solution and was allowed to stand for 5–48 h. The 1-aminohydantoin derivatives formed were separated by filtration in good to excellent yields based on **2**.[20] All compounds **4**, except **4a**, are new, and their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy[21] as well as by elemental analyses.[21]

Table 1. Structures, yields and melting points of the 1-aminohydantoins synthesized

Compound	Structure	Yield (%)	M.p. (°C)
4a		91	182-183
4b		95	204
4c		81	216-217
4d		68	181-183
4e		79	139-140
4f		80	174-175
4g		86	200-201
4h		63	97-98
4i		88	130-131

In both the ^{1}H and ^{13}C NMR spectra the signals corresponding to the protons and the carbons, respectively, of the two methyl groups of **4c** gave two singlets instead of one and a similar duplication was observed for the signals corresponding to the methyl and ethyl groups at the C5 position of **4d**. In both compounds the presence of an *ortho* substituent resulted in restricted rotation around the N3(hydantoin)–C1(phenyl) bond. In the ^{13}C NMR spectrum of **4d**, having an optically active center as well, the signals of most of all the other carbons were also doubled.

In summary, we have elaborated a versatile and general method for the synthesis of substituted 1-aminohydantoin derivatives. The semicarbazide-type products **2**, obtained by the addition reaction of an *N*-acyl-*N'*-(1-cyanoalkyl)hydrazine **1** and an isocyanate, were cyclized to yield imino-derivatives **3** which were subsequently hydrolyzed in the same medium to 1-aminohydantoin. For the preparation of hydrazines **1**, a large number of potential starting materials, i.e. aldehydes, ketones, carboxylic acids and hydrazides are available from commercial sources.

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20. The experimental conditions for the synthesis of 1-aminohydantoins is illustrated by the synthesis of *N-[3-(4-chlorophenyl)-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl]-benzamide* ***4b***: A solution of **1b** (R^1 = Ph, R^2 = R^3 = Me; 2.03 g, 10 mmol) and 4-chlorophenyl isocyanate (1.61 g, 10.5 mmol) in dichloromethane (10 ml) was stirred overnight, then the precipitated product was filtered by suction and washed with dichloromethane to obtain pure **2b** (R^1 = Ph, R^2 = R^3 = Me, R^4 = 4-ClPh). Yield: 73%; mp 164°C. To a suspension of **2b** (1.43 g, 4 mmol) in EtOH (10 ml) was added a solution of 0.2 M NaOEt in EtOH (1 ml, 0.2 mmol). The material dissolved within 2–3 min after which a precipitate appeared. After 2 h, 2N aqueous HCl (4 ml, 8 mmol) was poured into the reaction mixture which was then left at rt for 20 h. The resulting solid material was filtered by suction, washed with water and dried to give **4b** in 95% yield.
21. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) and ^{13}C NMR spectral, as well as elemental analysis data of the new 1-aminohydantoin derivatives.

4b: ^{1}H NMR: δ 1.55 (s, 6H), 7.40–7.48 (m, 6H), 7.54–7.58 (m, 1H), 7.95–7.97 (m, 2H), 10.21 (s, 1H). ^{13}C NMR: δ 22.08 (2C), 63.37, 127.01 (2C), 127.76 (2C), 128.18 (2C), 128.76 (2C), 129.75, 131.24, 132.21, 133.31, 152.62, 167.40, 173.71. Anal. calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.43; H, 4.51; N, 11.74; Cl 9.91. Found: C, 60.49; H, 4.43; N, 11.69; Cl, 9.98%.

4c: ^{1}H NMR: δ 1.51 and 1.54 (2s, 2×3H), 7.25–7.28 (m, 2H), 7.41–7.46 (m, 4H), 7.54–7.57 (m, 1H), 7.65–7.67 (m, 2H), 9.35 (s, 1H). ^{13}C NMR: δ 21.64, 22.81, 64.82, 127.41 (2C), 127.93, 128.49, 128.84, 130.17 (2C), 130.32, 130.70, 131.07, 132.44, 132.93, 153.94, 166.64, 173.47. Anal. calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.43; H, 4.51; N, 11.74; Cl 9.91. Found: C, 60.51; H, 4.47; N, 11.80, Cl, 9.96%.

4d: ^{1}H NMR: δ 0.95 and 0.99 (2t, 3H, J = 7.41 Hz), 1.49 and 1.52 (2s, 3H), 1.75–1.94 (m, 2H), 3.78 (s, 3H), 6.95–6.99 (m, 1H), 7.15–7.20 (m, 2H), 7.26–7.29 (m, 1H), 7.37–7.46 m (3H), 7.54–7.58 (m, 1H). ^{13}C NMR: δ 8.22 and 8.60, 21.23 and 21.44, 28.86 and 29.43, 55.53, 68.90 and 68.99, 111.81 and 111.88, 119.74, 119.85 and 119.91, 128.02 and 128.09, 129.14 and 129.18, 129.71 and 129.73, 130.60 and 130.65, 130.75, 130.96, 131.22 and 131.34, 131.60 and 131.63, 133.00 and 133.59, 154.95 and 155.03, 159.76, 166.64 and 166.74, 173.07 and 173.15. Anal. calcd for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; N, 10.46; Cl, 8.82. Found: C, 59.69; H, 4.97; N, 10.55; Cl, 8.75%.

4e: ^{1}H NMR: δ 1.29 (t, 3H, J = 7.14 Hz), 1.60–1.78 (m, 6H), 1.84–2.06 (m, 4H), 4.25 (q, 2H, J = 7.14 Hz), 7.39–7.40 (m, 5H). ^{13}C NMR: δ 14.38, 21.24 (2C), 24.37, 31.34 (2C), 62.92, 64.04, 127.34 (2C), 129.17 (2C), 129.82, 133.88, 153.48, 156.22, 172.72. Anal. calcd for $C_{17}H_{20}ClN_3O_4$: C, 55.82; H, 5.51; N, 11.49; Cl, 9.69. Found: C, 55.91; H, 5.47; N, 11.41; Cl, 9.78%.

4f: ^{1}H NMR: δ 3.12 (s, 3H), 3.79 (s, 3H), 5.35 (s, 1H), 6.91 (d, 2H, J = 8.89 Hz), 7.23 (d, 2H, J = 8.79 Hz), 7.30–7.34 (m, 2H), 7.48 (m, 2H), 7.68 (dd, 1H, J = 7.14 and 1.29 Hz). ^{13}C NMR: δ 25.43, 55.37, 65.45, 114.62 (2C), 124.15, 127.43 (2C), 128.66 (2C), 128.99 (2C), 130.45, 132.75, 157.78, 160.45, 166.61, 170.02. Anal. calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.63; H, 4.99; N, 12.31%.

4g: ^{1}H NMR: δ 1.19–1.43 (m, 6H), 1.40 (s, 6H), 1.66–1.86 (m, 2H), 2.08–2.18 (m, 2H), 3.91–3.99 (m, 1H), 7.27–7.31 (m, 2H), 7.43 (t, 2H, J = 7.45 Hz), 7.68 (d, 1H, J = 7.45 Hz). ^{13}C NMR: δ 22.06 (2C), 24.91, 25.72 (2C), 29.45 (2C), 51.91, 63.31, 127.32 (2C), 128.48 (2C), 139.51, 132.33, 155.39, 166.74, 175.01. Anal. calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.73; H, 6.98; N, 12.84%.

4h: ^{1}H NMR: δ 0.86 (t, 3H, J = 7.2 Hz), 1.22–1.30 (m, 2H), 1.38–1.46 (m, 2H), 3.15–3.20 (m, 2H), 4.58 (brs, 1H), 5.52 (m, 2H), 7.54 (m, 2H), 7.62 (m, 1H), 7.95 (d, 2H, J = 7.40 Hz). ^{13}C NMR: δ 13.66, 18.83, 31.89, 36.51, 40.68, 116.30, 127.69 (2C), 128.95 (2C), 130.73, 133.19, 156.51, 166.56. Anal. calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.99; H, 6.28; N, 15.34%.

4i: ^{1}H NMR: δ 1.49 (s, 9H), 1.50 (s, 6H), 6.65 (brs, 1H), 7.40 (s, 4H). ^{13}C NMR: δ 22.11 (2C), 28.04 (3C), 62.97, 82.71, 127.15 (2C), 129.15 (2C), 129.89, 133.86, 146.73, 154.91, 173.64. Anal. calcd for $C_{16}H_{20}ClN_3O_4$: C, 54.32; H, 5.70; N, 11.88; Cl, 10.02. Found: C, 54.41; H, 5.75; N, 11.81; Cl, 9.95%.