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A convenient synthesis of 3-amino-4-imino(thioxo)-imidazolidin-2-ones

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Abstract—Subsequent treatment of diethylphosphonopropyl α-aminonitriles with 1,1′-carbonyldiimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and hydrazines afforded substituted 3-amino-4-imino-imidazolidin-2-ones. Their acidic hydrolysis and their reactions with hydrogen sulfide are described.

1. Introduction

The chemistry and properties of hydantoins and their derivatives have been investigated for more than 140 years. The hydantoin moiety represents an important pharmacophore, which is present in various biologically active compounds. Over the past decades intensive research effort in industry and academia has been dedicated to the structural modification of hydantoins and their derivatives. Novel lead structures and drug candidates have emerged from this research and different types of hydantoin derivatives have been introduced into the market as pharmaceuticals.

The 1-aminohydantoin Nitrofurantoin[1,2] is an antimicrobial drug for the treatment of urinary tract infections, while its analog Dantrolene[1,2] represents a well-known skeletal muscle relaxant. Another 1-aminohydantoin, Azimilide,[1,2] is a promising drug candidate for the treatment of cardiac arrhythmia. Phenytoin,[3] a 5,5-diphenyl-imidazolidin-2,4-dione, is an anticonvulsant used for the treatment of epilepsy.

Sulfahydantoin[4] acts as a serine protease inhibitor and the glucopyranosylidene-spiro-thiohydantoin[5] is an efficient inhibitor of muscle and liver glycogen phosphorylases (Fig. 1).

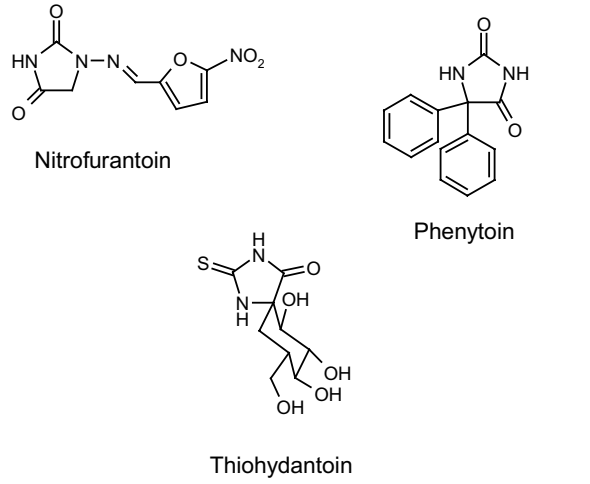

Figure 1. Selected hydantoin derivatives.

In recent years considerable effort has been devoted to the development of novel and more efficient methods for the preparation of hydantoin derivatives. Besides conventional multi-step methods, one-pot,[1] solid-phase[2] and microwave-assisted[6] approaches have been published. Our group reported the synthesis of 3-aralkoxy-4-imino-imidazolidin-2-ones[7] by treatment of α-cyanomethyl substituted aralkoxyureas with anhydrous EtOH–HCl as well as their base catalyzed Dimroth rearrangement into 4-aralkoxy-imino-imidazolidin-2-ones. We now describe a practical and efficient synthetic pathway for the preparation of 3-amino-4-imino(thioxo)-imidazolidin-2-ones (**4**, **5**).

Keywords: Diethylphosphonopropyl α-aminonitriles; 1,1′-Carbonyldiimidazole; 1,1′-Carbonyl-di-(1,2,4-triazole); Hydrazines; 3-Amino-4-imino(thioxo)-imidazolidin-2-ones.
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2. Results and discussion

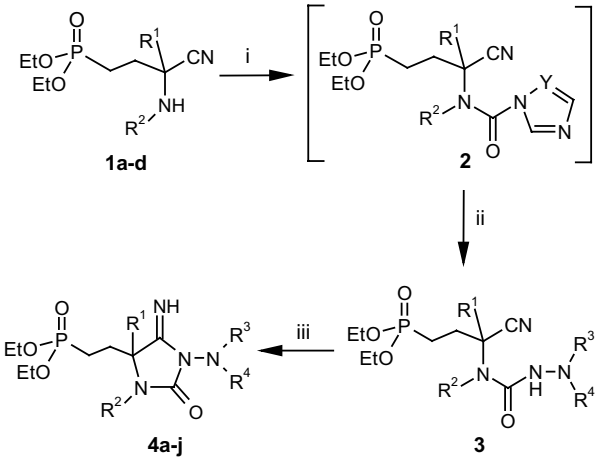
α-Aminonitriles (**1a–d**) have been prepared by Strecker synthesis and were used for the preparation of **4** after structure confirmation by ^{1}H and ^{13}C NMR.[7,8] Coupling of diethylphosphonopropyl α-aminonitriles (**1a–d**) with 1,1′-carbonyldiimidazole (CDI) or 1,1′-carbonyldi-(1,2,4-triazole) (CDT) in dry THF furnished the azolide-intermediates (**2**), which were converted into the open-chained intermediates (**3**) by treatment with various hydrazines. Nucleophilic attack of the semicarbazide nitrogen to the nitrile carbon in refluxing THF in the presence of triethylamine afforded 3-amino-4-imino-imidazolidin-2-ones (**4a–f,i,j**) in 59–73% yield. However, ring closure of *N*-substituted intermediates **3g,h** failed under similar reaction conditions. Finally, their cyclization was accomplished in the presence of sodium hydride in dry THF (Scheme 1).

In contrast to 3-aralkoxy-4-imino-imidazolidin-2-ones, which underwent Dimroth rearrangement to 4-aralkoxy-imino-imidazolidin-2-ones in the presence of triethylamine,[7] 3-amino-4-imino-imidazolidin-2-ones (**4**) are solid and stable compounds. According to NMR and IR spectra, recorded from the crude reaction mixtures, no Dimroth rearrangement of **4** to 4-hydrazono-imidazolidin-2-ones took place. Furthermore, IR, ^{1}H and ^{13}C NMR data of compounds **4** were consistent with those obtained for 3-aralkoxy-4-imino-imidazolidine-2-ones.

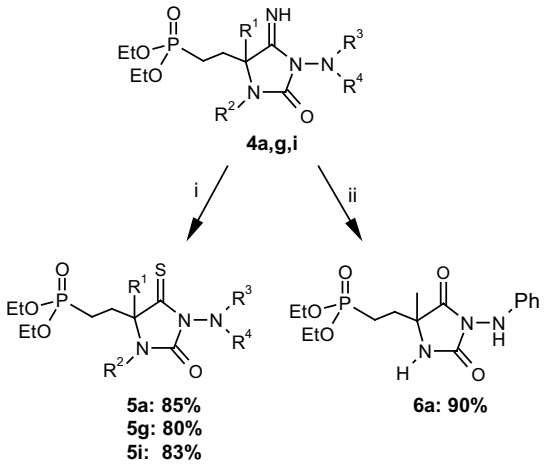
During the reaction the formation of intermediates **3**, which are characterized by a sharp (C=O) band at 1670–1680 cm^{-1} was monitored by IR spectroscopy. The disappearance of the (CN) band in the IR spectra at 2231 cm^{-1} and the appearance of a new sharp absorption band at 1745–1760 cm^{-1} clearly indicated the formation of **4** (Table 1).

Thionation of **4a,g,i** by hydrogen sulfide in dry dichloromethane in the presence of dry pyridine afforded 3-amino-4-thioxo-imidazolidin-2-ones (**5a,g,i**) while the acidic hydrolysis of **4a** furnished the imidazolidin-2,4-dione **6a** (Scheme 2).[7,9]

Finally, dealkylation of phosphonic esters **4a**, **5a** and **6a** with bromotrimethylsilane gave phosphonic acids **7**, **8**, **9**. (Scheme 3). The phosphonic acid group is present in various pharmaceuticals and pesticides and represents an important pharmacophore and carboxylic acid bioisoster.[10,11] The introduction of a phosphonic acid functionality offers access to water soluble hydantoin derivatives.



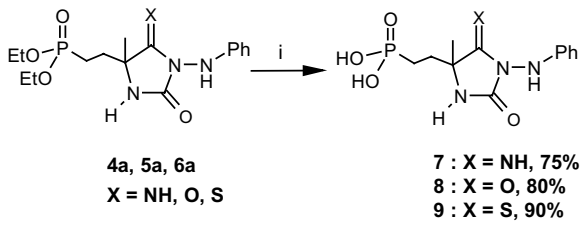
Scheme 1. Synthesis of 3-amino-4-imino-imidazolidin-2-ones (**4a–j**). Reagents and conditions: (i) CDI or CDT; (ii) $H_2N–NR^3R^4$; (iii) Et_3N/heating or THF, NaH; Y = CH, N.



Scheme 2. Thionation and acidic hydrolysis of **4**. Reagents and conditions: (i) H_2S, pyridine, CH_2Cl_2; (ii) 20% HCl/THF.

Table 1. Synthesis of 3-amino-4-imino-imidazolidin-2-ones (**4a–j**) from α-aminonitriles (**1a–d**)

4	R^1	R^2	R^3	R^4	4 Yield (%)
a	CH_3	H	H	C_6H_5	73
b	CH_3	H	H	4-F–C_6H_4	65
c	CH_3	H	H	H	63
d	CH_3	H	H	*t*-Bu	62
e	CH_3	H	H	2-Pyridyl	60
f	CH_3	H		$–(CH_2)_5–$	71
g	CH_3	CH_3		$–(CH_2)_5–$	59
h	CH_3	C_3H_5		$–(CH_2)_5–$	57
i	H	H	H	C_6H_5	65
j	H	H		$–(CH_2)_5–$	60



Scheme 3. Synthesis of phosphonic acids **7**, **8**, **9**. Reagents and conditions: (i) $TMSBr/CH_2Cl_2$ then THF/H_2O.

In summary, we have developed the first synthetic method for the preparation of substituted 3-amino-4-imino-imidazolidin-2-ones.[12,13] Our novel one-pot protocol allows the introduction of different types of substituents in the 1, 3 and 5 positions of the imidazolidin nucleus. In addition, compounds **4** are valuable precursors for the synthesis of 3-amino-4-thioxo-imidazolidin-2-ones (**5**) and 3-amino-imidazolidin-2,4-diones (**6**).[14] Currently we are investigating the Dimroth rearrangement of compounds **4** and the reactivity of the imino group. The results of these investigations will be reported in due course.

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12. *Procedure for the preparation of 3-amino-4-imino-imidazolidin-2-ones* (**4a–f,i,j**). A solution of α-amino- nitriles (**1a–d**) (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyldiimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) (10.5 mmol) in anhydrous THF (10 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate hydrazine (10 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, triethylamine (2.5 mL) was added and the reaction mixture was heated to 60–70 °C until a sharp band in the IR spectra appears at 1745–1760 cm^{-1}. After cooling to room temperature the reaction mixture was dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated and the remaining oil was crystallized from EtOAc/hexane to give **4a–f,i,j** as colorless solids. Due to its higher reactivity, CDT was used in case of α-aminonitriles derived from ketones.
13. *Typical experimental data for compounds* **4a**. *Diethyl 2-(4-imino-5-methyl-2-oxo-3-phenylaminio-imidazolidin-5-yl)ethylphosphonate.* Colorless solid (73%). Mp 169 °C (EtOAc/hexane); IR (KBr): ν = 3213, 1755, 1680, 1225, 1032 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.24 (t, J = 7.07 Hz, 6H), 1.37 (s, 3H), 1.41–1.98 (m, 4H), 3.89–4.08 (m, 4H), 6.65–7.20 (m, 5H), 7.41 (s, 1H), 8.04 (s, 1H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 16.69 (d, $^3J_{cp}$ = 6.14 Hz), 19.42 (d, $^1J_{cp}$ = 142.93 Hz), 24.92, 32.12 (d, $^2J_{cp}$ = 3.56 Hz), 58.70 (d, $^3J_{cp}$ = 17.29 Hz), 61.53 (d, $^2J_{cp}$ = 6.14 Hz), 112.50, 120.27, 129.47, 147.15, 154.80, 164.41; Anal. Calcd for $C_{16}H_{25}N_4O_4P$:C, 52.17; H, 6.84; N, 15.21. Found: C, 52.32; H, 6.94; N, 15.21.
14. *Typical experimental data for compound* **5a**. *Diethyl 2-(5-methyl-2-oxo-3-phenylaminio-4-thioxo-imidazolidin-5-yl)ethylphosphonate.* Colorless solid (85%). Mp 166 °C (Et_2O/hexane); IR (KBr): 3100, 1765, 1286, 1213, 1037 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 1.23 (t, J = 7.08 Hz, 6H), 1.48 (s, 3H), 1.63–2.01 (m, 4H), 3.93–4.03 (m, 4H), 6.69–7.18 (m, 5H), 8.78 (s, 1H), 9.78 (s, 1H); ^{13}C NMR (DMSO-d_6) δ: 16.67 (d, $^3J_{cp}$ = 5.37 Hz), 19.77 (d, $^1J_{cp}$ = 141.09 Hz), 27.73, 33.95 (d, $^2J_{cp}$ = 2.30 Hz), 61.63 (d, $^2J_{cp}$ = 6.90 Hz), 67.49 (d, $^3J_{cp}$ = 19.17 Hz), 112.78, 120.41, 129.40, 148.02, 154.29, 207.62; Anal. Calcd for $C_{16}H_{24}N_3O_4PS$:C, 49.86; H, 6.28; N, 10.90. Found: C, 49.77; H, 6.37; N, 10.74.