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Acylation or Phosphorylation of Hydroxyurea Unexpectedly Take Place on N rather than on O, Leading to the Formation of Amides Instead of the Expected Esters.

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Abstract: Attempted acylation of the anticancer agent hydroxyurea (HU) with acyl chlorides or anhydrides led to acylation on the NH group rather than on the OH. The structures of the products were confirmed by ^{15}N-HMBC NMR. An analogous reaction conducted with hydroxamic acids (RCONHOH) or *N*-hydroxycarbamates (ROCONHOH) led to acylation on the OH. Surprisingly, despite the established affinity of phosphorous to O, phosphorylation of HU also took place at the NH group instead of the OH. These results are rationalized based on the different dominant resonance structures of HU, the hydroxamic acids or the *N*-hydroxycarbamates.

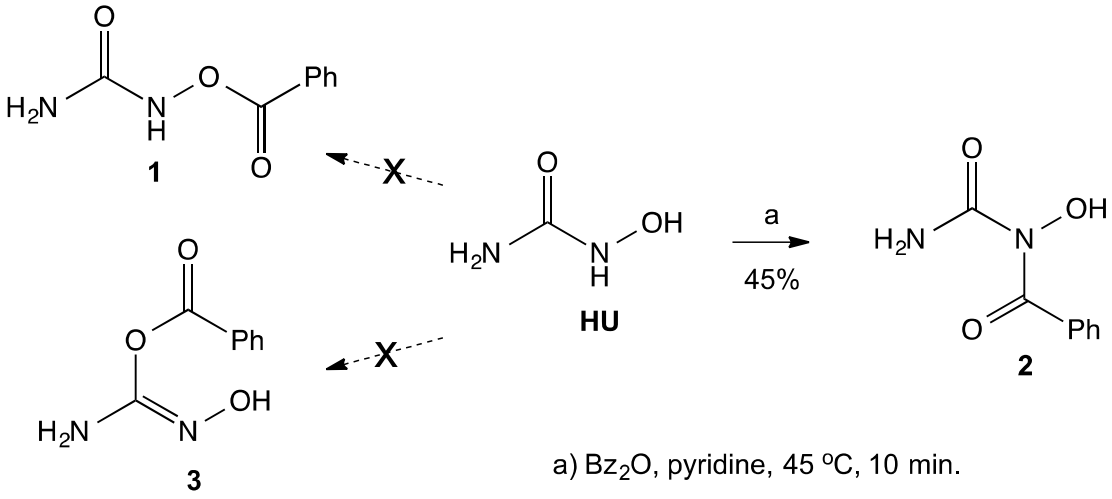
Results and Discussion

Previous studies from our laboratory have dealt with the synthesis and biological evaluation of various mutual prodrugs, where the main goal of those studies was to examine possible synergistic effects between the components of

the prodrugs. The investigations included the synthesis and biological evaluations of the following derivatives: a) *all-trans*-retinoic acid (ATRA), an anti-acne agent, linked to butyric acid, a histone deacetylase (HDAC) inhibitor; [1] b) tegafur, a prodrug of the anticancer agent 5-fluorouracyl (5-FU), linked to butyric acid; [2] c) a derivative of two HDAC inhibitors, 4-phenylbutyric acid and butyric acid, as an anticancer agent; [3] d) perphenazine, a dopamine antagonist bound to γ-aminobutyric acid (GABA), as an anti-schizophrenic agent; [4] e) 5-aminolevulinic acid (5-ALA) linked to butyric acid as an anticancer agent for photodynamic therapy; [5] f) the GABA amide of nortriptyline, an antidepressant, for the treatment of neuropathic pain. [6] Herein we describe studies related to a mutual prodrug of hydroxyurea (HU), an agent used in the treatment of myelocytic leukemia, and the HDAC inhibitors, valproic and butyric acids.

Although a large number of hydroxamic acid derivatives have been reported in the literature, [7] and many patents claim various uses for these compounds, only a few compounds that possess hydroxamic acid groups (R-CONHOH) are currently in clinical use, including: vorinostat, as a HDAC inhibitor, and HU as an anticancer agent. Thus, we intended to prepare and study the esters of HU connected to acidic HDAC inhibitors. A literature search of acylated HU derivatives revealed that very few publications claim the synthesis of HU esters, described as being synthesized by O-acylation of HU [8] or via the reaction of isocyanates with hydroxylamine. [9] Whereas Exner reported [10] that the benzoylation of HU with benzoic anhydride led to the benzoate ester **1** (Scheme 1), in our studies we found that the acylation took place easily on the secondary

nitrogen rather than on the hydroxyl group. Herein we report on various products obtained from the reaction of activated acids with HU. To prove our claim that the acylation takes place preferentially on the NH group, we repeated Exner's procedure [10] and found that the obtained product was the amide **2** [11] rather than the claimed ester **1**, or the acylated enolic form of HU **3** (Scheme 1)



Scheme 1: Benzoylation of HU

Since the ^{1}H NMR spectrum of the product is inconclusive as to the site of acylation, whether it takes place on the N or on either of the O's, and in the ^{13}C NMR the chemical shift of the carbonyl of the acyl group does not readily distinguish between a C=O that belongs to an ester or to an amide, we resorted to determine the ^{15}N-HMBC NMR spectrum of the product. This experiment, based on the ^{15}N-^{1}H coupling identifies unambiguously, NH or NH_2 groups, as the ^{15}N signal of these is split in the ^{1}H dimension into a doublet (J = *ca*. 90 Hz) due to the one-bond coupling in the presence of –NH- or –NH_2. When the H is not directly attached to the N, but is found 2 or three atoms away, the longer-

range coupling constants (^2J and ^3J) are much smaller, and even if their correlation peaks appear, they are not visibly split. Furthermore, the chemical shift of the N in NH_2 groups in ureas is usually found at ~-300 ppm, that of amides NCOR at ~-200 ppm, and that of oximes =N-OH at ~-50 ppm. [12] By examination of the NMR spectrum, we can identify which of the protons on a heteroatom are connected to a N atom and by exclusion, those that are connected to O. In the spectrum of the benzoylated product of HU the following observations are made: a) the ^{15}N-HMBC showed an N signal at -305.8 ppm, which was attached through one bond to the two H's at 6.36 ppm, indicating the presence of an amide $–CONH_2$; b) a second N that appears at ~ -200 ppm indicative of an NCOR; c) no N is found to have chemical shift of ~ -50 ppm; and e) the other ^{1}H on a heteroatom (δ 9.24) is not connected to a N and is therefore assigned to the OH group. Based on these observations, the assignment of the structure of the product is that of compound **2** (Fig. 1).

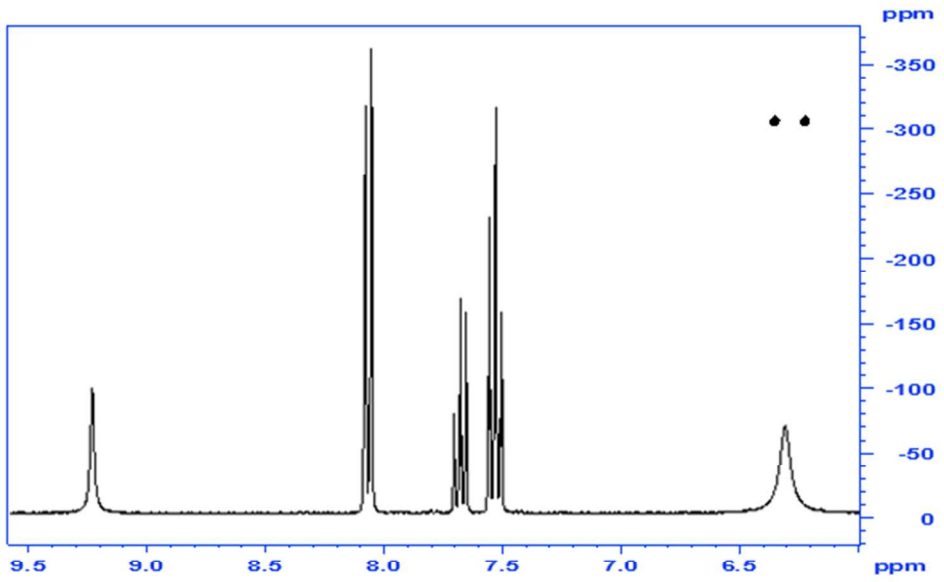


Figure 1: $^{1}Hx^{15}N$ NMR **correlation** spectrum of compound **2**, the *N*-benzoylated product of HU; inset: ^{1}H-^{1}D spectrum

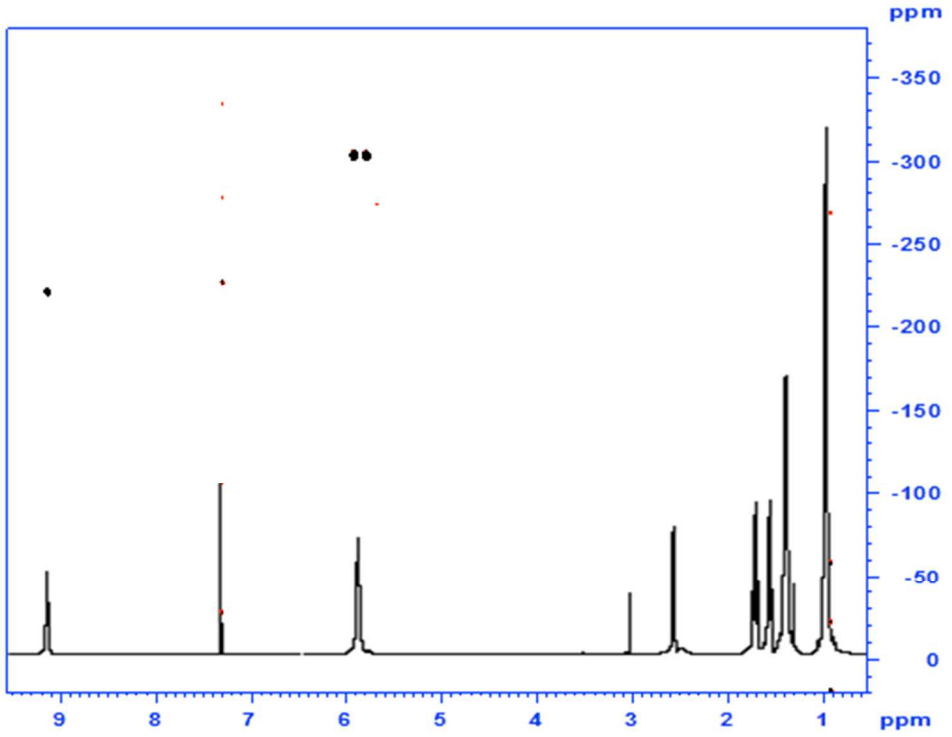
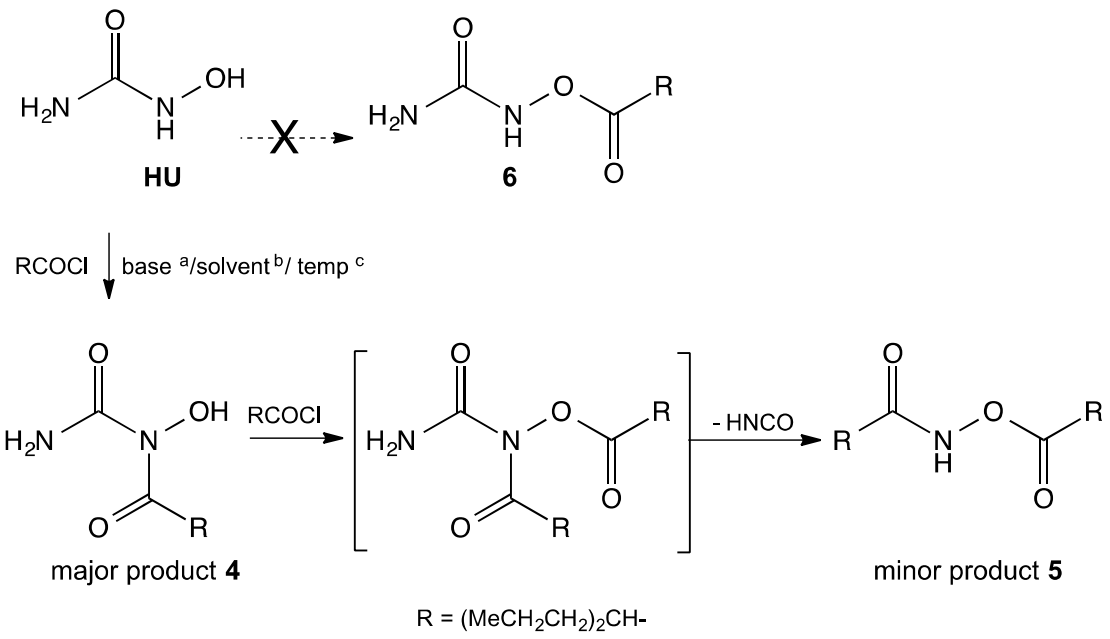


Figure 2: $^{1}Hx^{15}N$ NMR correlation spectrum of compound **4**, the *N*-valproylated product of HU; inset: ^{1}H-^{1}D spectrum

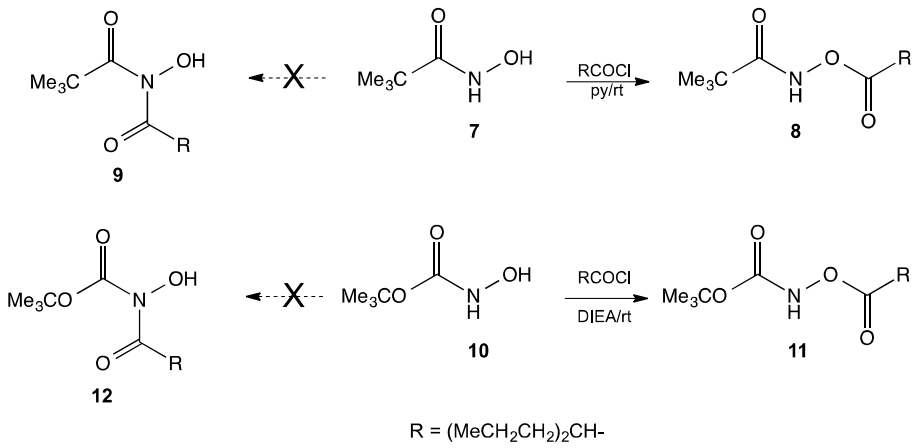
When analogous acylations of HU were carried out with valproyl chloride the main product **4** was again found to be that of *N*-acylation. In addition, the acylation led to the formation of a small amount of the *N,O*-bis-valproylated hydroxylamine **5**, the formation of which may be accounted for by decomposition of an *N,O*-bis-valproylated HU intermediate with concomitant release of HNCO, or by initial breakdown of **4** to give the *N*-acylated hydroxylamine, which underwent further *O*-acylation with another equivalent of the valproyl chloride to give compound **5** (Scheme 2). A similar reaction was reported by Exner [10] involving the exclusive formation of the analog of **5** (R = Ph) [13] upon treatment of HU with benzoyl chloride.



Conditions explored: a) DMAP or KOH with or without Aliquat 336; b) DMF or pyridine or DMF/THF or DMF/DCM or water; c) -60 to 23 °C. Best yield **4** (31%) + **5** (4%) when carried out in DMF/DMAP/ -41 °C (MeCN-dry ice)/30 min [Nassdyuk, T. M. [14]]

Scheme 2: Reaction of HU with valproyl or butyryl chloride

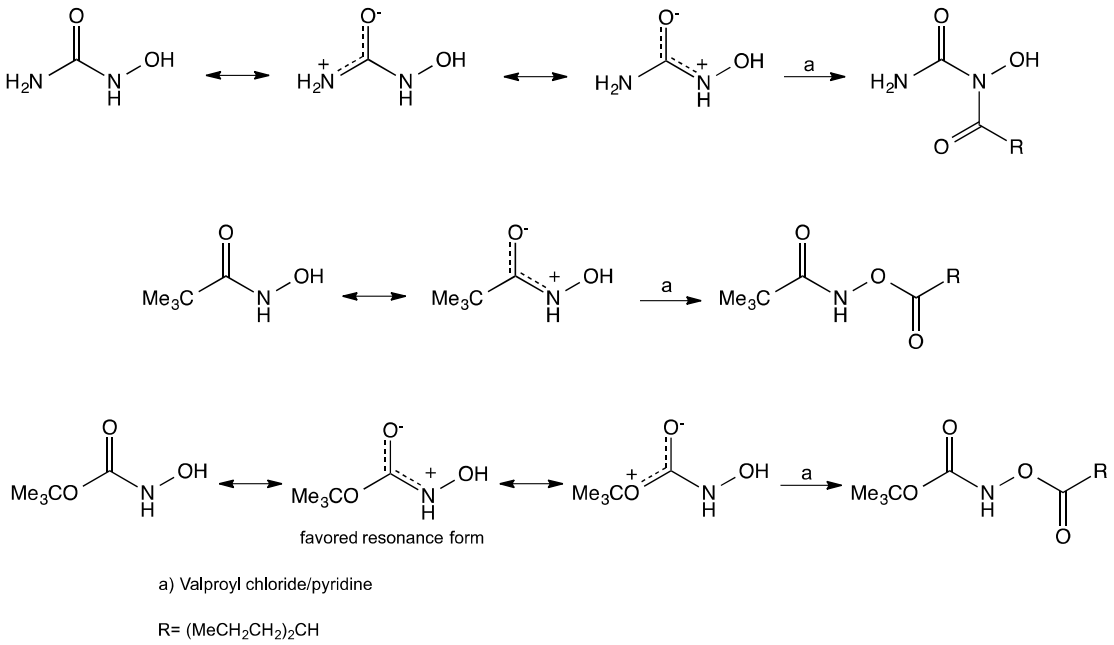
Since HU possess a -CONHOH group, analogous to that found in hydroxamic acids, we examined the reactions of *N*-hydroxypivalamide **7** [15] and the *N*-hydroxycarbamate **10** [16] with valproyl chloride. In these cases the products of *O*-acylation **8** and **11** formed readily, and no *N*-acylated products **9** or **12** were detected. This outcome shows that HU is an unusual hydroxamic acid and the presence of the NH_2 group instead of alkyl or alkoxy groups caused the HU to react differently (Scheme 3).



Scheme 3: *O*-Acylation of a hydroxamic acid and an *N*-hydroxycarbamate

In an attempt to understand the different behavior of HU toward acylation in comparison to other hydroxamic acid analogs we compared the resonance structures expected for these compounds. In the case of HU, we suggest that the primary resonance takes place between the unshared electrons on the NH_2 nitrogen and the oxygen of the carbonyl, whereas in the hydroxamic acid and the *N*-hydroxycarbamate the main resonance takes place between the

unshared electrons on the NH nitrogen and the oxygen of the carbonyl (Scheme 4). Thus, in the case of the HU the unshared electrons on the NH group are readily available for nucleophilic attack leading to the found *N*-hydroxyimide. Further support for this suggestion is based on the fact that X-ray crystallography of HU reveals that the length of the C-NH2 bond is 1.328A whereas that of the C-NHOH is 1.347A. [17] This length difference may indicate that the C-NH2 contributes the dominant resonance structure and might have more Sp2 hybridization, making the N of the -NHOH group more basic-nucleophilic leading to the observed N-acylation. This observation, however does not clarify why the acylation takes place on the N and not on the O of the NHOH, and moreover it does not rationalize why the phosphorylation also takes place on the N rather than on the O, despite the well-established affinity of P to O. Whereas in the hydroxamic acid and the *N*-hydroxycarbamate the electron concentration of the NH is diminished, leading to the acylation of the OH groups.

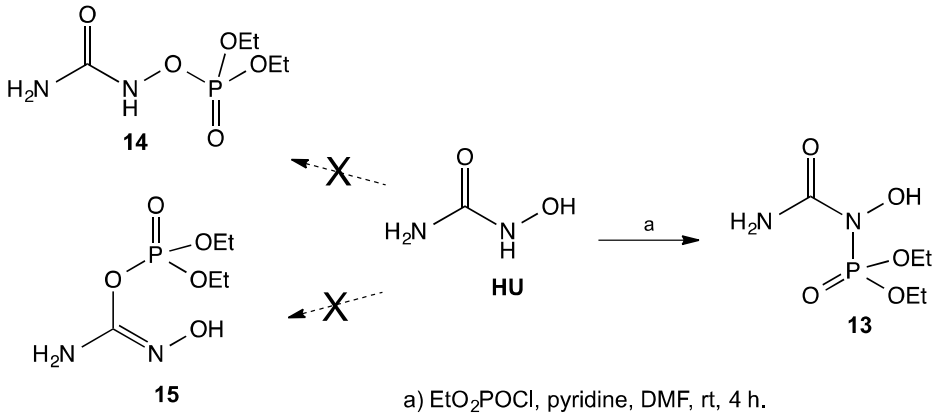


Scheme 4: Some suggested resonance structures and the obtained acylation products of HU, a hydroxamic acid and an *N*-hydroxycarbamate

An additional cause for the preference of NH over the NH_2 as the nucleophilic site comes from the α-effect. [18] This effect is observed in cases where a lone pair, carrying atom resides α to the nucleophilic atom. The anion of hydrogen peroxide is a classic example of this group of nucleophiles, which exhibit an enhanced nucleophilicity mainly towards compounds with a low lying LUMO. [18e] Hence, because of the neighboring oxygen atom, the NH will be more nucleophilic than the NH_2 group.

In view of the unexpected course of HU acylation described above, we proceeded with an attempted phosphorylation of HU. In this case, based on the well established, high-affinity of phosphorous to oxygen, it was expected that the phosphorylation would take place on the oxygen of HU. Surprisingly, when

HU was reacted with diethyl chlorophosphate the phosphorylation again took place on the NH and not on the OH to give the corresponding diethyl phosphoramidate **13** instead of the phosphates **14** or **15** (Scheme 5). The structure of the isolated product **13** was also established by its ^{15}N-HMBC NMR and by the chemical shifts in the ^{15}N NMR spectrum, where the N's have chemical shifts of ~ -300 ppm and ~ -200 ppm, and not ~ -50 ppm as would have been expected had the compound contain an =N-OH group as that shown in structure **15** (see experimental). It appears that based on the above suggested resonance argument, the N in the NH group is of sufficiently nucleophilic character that it overcomes the well-established affinity of O to P, leading to the *N*-phosphorylated product.



Scheme 5: Phosphorylation of HU

Conclusion: In conclusion, several attempts were made to synthesize the valproate ester of HU, **6,** as a potential mutual prodrug of the HDAC inhibitor valproic acid and the established anticancer agent HU. A literature search of

acylated HU derivatives revealed that very few publications claim the synthesis of HU esters. Whereas an early publication claimed that the benzoylation of HU led to the benzoate ester, **1**, in our studies we found that the acylation took place easily on the secondary N to give compound **2** rather than on the hydroxyl group. Moreover, and surprisingly, in the course of further investigations it was found that even phosphorylation of HU took place on the N rather than on the O, leading to the phosphoramide **13**. This result was highly unexpected based on the well established, high-affinity of phosphorous to oxygen. The analogous acylation reaction of the hydroxamic acid **7** or the *N*-hydroxycarbamate **10**, gave the *O*-acylated products **8** and **11**. The structural assignments of the products were based on their ^{15}N-HMBC NMR spectra. These results support our experimental findings and show that HU is an unusual hydroxamic acid and the presence of the NH_2 group rather than alkyl or alkoxy groups, found in hydroxamic acids, caused it to react differently. We rationalized these results based on the different resonance structures of HU, the hydroxamic acid and an *N*-hydroxycarbamate.

General Information: ^{1}H, ^{13}C and ^{15}N NMR spectra were obtained on Bruker Avance-II-200, DPX-300, DMX-600 and Avance-III-700 spectrometers. Chemical shifts for ^{1}H and ^{13}C are expressed in ppm downfield from Me_4Si (TMS) used as internal standard and for ^{15}N are related to neat nitromethane as an external standard; the chemical shifts for ^{15}N were determined indirectly from the ^{15}N-HMBC spectra. The values are given in δ scale. LRMS were also obtained on a QToF micro (Waters UK) spectrometer in ESI (= Electronspray

Ionization), HRMS were obtained on an AutoSpec Premier (Waters UK) spectrometer in EI^+ mode, and SYNAPT spectrometer (Waters UK). Progress of the reactions was monitored by TLC on silica gel (Merck, Art. 5554). Flash chromatography was carried out on silica gel (Merck, Art. 9385). Melting points were determined on a Fisher-Johns apparatus. The commercially available valproic acid and HU were used without further purification. The nomenclature of the compounds was assigned according to ChemDraw Ultra v. 11.0.1 (CambridgeSoft). Valproyl chloride [19] and *N*-hydroxypivalamide [15] and *N-Boc*-hydroxylamine[16] were prepared according to known procedures.

***N*-Carbamoyl-*N*-hydroxybenzamide, (2).** [11]

The following procedure is analogous to that described by Exner [10] where the chromatographic purification has been added. To a solution of hydroxyurea (0.5 g, 6.57 mmol) in dry pyridine at 45 °C, benzoic anhydride (1.48 g, 6.57 mmol) was added slowly. The solution was then heated for 10 min at 45 °C. The solvent was then evaporated and the residue was purified by flash chromatography silica gel, eluent EtOAc/*n*-hexane 1:1) to give **2** (45% yield, mp 125-127 °C).

^{1}H NMR (300 MHz, Acetone-D_6): δ: 6.36 (bs, 2H), 7.56 (t, *J* = 15.93 Hz, 2H), 7.71 (t, *J* = 15.93 Hz, 2H), 8.10 (d, *J* = 6.37 Hz, 2H), 9.24 (bs, 1H).

^{13}C NMR (75 MHz, Acetone-D_6): δ: 128.68, 129.60, 130.48, 134.74, 160.48, 166.19.

^{15}N NMR (indirectly from HMBC spectrum): δ: -305.8 (*N*H_2).

MS (ES^+) m/z 181 (MH^+, 100); 203 ($[M+Na]^+$, 96).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55; O, 26.64. found: C, 53.48; H, 4.38; N, 15.35; O, 26.14.

***N*-Carbamoyl-*N*-hydroxy-2-propylpentanamide (4)** and **2-Propyl-*N*-((2-propylpentanoyl)oxy)pentanamide (5).** [13]

To a solution of hydroxyurea (0.5 g, 6.57 mmol) in dry DMF under N_2 was added DMAP (0.8 g, 6.57 mmol) followed by valproyl chloride (1.07 g, 6.57 mmol). The mixture was stirred at -41 ^oC (acetonitrile/dry ice bath) for 30 min and was then evaporated. The residue, which contained a mixture of **4** and **5** was purified by chromatography (EtOAc/*n*-hexane 1:20 -> 1:1), to give **5** as a white solid, mp 45-47 ^oC, (4% yield) and **4** as a yellowish oil (31% yield).

^1H NMR of compound **4** (700 MHz, $CDCl_3$): δ: 0.91 (t, J = 7 Hz, 6H), 1.33 (m, 4H), 1.51 (m, 2H), 1.66 (m, 2H), 2.52 (m, 1H), 5.85 (bs, 2H), 9.14 (bs, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ: 13.90, 20.54, 34.40, 43.40, 160.09, 174.66.

^{15}N NMR (obtained indirectly from the HMBC spectrum): δ: -221 (*N*-OH), -303 (NH_2).

MS (ES^+) m/z 203 (MH^+, 100); 225 ($[M+Na]^+$, 96).

HRMS calcd for $C_9H_{18}N_2O_3Na$ (M+, Na^+) 225.1222, found 225.1215.

^1H NMR of compound **5** (700 MHz, $CDCl_3$): δ: 0.91 (m, 12H), 1.28-1.45 (m, 10H), 1.51 (m, 2H), 1.67 (m, 4H), 2.15 (m, 1H), 2.57 (m, 1H), 8.95 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ: 13.94, 14.05, 20.51, 20.65, 34.43, 34.86, 43.19, 44.24, 174.40, 174.98.

^{15}N NMR (obtained indirectly from the HMBC spectrum): δ: -208.8.

MS (ES^+) m/z 286 (MH^+, 100); 308 ($[M+Na]^+$, 9).

HRMS (APPI$^+$) calcd for $C_{16}H_{31}NO_3Na$ (M+, Na^+) 308.2202, found 308.2209.

***N*-(2-Propylpentanoyloxy)pivalamide (8).** To a solution of *N*-hydroxypivalamide **7** [15] (0.3 g, 2.56 mmol) in dry pyridine under N_2 was added valproyl chloride (0.4 g, 2.56 mmol). The mixture was stirred at ~23 ^oC for 4 h, was then concentrated and the residue was purified by column chromatography (EtOAc/*n*-hexane 1:20), to give **8** as a white solid, mp 60-62 ^oC (90% yield).

^1H NMR (700 MHz, $CDCl_3$): δ: 0.91 (t, J = 7 Hz, 6H), 1.28 (bs, 9H), 1.38 (m, 4H), 1.51 (m, 2H), 1.68 (m, 2H), 2.57 (m, 1H), 9.04 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ: 13.94, 20.49, 27.21, 34.42, 38.68, 43.22, 175.17, 176.85.

^{15}N NMR (obtained indirectly from the HMBC spectrum, 700 MHz, $CDCl_3$): δ: -212.2.

MS (ES$^+$) m/z 244 (MH^+, 100), 266 ($[M+Na]^+$, 28.86).

Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76; found: C, 63.46; H, 10.75; N, 5.81.

***tert*-Butyl((2-propylpentanoyl)oxy)carbamate (11).**

To a solution of *N-Boc*-hydroxylamine **10** [16] (0.1 g, 0.75 mmol) in dry DCM under N_2 were added DIEA (0.1 g, 0.75 mmol) followed by valproyl chloride (0.12 g, 0.75 mmol). The mixture was stirred at room temperature for 30 min, concentrated, diluted with EtOAc and acidified 1M $KHSO_4$. The layers separated and the organic phase was washed with $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The residue was purified by chromatography (EtOAc/*n*-hexane 1:10) to give **11** as a clear oil (81% yield).

^{1}H NMR (700 MHz, $CDCl_3$): δ: 0.84 (m, 6H), 1.28 (m, 4H), 1.40 (m, 9H), 1.60 (s, 2H), 2.46(m, 1H), 7.98 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ: 13.74, 20.30, 27.87, 34.19, 42.97, 82.74, 155.54, 175.64.

^{15}N NMR (obtained indirectly from the HMBC spectrum, 700 MHz, Acetone-D_6): δ: -240.0.

MS (ES^+) m/z 282 ($[M+Na]^+$, 40).

HRMS ($APPI^-$) calcd for $C_{13}H_{25}NO_4$ (M^-) 258,1705, found 258.1718.

Diethyl carbamoyl(hydroxy)phosphoramidate (13).

To a solution of hydroxyurea, (0.2 g, 2.63 mmol) in dry pyridine at ice bath temperature, was dropwise added diethyl chlorophosphate (0.45 g, 2.63 mmol). The mixture was stirred at ~23 ^{o}C for 4 h, a precipitate that formed was filtered, the filtrate was evaporated and the residue was purified by chromatography (DCM/MeOH 30:1) to give **13** as a white solid, 115-117 ^{o}C (25% yield).

^{1}H NMR (700 MHz, $CDCl_3$): δ: 1.37 (t, *J* = 8 Hz, 6H), 4.26 (m, 4H), 6.22 (s, 2H), 8.98 (s, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ: 16.03 (d, *J* = 6 Hz), 65.72 (d, *J* = 6 Hz), 161.47 (d, *J* = 4 Hz).

^{15}N NMR (indirectly from HMBC spectrum): δ: -220.1 (*N*-OH), -300.8 (NH_2CO).

TOF MS (ES^+) m/z 235 ($[M+Na]^+$, 100).

^{31}P NMR (400 MHz, $CDCl_3$): δ: 1.16

Anal. Calcd for $C_5H_{13}N_2O_5P$: C, 28.31; H, 6.18; N, 13.21; found: C, 28.84; H, 6.15; N, 13.06.

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