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Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones: a novel class of 4-iminohydantoins

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Abstract—Reactions of diethylphosphonoalkyl α-aminonitriles with 1,1′-carbonyl-diimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and *O*-substituted hydroxylamines under acidic conditions gave 3-alkoxy-4-imino-imidazolidin-2-ones, whereas in presence of triethylamine 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones were formed.
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1. Introduction

Development of preparative simple methods for the synthesis of new analogs of bioactive heterocyclic compounds represents an important task in synthetic organic and medicinal chemistry. The hitherto unknown 3-aralkoxy-4-imino-imidazolidin-2-ones (**I**) are analogs of 4-imino-hydantoins (**II**), a class of compounds which has attracted considerable attention in medicinal chemistry due to their antiandrogenic, antineoplastic, immunomodulating and schistosomicides properties.[1–4] Phosphonic acids have found wide applications as pesticides and pharmaceuticals and represent important bioisosters of carboxylic acids.[5–7] As a part of our ongoing studies on biologically active phosphonic acids and on the synthesis of new analogs of bioactive heterocyclic compounds we investigated the applicability of diethylphosphonoalkyl α-aminonitriles as starting materials for the synthesis of **I** (Fig. 1).

Figure 1. 3-Aralkoxy-4-imino-imidazolidin-2-ones (**I**) and 4-iminohydantoins (**II**).

Keywords: 3-Aralkoxy-4-imino-imidazolidin-2-ones; 4-Alkoxy(aralkoxy)imino-imidazolidin-2-ones; Diethylphosphonoalkyl α-aminonitriles; Dimroth rearrangement.
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2. Results and discussion

α-Aminonitriles (**1a–d**) have been prepared by Strecker synthesis and were used for the synthesis of **4**, **5** after structure confirmation by ^{1}H and ^{13}C NMR.[8] Successive treatment of diethylphosphonoalkyl α-aminonitriles (**1a–d**) with 1,1′-carbonyldiimidazole (CDI) or 1,1′-carbonyl-di-(1,2,4-triazole) (CDT) and O-substituted hydroxylamines led to open-chained alkoxy(aralkoxy)ureas intermediates (**3**), which upon heating in the presence of a base (e.g., triethylamine) furnished 4-alkoxy(aralkoxy)-imino-imidazolidin-2-ones **5**, which arose from **4** by base catalyzed Dimroth rearrangement in 50–75% overall yield.[9,10]

The structure of Dimroth rearrangement product **5f** was elucidated by X-ray crystal structure analysis. The crystal structure clearly showed that the 4-methylbenzyloxy-imino group is located at the C-3 of the imidazolidine nucleus and that only a hydrogen atom is attached to the N-1 ring nitrogen (Fig. 2).

Ring closure of intermediates **3a**,**b** in anhydrous EtOH–HCl and treatment of the resulting hydrochlorides of **4** with K_2CO_3 solution provided the desired isomeric 3-aralkoxy-4-imino-imidazolidin-2-ones (**4a–f**) as oily compounds in 60–75% yield (Scheme 1, Table 1).

By refluxing **4e** in THF for half an hour in presence of triethylamine we succeeded to prove the rearrangement of **4f** to **5f**. Discrimination between the structures of compounds **4** and **5** was accomplished by spectroscopic methods, by treatment of **4**, **5** with phenylisocyanate and by the acidic hydrolysis of **4b** into the corresponding

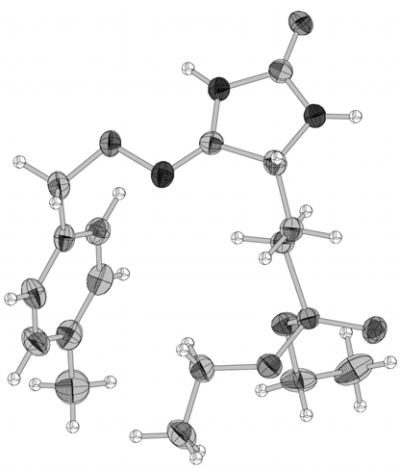


Figure 2. Perspective view of the X-ray crystal structure of **5f**.

imidazolidin-2,4-dione **6**. While the IR spectra of **4** where characterized by strong (C═O) absorption bands at 1758–1763 cm^{-1}, the spectra of **5** showed hypsochromic shifted (C═O) absorptions at 1730–1740 cm^{-1}.

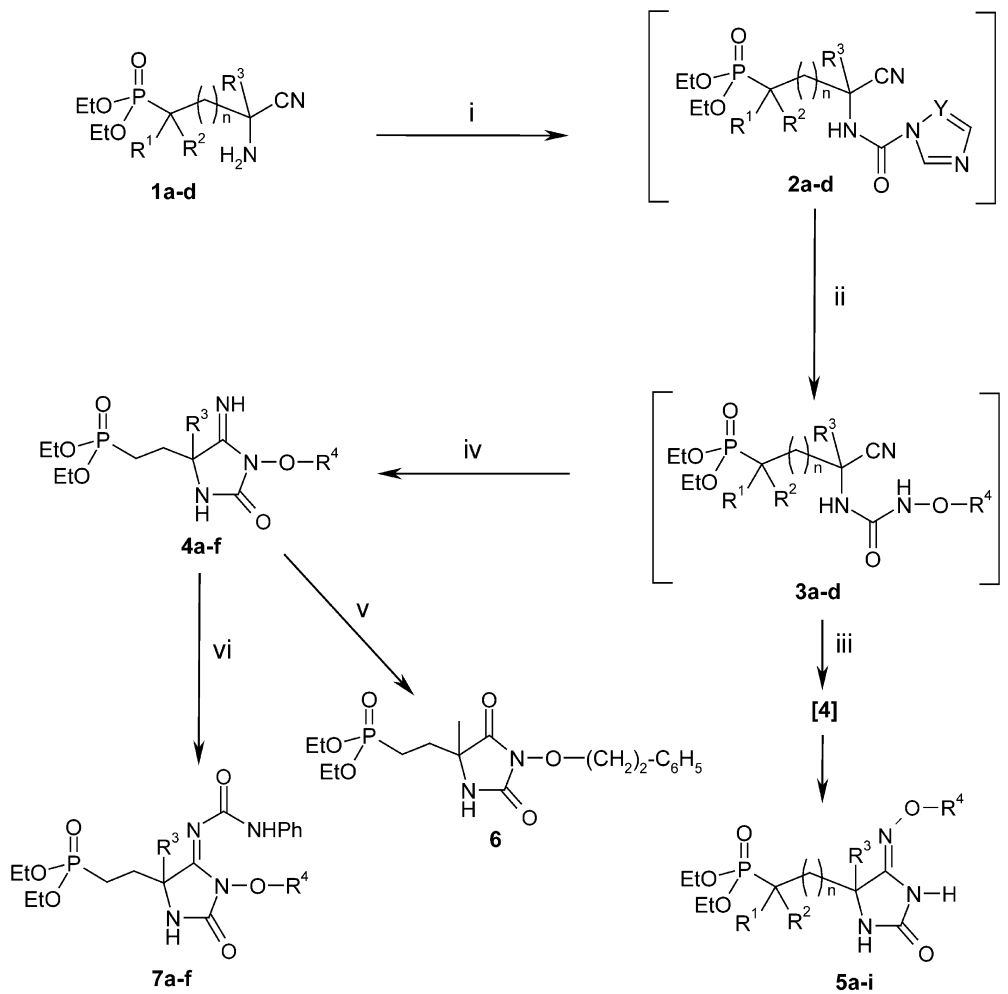
Furthermore, reactions of **4a–f** with phenylisocyanate afforded the corresponding urea derivatives **7a–f** as stable and solid compounds in 82–85% yield, whereas no reaction was observed when **5f** was treated with phenylisocyanate under similar reaction conditions.

Catalytic hydrogenation of **5a** and **7a** led to semicyclic hydroxamidines **8a** and **10a**, which can serve as bioisosters of hydroxamic acids due to their ability to act as chelators for various metal cations. Dealkylation of phosphonic esters **5a–d,k** and **7b,c** with bromotrimethylsilane gave phosphonic acids **9a–d,k** and **11b,c** (Scheme 2).

The structures of all novel compounds were confirmed by IR, ^{1}H, ^{13}C NMR spectra and mass spectra or elemental analysis.

3. Conclusion

In conclusion, we have developed the first synthesis of 3-aralkoxy-4-imino-imidazolidine-2-ones **4** and a new convenient one pot method for the preparation of 4-alkoxy(aralkoxy)imino-imidazolidine-2-ones **5** by



Scheme 1. Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones (**4a–f**) and 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones (**5a–i**). Reagents: i: CDI or CDT; ii: H_2NOR^4; iii: Et_3N/heating; iv: EtOH-HCl, K_2CO_3; v: 20% HCl; vi: PhNCO; *n=0*, 1; Y=CH, N; R^1, R^2, R^3=H, CH_3; R^4=$C_6H_5CH_2$-$C_6H_5(CH_2)_2$, 4-CH_3-$C_6H_4CH_2$, CH_3, 4-Br-$C_6H_4CH_2$.

Table 1. 3-Aralkoxy-4-imino-imidazolidin-2-ones (**4**, **7**) and 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones (**5**)

Compound	*n*	R^1	R^2	R^3	R^4	Yield (%)
4a	1	H	H	CH_3	$C_6H_5CH_2$	65
4b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	75
4c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	60
4d	1	H	H	H	$C_6H_5CH_2$	62
4e	1	H	H	H	$C_6H_5(CH_2)_2$	68
4f	1	H	H	H	4-CH_3-C_6H_4-CH_2	70
5a	1	H	H	CH_3	$C_6H_5CH_2$	75
5b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	70
5c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	72
5d	1	H	H	H	$C_6H_5CH_2$	55
5e	1	H	H	H	$C_6H_5(CH_2)_2$	52
5f	1	H	H	H	4-CH_3-C_6H_4-CH_2	60
5g	1	H	H	H	CH_3	55
5h	1	H	H	H	4-Br-C_6H_4-CH_2	60
5i	0	H	H	H	$C_6H_5CH_2$	60
5j	0	H	H	H	$C_6H_5(CH_2)_2$	60
5k	1	CH_3	CH_3	H	$C_6H_5CH_2$	52
5l	1	CH_3	CH_3	H	CH_3	50
7a	1	H	H	CH_3	$C_6H_5CH_2$	85
7b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	85
7c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	80
97d	1	H	H	H	$C_6H_5CH_2$	82
7e	1	H	H	H	$C_6H_5(CH_2)_2$	83
7f	1	H	H	H	4-CH_3-C_6H_4-CH_2	85

reacting diethylphosphonoalkyl α-aminonitriles with 1,1′-carbonyldiimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and O-substituted hydroxylamines. Furthermore we got access to the corresponding hydroxyamidine derivatives **8a**, **10a** and phosphonic acids **9**, **11**.

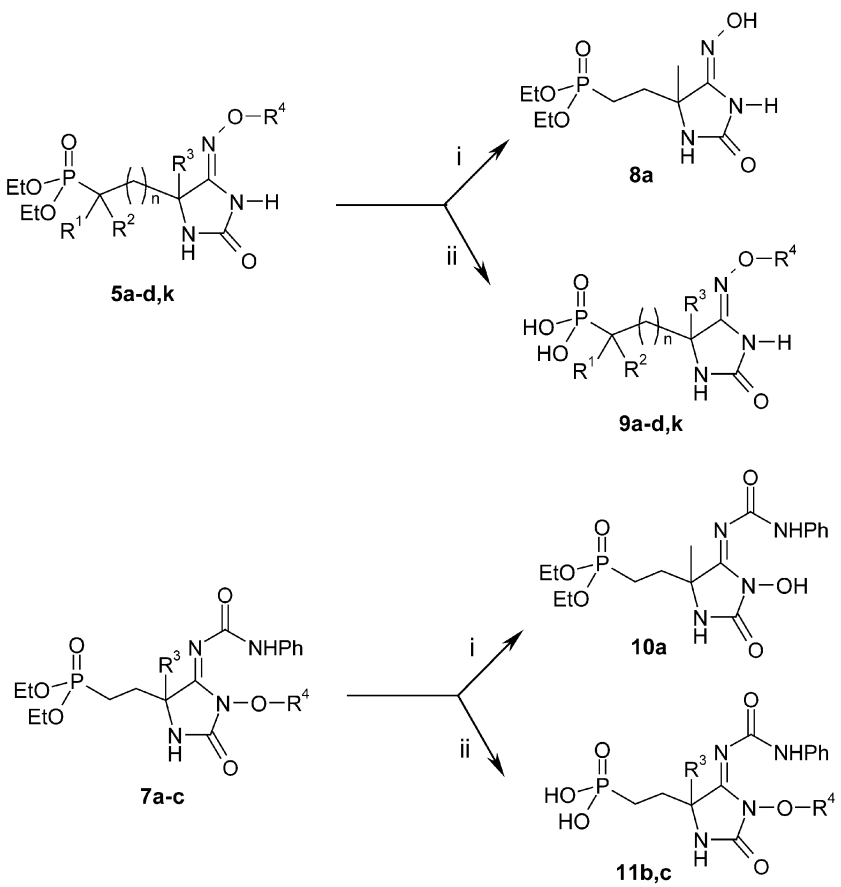
4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400.1 MHz) und ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6, D_2O and $CDCl_3$ as solvents. Mass spectra were recorded on a Finnigan MAT 311A and on a VG 70-250S (VG Analytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100–200, active 60 Å).

Previously unreported aminonitriles (**1c**,**d**) have been prepared according to an established literature procedure.[8]

4.1.1. 3-Amino-3-cyano-1,1-dimethyl-propylphosphonic acid diethyl ester (1c). Colorless oil (94%), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (q, J=10.43 Hz, 6H), 1.34 (t,



Scheme 2. Synthesis of hydroxyamidines (**8a**, **10a**) and phosphonic acids (**9**, **11**). Reagents: i: H_2/Pd-C; ii: TMSBr; R^1, R^2, R^3=H, CH_3; R^4=$C_6H_5CH_2$, $C_6H_5(CH_2)_2$, 4-CH_3-$C_6H_4CH_2$, CH_3; n=0, 1.

J=7.12 Hz, 6H), 1.78 (s, 2H), 1.91–2.10 (m, 2H), 4.03–4.18 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.60 Hz), 22.57 (d, $^2J_{cp}$=3.05 Hz), 23.59 (d, $^2J_{cp}$=3.56 Hz), 34.34 (d, $^1J_{cp}$=143.42 Hz), 40.27 (d, $^3J_{cp}$=7.63 Hz), 44.07, 62.58 (d, $^2J_{cp}$=7.63 Hz), 123.37; MS(EI) 248.

4.1.2. 3-Amino-3-cyano-3-methyl-propylphosphonic acid diethyl ester (1d). Colorless oil (95%), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.34 (t, J=7.12 Hz, 6H), 1.49 (s, 3H), 1.81 (s, 2H), 1.89–2.03 (m, 4H), 4.07–4.17 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.84 (d, $^3J_{cp}$=5.59 Hz), 21.55 (d, $^1J_{cp}$=143.44 Hz), 27.55, 35.21 (d, $^2J_{cp}$=3.96 Hz), 50.23 (d, $^3J_{cp}$=19.84 Hz), 62.29 (d, $^2J_{cp}$=6.61 Hz), 123.98. MS(EI) 234.

4.2. General procedure for the preparation of 4a–f

A solution of aminonitriles (**1a**–**d**) (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 min to a suspension of 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 hydroxylamine (10 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, the remaining residue dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the resulting oil was dissolved in anhydrous EtOH–HCl (15 mL). The reaction mixture was stirred at room temperature for 4 days, the solvent was evaporated under reduced pressure and the remaining hydrochlorides of **4a**–**f** were dissolved in water. Afterwards the pH was adjusted to 8 with K_2CO_3 solution under ice cooling in order to liberate the free bases (**4a**–**f**). The aqueous layer was extracted with diethyl ether, dried over $MgSO_4$ and the solvent was evaporated to give **4a**–**f** as oily products.

4.2.1. Diethyl 2-(3-benzyloxy-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (4a). Colorless oil (65%), IR (film): ν=1763 (C=O), 1682 (C=N), 1245, 1218 (P=O), 1050, 1025 (POC), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.38 (s, 3H), 1.49–2.01 (m, 4H), 4.02–4.13 (m, 4H), 5.12 (s, 2H), 6.65 (s, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=6.10 Hz), 20.37 (d, $^1J_{cp}$=142.93 Hz), 26.27, 32.26 (d, $^2J_{cp}$=3.56 Hz), 59.24 (d, $^3J_{cp}$=17.29 Hz), 62.37 (d, $^2J_{cp}$=6.61 Hz), 79.17, 128.91, 129.63, 130.56, 136.53, 152.04, 160.17; MS(EI) 384.

4.2.2. Diethyl 2-(4-imino-5-methyl-2-oxo-3-phenylethyl-oxy-imidazolidin-5-yl)ethylphosphonate (4b). Colorless oil (75%); IR (film): ν=1760 (C=O), 1680 (C=N), 1248, 1225 (P=O), 1050, 1025 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.46 (s, 3H), 1.64–2.09 (m, 4H), 3.05 (t, J=6.78 Hz, 2H), 4.03–4.13 (m, 4H), 4.29–4.36 (m, 2H), 6.61 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=6.10 Hz), 20.48 (d, $^1J_{cp}$=142.93 Hz), 26.03, 32.45 (d, $^2J_{cp}$=3.56 Hz), 34.98, 59.14 (d, $^3J_{cp}$=17.29 Hz), 62.40 (d, $^2J_{cp}$=6.10 Hz), 78.12, 127.31, 129.12, 129.27, 137.50, 153.50; MS(EI) 397.

4.2.3. Diethyl 2-[4-imino-5-methyl-3-(4-methylbenzyl-oxy)-2-oxo-imidazolidin-5-yl]ethylphosphonate (4c). Colorless oil (60%), IR (film): ν=1758 (C=O), 1682 (C=N), 1245, 1220 (P=O), 1057, 1030 (POC), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.38 (s, 3H), 1.47–2.00 (m, 4H), 2.35 (s, 3H), 4.01–4.12 (m, 4H), 5.05 (s, 2H), 6.67 (s, 1H), 7.19 (d, J=7.63 Hz, 2H), 7.34 (d, J=7.89 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=5.59 Hz), 20.41 (d, $^1J_{cp}$=143.43 Hz), 21.26, 26.32, 32.32 (d, $^2J_{cp}$=3.56 Hz), 59.18 (d, $^3J_{cp}$=17.81 Hz), 62.30 (d, $^2J_{cp}$=5.59 Hz), 79.15, 129.92, 130.51, 131.50, 139.98, 153.82, 162.62; MS(EI) 397.

4.2.4. Diethyl 2-(3-benzyloxy-4-imino-2-oxo-imidazolidin-5-yl)ethylphosphonate (4d). Colorless oil (62%), IR (film): ν=1763 (C=O), 1682 (C=N), 1245, 1220 (P=O), 1245, 1025 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H),1.68–2.19 (m, 4H), 4.01–4.15 (m, 5H), 4.97–5.14 (m, 2H), 6.66 (s, 1H), 7.33–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.59 Hz), 21.43 (d, $^1J_{cp}$=142.42 Hz), 27.05 (d, $^2J_{cp}$=4.07 Hz), 54.26 (d, $^3J_{cp}$=13.73 Hz), 62.43 (d, $^2J_{cp}$=6.62 Hz), 79.35, 128.09, 129.22, 130.38, 134.48, 152.67, 160.09; MS (EI) 369.

4.2.5. Diethyl 2-(4-imino-2-oxo-3-phenylethyloxy-imidazolidin-5-yl)-ethylphosphonate (4e). Colorless oil (68%); IR (film): ν=1758 (C=O), 1681 (C=N), 1248, 1215 (P=O), 1030 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.73–2.26 (m, 4H), 2.88–3.14 (m, 2H), 3.98–4.19 (m, 5H), 4.27–4.37 (m, 2H), 7.21–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.60 Hz), 21.61 (d, $^1J_{cp}$=143.44 Hz), 27.10 (d, $^2J_{cp}$=4.58 Hz), 35.00, 54.31 (d, $^3J_{cp}$=12.72 Hz), 62.50 (d, $^2J_{cp}$=3.56 Hz), 75.59, 126.72, 127.27, 128.96, 129.41, 148.25, 154.37; MS(EI) 384.

4.2.6. Diethyl 2-[4-imino-3-(4-methylbenzyloxy)-2-oxo-imidazolidin-5-yl]ethylphosphonate (4f). Colorless oil (70%); IR (film): ν=1760 (C=O), 1681 (C=N), 1250, 1225 (P=O), 1020 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.66–2.17 (m, 4H), 2.36 (s, 3H), 4.03–4.16 (m, 5H), 4.93–5.10 (m, 2H), 6.71 (s, 1H), 7.19 (d, J=7.88 Hz, 2H), 7.33 (d, J=7.88 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=6.10 Hz), 21.39 (d, $^1J_{cp}$=142.93 Hz), 21.72, 26.99 (d, $^2J_{cp}$=4.07 Hz), 54.24 (d, $^3J_{cp}$=13.22 Hz), 62.40 (d, $^2J_{cp}$=4.58 Hz), 79.23, 128.70, 129.52, 131.50, 139.75, 154.54, 160.45; MS(EI) 384.

4.3. General procedure for the preparation of 5a–l

A solution of aminonitriles (**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 hydroxylamine (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 for 45–75 min. After cooling to room temperature, the reaction mixture was dissolved in EtOAc and washed with brine and water in order to remove 1,2,4-1*H*-triazole. The organic layer was dried over $MgSO_4$, concentrated and the

remaining oil was crystallized from EtOAc/hexane or purified by column chromatography on silica gel with EtOAc or EtOAc/MeOH (9.5:0.5) as eluents to give **5a–l** as colorless solids. Due to its higher reactivity, CDT was used in case of aminonitriles derived from ketones. In case of aminonitriles derived from aldehydes CDT led to 6–10% higher yields than CDI. Yields of compounds **5** are however reported for reactions run with CDI.

4.3.1. Diethyl 2-(4-benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (5a). Colorless crystals (75%). Mp 102 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1247, 1215 (P=O), 1053, 1028 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.45 (s, 3H), 1.54–2.04 (m, 4H), 3.98–4.13 (m, 4H), 5.00 (s, 2H), 6.18 (s, 1H), 7.28–7.36 (m, 5H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=6.10 Hz), 20.04 (d, $^1J_{cp}$=142.93 Hz), 26.51, 32.86 (d, $^2J_{cp}$=3.56 Hz), 59.98 (d, $^3J_{cp}$=18.31 Hz), 61.81 (d, $^2J_{cp}$=2.04 Hz), 76.11, 127.94, 128.11, 128.39, 137.54, 152.73, 155.88. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.25; H, 6.83; N, 10.96. Found: C, 53.13; H, 6.89; N, 10.55.

4.3.2. Diethyl 2-(5-methyl-2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethylphosphonate (5b). Colorless crystals (70%). Mp 115 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1678 (C=N), 1248, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.48 (s, 3H), 1.69–2.08 (m, 4H), 2.95 (t, J=6.87 Hz, 2H), 4.04–4.14 (m, 4H), 4.19 (t, J=7.12 Hz, 2H), 6.18 (s, 1H), 7.19–7.31 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.45 (d, $^3J_{cp}$=5.59 Hz), 20.26 (d, $^1J_{cp}$=142.92 Hz), 26.41, 33.03 (d, $^2J_{cp}$=3.56 Hz), 35.53, 59.96 (d, $^3J_{cp}$=18.31 Hz), 61.87 (d, $^2J_{cp}$=4.07 Hz), 74.63, 126.32, 128.45, 128.93, 138.52, 152.17, 155.90. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.36; H, 7.10; N, 10.49.

4.3.3. Diethyl 2-[5-methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphospho-nate (5c). Colorless crystals (72%). Mp 140 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1250, 1217 (P=O), 1055, 1022 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.46 (s, 3H), 1.53–2.04 (m, 4H), 2.34 (s, 3H), 3.98–4.09 (m, 4H), 4.96 (J=11.82 Hz, 2H), 6.12 (s, 1H), 7.15 (d, J=7.63 Hz, 2H), 7.23 (d, J=8.14 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=5.59 Hz), 20.06 (d, $^1J_{cp}$=142.93 Hz), 21.20, 26.54, 32.91 (d, $^2J_{cp}$=3.57 Hz), 59.96 (d, $^3J_{cp}$=17.80 Hz), 61.82 (t, $^2J_{cp}$=5.08 Hz), 76.08, 128.32, 129.09, 134.36, 137.76, 152.50, 155.66. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.49; H, 7.13; N, 10.49.

4.3.4. Diethyl 2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate (5d). Colorless crystals (55%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1676 (C=N), 1245, 1210 (P=O), 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.70–2.10 (m, 4H), 4.02–4.15 (m, 4H), 4.37 (t, J=5.09 Hz, 1H), 5.00 (s, 2H), 6.47 (s, 1H), 7.28–7.35 (m, 5H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=5.59 Hz), 20.79 (d, $^1J_{cp}$=142.42 Hz), 27.61 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=15.77 Hz), 61.89 (d, $^2J_{cp}$=2.55 Hz), 76.13, 127.97, 128.12, 128.40, 137.52, 149.92, 156.97. Anal. Calcd for $C_{16}H_{24}N_3O_5P$: C, 52.03; H, 6.55; N, 11.38. Found: C, 51.88; H, 6.52; N, 11.19.

4.3.5. Diethyl 2-(2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethylphosphonate (5e). Colorless crystals (52%). Mp 129 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1676 (C=N), 1245, 1213 (P=O), 1052, 1033 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.33 (t, J=7.12 Hz, 6H), 1.78–2.18 (m, 4H), 2.95 (t, J=6.86 Hz, 2H), 4.02–4.12 (m, 4H), 4.19 (t, J=7.12 Hz, 2H), 4.39 (t, J=5.09 Hz, 1H), 6.39 (s, 1H), 7.14–7.28 (m, 5H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.46 (d, $^3J_{cp}$=6.11 Hz), 21.16 (d, $^1J_{cp}$=142.42 Hz), 27.84 (d, $^2J_{cp}$=4.57 Hz), 35.55, 54.31 (d, $^3J_{cp}$=14.24 Hz), 61.99 (d, $^2J_{cp}$=4.07 Hz), 74.69, 126.34, 128.46, 128.92, 138.49, 149.48, 156.79. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.26; H, 6.82; N, 10.96. Found: C, 53.26; H, 7.00; N, 10.96.

4.3.6. Diethyl 2-[4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonate (5f). Colorless crystals (60%). Mp 98 °C (EtOAc/hexane); IR (KBr): ν=1732 (C=O), 1678 (C=N), 1240, 1210 (P=O), 1048, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.75–2.11 (m, 4H), 2.34 (s, 3H), 4.03–4.13 (m, 4H), 4.37 (t, J=5.34 Hz, 1H), 4.95 (s, 2H), 6.35 (s, 1H), 7.15 (d, J=7.89 Hz, 2H), 7.89 (d, J=7.89 Hz, 2H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=6.10 Hz), 20.89 (d, $^1J_{cp}$=142.93 Hz), 21.21, 27.67 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=14.75 Hz), 61.94 (d, $^2J_{cp}$=4.07 Hz), 76.09, 128.33, 129.11, 134.37, 137.80, 149.73, 156.74. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.26; H, 6.82; N, 10.96. Found: C, 53.21; H, 6.98; N, 10.99, deposition number for the X-ray crystal structure of **5f**: CCDC 215669.

4.3.7. Diethyl 2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate (5g). Colorless crystals (55%). Mp 112 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1240, 1211 (P=O), 1050, 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.33 (t, J=7.12 Hz, 6H), 1.77–2.16 (m, 4H), 3.80 (s, 3H), 4.08–4.15 (m, 4H), 4.39 (t, J=5.08 Hz, 1H), 6.34 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.83 (d, $^3J_{cp}$=6.11 Hz), 21.43 (d, $^1J_{cp}$=142.93 Hz), 28.17 (d, $^2J_{cp}$=4.07 Hz), 54.67 (d, $^3J_{cp}$=15.77 Hz), 62.39 (d, $^2J_{cp}$=4.58 Hz), 62.44, 149.75, 157.66. MS(FAB); calcd for $C_{10}H_{20}N_3O_5P$: 294.1219; found: 294.1228.

4.3.8. Diethyl 2-[4-(4-bromobenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonate (5h). Colorless crystals (60%). Mp 120 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1680 (C=N), 1240, 1213 (P=O), 1040, 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.70–2.10 (m, 4H), 4.02–4.12 (m, 4H), 4.37 (t, J=5.34 Hz, 1H), 4.94 (s, 2H), 6.70 (s, 1H), 7.21 (d, J=8.40 Hz, 2H), 7.46 (d, J=8.40 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=6.10 Hz), 20.80 (d, $^1J_{cp}$=142.93 Hz), 27.60 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=15.77 Hz), 61.97 (d, $^2J_{cp}$=2.54 Hz), 75.27, 129.77, 131.52, 135.14, 136.67, 150.19, 157.13. Anal. Calcd for

$C_{16}H_{23}BrN_3O_5P$: C, 42.87; H, 5.17; N, 9.37. Found: C, 42.93; H, 5.17; N, 9.38.

4.3.9. Diethyl (4-benzyloxyimino-2-oxo-imidazolidin-5-yl)methylphosphonate (5i). Colorless crystals (60%). Mp 110 °C (EtOAc/hexane); IR (KBr): ν=1730 (C=O), 1686 (C=N), 1240, 1207 (P=O); 1050, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.34 (t, J=7.12 Hz, 6H), 1.71–2.16 (m, 2H), 4.10–4.18 (m, 4H), 4.54 (t, J=8.39 Hz, 1H), 5.00 (s, 2H), 7.26 (s, 1H), 7.29–7.38 (m, 5H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (t, $^3J_{cp}$=5.60 Hz), 31.63 (d, $^1J_{cp}$=140.89 Hz), 49.70 (d, $^2J_{cp}$=5.09 Hz), 62.33 (d, $^2J_{cp}$=6.61 Hz), 76.30, 128.09, 128.18, 128.44, 137.26, 149.63 (d, $^3J_{cp}$=19.83 Hz), 155.77. Anal. Calcd for $C_{15}H_{22}N_3O_5P$: C, 50.70; H, 5.95; N, 11.82. Found: C, 50.34; H, 6.26; N, 11.69.

4.3.10. Diethyl (2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)methylphosphonate (5j). Colorless crystals (60%). Mp 138 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1684 (C=N), 1250, 1210 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.35 (t, J=7.12 Hz, 6H), 1.97–2.39 (m, 2H), 2.95 (t, J=7.12 Hz, 2H), 4.07–4.16 (m, 4H), 4.20 (t, J=6.87 Hz, 2H), 4.56 (m, 1H), 5.91 (s, 1H), 7.19–7.32 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (t, $^3J_{cp}$=6.10 Hz), 31.68 (d, $^1J_{cp}$=140.89 Hz), 35.56, 49.70 (d, $^2J_{cp}$=5.09 Hz), 62.36 (d, $^2J_{cp}$=6.61 Hz), 74.78, 126.35, 128.47, 128.92, 138.43, 149.22 (d, $^3J_{cp}$=19.83 Hz), 155.82. Anal. Calcd for $C_{16}H_{24}N_3O_5P$: C, 52.03; H, 6.54; N, 11.37.Found: C, 52.17; H, 6.70; N, 11.41.

4.3.11. Diethyl 2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonate (5k). Colorless crystals (52%). Mp 133 °C (EtOAc/hexane); IR (KBr): ν=1730 (C=O), 1674 (C=N), 1240, 1209 (P=O), 1055, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.23 (q, 6H), 1.33 (t, J=7.12 Hz, 6H), 1.71–2.08 (m, 2H), 4.08–4.19 (m, 4H), 4.42 (d, J=10.68 Hz, 1H), 5.00 (s, 2H), 7.26 (s, 1H), 7.30–7.36 (m, 5H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.49 (d, $^3J_{cp}$=5.6 Hz), 21.05, 26.05 (d, $^1J_{cp}$=4.58 Hz), 33.62 (d, $^1J_{cp}$=142.42 Hz), 45.45, 51.37 (d, $^3J_{cp}$=2.04 Hz), 62.49 (d, $^2J_{cp}$=7.12 Hz), 76.13, 128.00, 128.17, 128.40, 137.38, 151.46, 155.82. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.45; H, 7.06; N, 10.58.

4.3.12. Diethyl 2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonate (5l). Colorless crystals (50%). Mp 139 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1676 (C=N), 1250, 1210 (P=O), 1057, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.24 (q, 6H), 1.33 (t, J=7.12 Hz, 6H), 1.78–2.10 (m, 2H), 3.80 (s, 3H), 4.10–4.17 (m, 4H), 4.44 (d, J=10.93 Hz, 1H), 7.28 (s, 1H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.46 (d, $^3J_{cp}$=5.60 Hz), 21.05, 26.02 (d, $^2J_{cp}$=4.07 Hz), 33.62 (d, $^1J_{cp}$=142.42 Hz), 45.48, 51.33 (d, $^3J_{cp}$=2.03 Hz), 61.94, 62.42 (d, $^2J_{cp}$=7.12 Hz), 150.97, 156.24. Anal. Calcd for $C_{12}H_{24}N_3O_5P$: C, 44.85; H, 7.52; N, 13.07. Found: C, 44.97; H, 7.49; N, 13.04.

4.3.13. Diethyl 2-(5-methyl-2,4-dioxo-3-phenylethoxy-imidzoldin-5-yl)ethylphosphonate (6). Aqueous HCl (15 mL, 20%) was added to a solution of **4b** (3 mmol) in THF (3 mL) and the mixture was stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was chromatographed using EtOAc/MeOH (95:5) to give **6**. Colorless oil (60%); IR (film): ν=1784, 1732 (C=O), 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.43 (s, 3H), 1.63–2.06 (m, 4H), 3.09 (t, J=7.38 Hz, 2H), 4.03–4.14 (m, 4H), 4.34 (t, J=7.38 Hz, 2H), 7.07 (s, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR (CDCl3) δ (ppm): 16.39 (d, $^3J_{cp}$=5.59 Hz), 19.56 (d, $^1J_{cp}$=143.43 Hz), 23.51, 30.38 (d, $^2J_{cp}$=3.56 Hz), 34.44, 59.66 (d, $^3J_{cp}$=16.79 Hz), 62.25 (d, $^2J_{cp}$=4.07 Hz), 78.14, 126.71, 128.60, 128.96, 138.68, 152.57, 170.78. Anal. Calcd for $C_{18}H_{27}N_2O_6P$: C, 54.26; H, 6.83; N, 7.03. Found: C, 54.22; H, 6.95; N, 7.06.

4.4. General procedure for the preparation of 7a–f

Phenylisocyanate (3 mmol) was added to a solution of **4a–f** (3 mmol) in anhydrous THF (10 mL) under ice cooling, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the remaining oil was purified by column chromatography on silica gel with EtOAc/MeOH (9.5:0.5) as an eluent. Crystallization from EtOAc/hexane afforded **7a–f** as colorless solids.

4.4.1. Diethyl 2-(3-benzyloxy-5-methyl-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)-ethylphosphonate (7a). Colorless crystals (85%). Mp 103 °C (EtOAc/hexane); IR (KBr): ν=1773, 1713 (C=O), 1647 (C=N), 1245, 1220 (P=O), 1050, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.63 (s, 3H), 1.82–2.25 (m, 4H), 4.02–4.13 (m, 4H), 5.19 (q, J=8.51 Hz, 2H), 6.85 (s, 1H), 7.05–7.49 (m, 10H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.39 (d, $^3J_{cp}$=5.60 Hz), 19.87 (d, $^1J_{cp}$=142.96), 25.44, 31.79 (d, $^2J_{cp}$=2.54 Hz), 62.19, 62.22, 78.89, 119.35, 123.44, 128.27, 128.84, 129.08, 129.08, 130.30, 133.30, 152.90, 160.82, 167.46. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.16; H, 6.38; N, 10.94.

4.4.2. Diethyl 2-(5-methyl-2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate(7b). Colorless crystals (85%). Mp 123 °C (EtOAc/hexane); IR (KBr): ν=1768, 1718 (C=O),1648 (C=N), 1245, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.29 (t, J=7.12 Hz, 6H), 1.61 (s, 3H), 1.82–2.24 (m, 4H), 2.75–2.95 (s, br 2H), 4.03–4.13 (m, 4H), 4.32–4.39 (m, 2H), 6.89 (s, 1H), 7.04–7.69 (m, 10H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.39 (t, $^3J_{cp}$=5.60 Hz), 19.80 (d, $^1J_{cp}$=142.42 Hz), 25.42, 31.78 (d, $^2J_{cp}$=3.56 Hz), 34.15, 60.41, 62.24, 77.72, 118.88, 120.08, 123.34, 128.46, 128.60, 128.86, 138.69, 138.70, 152.82, 160.00, 168.10. Anal. Calcd for $C_{25}H_{33}N_4O_6P$: C, 58.13; H, 6.43; N, 10.84. Found: C, 58.23; H, 6.57; N, 10.80.

4.4.3. Diethyl 2-[4-methyl-3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoyliminoimidazolidin-5-yl]ethylphosphonate (7c). Colorless crystals (80%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1778, 1707 (C=O), 1646 (C=N), 1250, 1230 (P=O), 1048, 1025 (POC) cm^{-1}; ^1H NMR

($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.62 (s, 3H), 1.74–2.04 (m, 4H), 2.28 (s, 3H), 4.01–4.12 (m, 4H), 5.14 (q, J=8.39 Hz, 2H), 6.83 (s, 1H), 6.90–7.40 (m, 9H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.79 (d, $^3J_{cp}$=5.60 Hz), 19.75 (d, $^1J_{cp}$=142.42 Hz), 21.69, 25.81 32.17, 62.56, 62.62, 79.21, 119.68, 123.83, 128.80, 129.22, 129.35, 130.72, 130.70, 138.90, 152.93, 160.71, 167.72. Anal. Calcd for $C_{25}H_{33}N_4O_6P$: C, 58.13; H, 6.43; N, 10.84. Found: C, 58.04; H, 6.47; N, 10.83.

4.4.4. Diethyl 2-(3-benzyloxy-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate (7d). Colorless crystals (82%). Mp 101 °C (EtOAc/hexane); IR (KBr): ν=1778, 1710 (C=O), 1666 (C=N), 1245, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.25 (d, J=7.13 Hz, 6H), 1.75–2.30 (m, 4H), 4.01–4.20 (m, 4H), 4.79 (s, 1H), 5.19 (s, 2H), 6.90 (s, 1H), 7.10–7.40 (m, 10H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=5.60 Hz), 21.45 (d, $^1J_{cp}$=143.44 Hz), 25.02 (d, $^2J_{cp}$=4.58 Hz), 54.90 (d, $^3J_{cp}$=11.70 Hz), 62.20 (d, $^2J_{cp}$=6.61 Hz), 78.80, 120.21, 123.45, 128.51, 128.89, 129.13, 129.24, 130.07, 130.25, 153.01, 160.11, 167.73. Anal. Calcd for $C_{23}H_{29}N_4O_6P$: C, 56.55; H, 5.98; N, 11.46. Found: C, 56.65; H, 6.12; N, 11.40.

4.4.5. Diethyl 2-(2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethyl-phosphonate (7e). Colorless crystals (83%). Mp 118 °C (EtOAc/hexane); IR (KBr): ν=1775, 1710 (C=O), 1660 (C=N), 1248, 1228 (P=O), 1048, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.80–2.30 (m, 4H), 2.75–2.90 (br, 2H), 4.08–4.20 (m, 4H), 4.30–4.39 (m, 2H), 4.80 (s, 1H), 6.90 (s, 1H), 7.10–7.60 (m, 11H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.40 (t, $^3J_{cp}$=6.10 Hz), 21.40 (d, $^1J_{cp}$=143.43 Hz), 25.02 (d, $^2J_{cp}$=4.55 Hz), 34.20, 54.91 (d, $^3J_{cp}$=14.24 Hz), 62.19 (d, $^2J_{cp}$=6.61 Hz), 78.80, 118.22, 120.96, 123.53, 128.77, 129.00, 129.24, 130.07, 138.50, 153.01, 160.21, 167.70. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.27; H, 6.42; N, 10.88.

4.4.6. Diethyl 2-[3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl]-ethylphosphonate (7f). Colorless crystals (85%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1772, 1705 (C=O), 1660 (C=N), 1245, 1218 (P=O), 1052, 1020 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.28 (t, J=6.87 Hz, 6H), 1.77–1.91 (m, 4H), 2.34 (s, 3H), 4.01–4.12 (m, 4H), 4.97 (s, 1H), 5.16 (s, 2H), 7.07–7.62 (m, 11H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.32 (d, $^3J_{cp}$=6.10 Hz), 21.33 (d, $^1J_{cp}$=143.40), 26.17 (d, $^2J_{cp}$=4.58 Hz), 54.46 (d, $^3J_{cp}$=14.24 Hz), 62.17 (d, $^2J_{cp}$=6.61 Hz), 78.79, 119.00, 120.25, 123.47, 123.79, 129.01, 129.15, 130.31, 138.30, 152.70, 160.73, 167.26. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.35; H, 6.45; N, 10.92.

4.5. General procedure for the preparation 8a, 10a

Compounds **5a**,**7a** were hydrogenated in MeOH using catalytic amounts of 10% Pd/C for 3 h. The suspension was filtrated and the solvent was evaporated.

4.5.1. Diethyl 2-(4-hydroxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (8a). Colorless crystals (92%). Mp 189 °C (EtOAc/hexane); IR (KBr): ν=1718 (C=O), 1691 (C=N), 1245, 1225 (POC), 1050, 1028 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.22 (t, J=7.12 Hz, 6H), 1.27 (s, 3H), 1.45–1.77 (m, 4H), 3.91–4.08 (m, 4H), 7.44 (s, 1H), 9.70 (s, 1H), 9.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.17 (d, $^3J_{cp}$=5.59 Hz), 19.56 (d, $^1J_{cp}$=140.90 Hz), 26.03, 32.87 (d, $^2J_{cp}$=3.05 Hz), 58.23 (d, $^3J_{cp}$=19.84 Hz), 60.96 (d, $^2J_{cp}$=6.62 Hz), 152.39, 156.37. Anal. Calcd for $C_{10}H_{20}N_3O_5P$: C, 40.95; H, 6.87; N, 14.32. Found: C, 40.70; H, 7.01; N, 14.20.

4.5.2. Diethyl 2-(3-hydroxy-5-methyl-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)ethyl-phosphonate (10a). Colorless crystals (90%). Mp 189 °C (EtOAc/hexane); IR (KBr): ν=1792, 1724 (C=O), 1655 (C=N), 1250, 1225 (P=O), 1050, 1020 (POC) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.21 (t, J=7.12 Hz, 6H), 1.41 (s, 3H), 1.63–1.99 (m, 4H), 3.94–4.02 (m, 4H), 6.96–7.44 (m, 5H), 7.55 (s, 1H), 8.22 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.14 (d, $^3J_{cp}$=6.11 Hz), 20.50 (d, $^1J_{cp}$=143.94 Hz), 24.88, 31.59, 61.03, 61.07, 118.05, 121.67, 128.66, 139.62, 152.44, 159.69, 167.83. Anal. Calcd for $C_{17}H_{25}N_4O_6P$: C, 49.51; H, 6.11; N, 13.68. Found: C, 49.32; H, 5.93; N, 13.69.

4.6. General procedure for the preparation of phosphonic acids 9,11

Bromotrimethylsilane (6 mmol) was added to a solution of **5** or **7** (1 mmol) in dry CH_2Cl_2 (10 mL) under ice cooling and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was dissolved in THF (3 mL). Water (0.1 mL) was added and the mixture was stirred for 10 min. Afterwards EtOAc (10 mL) was added and a solid product was filtrated and recrystallized from CH_2Cl_2/MeOH/EtOAc to yield colorless solids.

4.6.1. 2-(4-Benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonic acid (9a). Colorless crystals (82%). Mp 192 °C; IR (KBr): ν=2890 (POH), 1740 (C=O), 1680 (C=N), 1215 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.25 (s, 3H), 1.30–1.74 (m, 4H), 4.94 (s, 2H), 7.24–7.39 (m, 5H), 7.61 (s, 1H), 10.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.42 (d, $^1J_{cp}$=138.35 Hz), 26.39, 34.09 (d, $^2J_{cp}$=3.05 Hz), 59.10 (d, $^3J_{cp}$=19.33 Hz), 75.13, 127.72, 127.86, 128.43, 138.58, 154.47, 156.57. Anal. Calcd for $C_{13}H_{18}N_3O_5P$: C, 47.71; H, 5.54; N, 12.84. Found: C, 47.53; H, 5.69; N, 12.51.

4.6.2. 2-(5-Methyl-2-oxo-4-phenethyloxyimino-imidazolidin-5-yl)ethylphosphonic acid (9b). Colorless crystals (80%). Mp 199 °C; IR (KBr): ν=2885 (POH), 1735 (C=O), 1675 (C=N), 1220 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.29 (s, 3H), 1.40–1.84 (m, 4H), 2.88 (t, J=6.87 Hz, 2H), 4.04 (t, J=6.61 Hz, 2H), 7.19–7.30 (m, 5H), 7.60 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.55 (d, $^1J_{cp}$=137.84 Hz), 26.41, 34.21, 35.25, 59.10 (d, $^3J_{cp}$=19.33 Hz), 74.12, 126.36, 126.58, 129.40, 139.16, 154.01, 156.61. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 48.98; H, 6.11; N, 12.02.

4.6.3. 2-[5-Methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonic acid (9c). Colorless

crystals (80%). Mp 205 °C; IR (KBr): ν=2900 (POH), 1735 (C═O), 1670 (C═N), 1225 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.25 (s, 3H), 1.39–1.73 (m, 4H), 2.28 (s, 3H), 4.88 (s, 2H), 7.14 (d, J=7.88, 2H), 7.26 (d, J=7.88, 2H), 7.61 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.13, 22.42 (d, $^1J_{cp}$=138.35 Hz), 26.40, 34.12, 59.07 (d, $^3J_{cp}$=19.32 Hz), 75.06, 128.01, 129.00, 135.50, 136.87, 154.35, 156.57. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 49.00; H, 6.10; N, 12.12.

4.6.4. 2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonic acid (9d). Colorless crystals (82%). Mp 204 °C; IR (KBr): ν=2880 (POH), 1740 (C═O), 1670 (C═N), 1215 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.63–1.85 (m, 4H), 4.22 (t, J=6.61 Hz, 1H), 4.94 (q, J=12.84 Hz, 2H), 7.32–7.39 (m, 5H), 7.68 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.16 (d, $^1J_{cp}$=138.35 Hz), 28.98, 53.79 (d, $^2J_{cp}$=18.82 Hz), 75.09, 127.73, 127.88, 128.47, 138.71, 151.62, 157.72. Anal. Calcd for $C_{12}H_{16}N_3O_5P$: C, 46.01; H, 5.14; N, 13.41. Found: C, 45.80; H, 5.28; N, 13.21.

4.6.5. 2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonic acid (9k). Colorless crystals (83%). Mp 200 °C; IR (KBr): ν=2895 (POH), 1735 (C═O), 1670 (C═N), 1210 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.09 (q, 6H), 1.74–1.79 (m, 2H), 4.33 (t, J=6.11 Hz, 1H), 4.94 (q, J=12.71 Hz, 2H), 7.26–7.89 (m, 5H), 7.71 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.08, 24.45 (d, $^1J_{cp}$=2.54 Hz), 33.14 (d, $^1J_{cp}$=138.86 Hz), 44.14, 50.84 (d, $^3J_{cp}$=7.12 Hz), 75.08, 127.72, 127.85, 128.45, 138.67, 152.80, 157.54. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 48.98; H, 6.15; N, 12.01.

4.6.6. 2-(5-Methyl-2-oxo-3-phenylethyloxy-4-phenyl-carbamoyl-iminoimidazolidin-5-yl)ethyl-phosphonic acid (11b). Colorless crystals (75%). Mp 216 °C; IR (KBr): ν=2880 (POH), 1765, 1720 (C═O), 1650 (C═N), 1215 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.30 (s, 3H), 1.46–1.99 (m, 4H), 2.96 (t, J=7.12 Hz, 2H), 4.24 (t, J=6.87 Hz, 2H), 6.88 (s, 1H), 7.18–7.46 (m, 10H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.36 (d, $^1J_{cp}$=137.84 Hz), 23.38, 31.62 (d, $^2J_{cp}$=2.54 Hz), 59.04, 59.23, 78.55, 118.06, 120.92, 121.38, 128.92, 129.29, 130.17, 139.61, 152.78, 164.78, 171.76. Anal. Calcd for $C_{21}H_{25}N_4O_6P$: C, 54.78; H, 5.47; N, 12.16. Found: C, 54.94; H, 5.62; N, 11.89.

4.6.7. 2-(5-Methyl-4-methylbenzyloxy-2-oxo-4-phenyl-carbamoylimino-imidazolidin-5-yl)ethylphosphonic acid (11c). Colorless crystals (70%). Mp 204 °C; IR (KBr): ν=2885 (POH), 1775, 1705 (C═O), 1650 (C═N), 1230 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.29 (s, 3H), 1.43–1.99 (m, 4H), 2.60 (s, 3H), 5.01 (s, 1H), 6.86–7.43 (m, 9H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.23, 22.36 (d, $^1J_{cp}$=137.84 Hz), 23.36, 31.62 (d, $^2J_{cp}$=2.54 Hz), 59.13 (d, $^3J_{cp}$=19.33 Hz), 78.55, 118.06, 118.35, 121.38, 128.92, 129.29, 130.17, 140.90, 153.78, 171.76. Anal. Calcd for $C_{21}H_{25}N_4O_6P$: C, 54.78; H, 5.47; N, 12.16. Found: C, 54.54; H, 5.27; N, 11.93.

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