An Improved Synthesis of *O*-Benzoyl Protected Hydroxamates

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Several primary amines (R-NH_2) were converted to their corresponding *O*-benzoyl protected hydroxamates under biphasic conditions. The intermediate (benzoyloxy)amines (R-NHOCOPh) were generated using benzoyl peroxide dissolved in CH_2Cl_2 and an aqueous carbonate buffer (pH 10.5) at room temperature. Subsequent acylation with R′COCl gave the protected hydroxamates (R′CONROCOPh) in good overall yields (56−89%).

Introduction

Iron is essential for life. To access this important micronutrient, microorganisms synthesize low molecular weight, virtually ferric ion specific ligands (i.e., siderophores) from amino acid sources such as L-ornithine and L-lysine.[1] Decarboxylation of these amino acids provides a source of the diamines: putrescine and cadaverine, respectively. In *Streptomyces pilosus* bacteria these diamines are oxidized, acylated, and coupled together to generate a variety of ligands containing hydroxamic acid [R′-C(O)N(OH)R] linkages. The best known of these ligands is deferrioxamine B (**1**, DFO),[2] an efficient iron chelating agent, which has an iron binding constant near 10^{30} M^{-1}.[3] In general, bacteria and other microorganisms use siderophores to bind exogenous iron(III) and to incorporate it into their cells. Three of these siderophores[2,4−7] are shown in Figure 1.

Interestingly, the ligand used by *S. pilosus* to access iron from its environment has found clinical use in the treatment of iron-overloaded humans.[8] In humans, iron is usually stored by the protein ferritin. The ability of DFO to compete for ferric ion in vivo and to convert it into a form excretable in the bile and urine enables the clearance of iron from mammals. In fact, **1** as its methanesulfonate salt (Novartis tradename: Desferal) has been used clinically in the treatment of iron poisoning for over 35 years.[9] However, the triweekly regimen of intravenous DFO infusions raises issues of patient compliance. Therefore, research has focused on the development of orally active iron chelators.[10]

To evaluate different iron binding ligands, medicinal chemists have desired new synthetic methods to access complex hydroxamic acids. To this end, organic chemists have struggled to provide selective reagents, which would allow for the transformation of a primary amine into a hydroxamic acid. As a result, the oxidation and *N*-acylation of primary amines (**A**) to their corresponding *O*-benzoyl protected hydroxamates (**C**) is a useful synthetic transformation for which few reliable methods exist (Scheme 1).

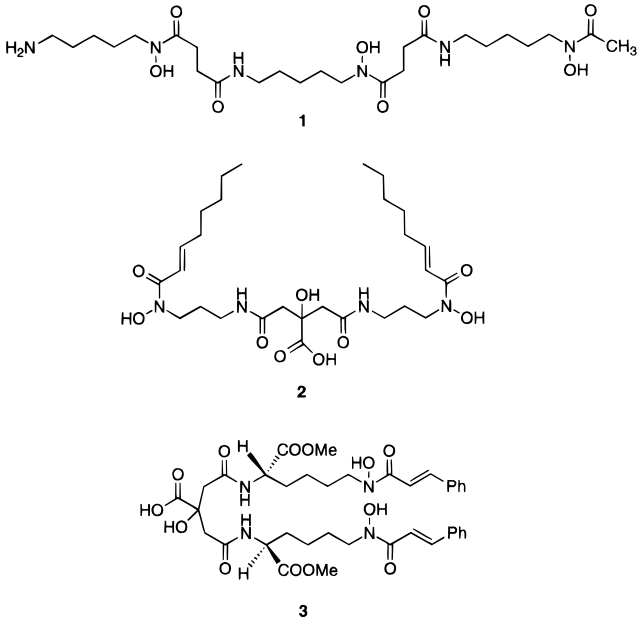

Figure 1. Deferrioxamine B (**1**), Acinetoferrin (**2**), and Nannochelin A (**3**).

In 1983, Ganem and Biloski demonstrated the conversion of secondary amines to (benzoyloxy)amines using benzoyl peroxide (BPO) as the oxidant.[11] In 1990, Milewska and Chimiak illustrated the oxidation of the free *N*δ-amine of *N*α-(benzyloxycarbonyl)-L-ornithine *tert*-butyl ester with BPO to the corresponding *N*δ-(benzoyloxy)amine, followed by *N*δ-acetylation with acetyl chloride.[12] This useful two-step transformation was employed in the synthesis of a novel siderophore, nannochelin A (**2**), albeit in 25% yield.[6]

Our focus was to evaluate a variety of reaction parameters to increase the yield and selectivity of the benzoyl peroxide mediated process. Optimization of this process is important as the intermediate (benzoyloxy)amines offer one entry to α,β-unsaturated hydroxamic acid architec-

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

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(2) Bergeron, R. J.; McManis J. S. *CRC Handbook of Microbial Iron Chelates*; CRC Press: Boca Raton, FL, 1991; pp 271−304.
(3) Anderegg, G.; L'Eplattenier, F.; Schwarzenbach, G. *Helv. Chim. Acta* **1963**, *46*, 1409.
(4) Okujo, N.; Sakakibara, Y.; Yoshida, T.; Yamamoto, S. *Biometals* **1994**, *7*, 170−176.
(5) Bergeron, R. J.; McManis, J. S.; Phanstiel IV, O.; Vinson, J. R. T. *J. Org. Chem.* **1995**, *60*, 109−114.
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(7) Kunze, B.; Trowitzsch-Kienast, W.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1992**, *45*, 147−150.
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(10) Singh, S. *Chem. Ind. (London)* **1994**, 452−455.
(11) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537.
(12) Milewska, M. J.; Chimiak, A. *Synthesis* **1990**, 233−234.

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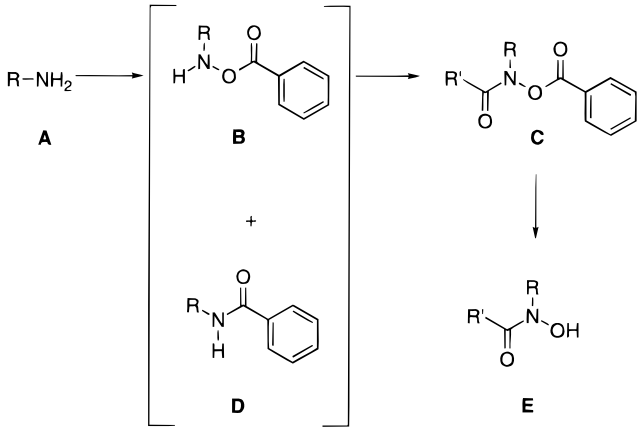
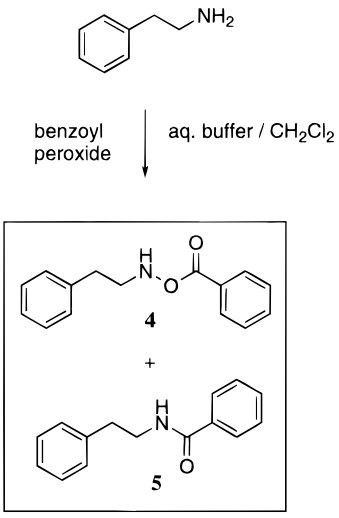
Scheme 1. Oxidation, Acylation, and Deprotection Steps for Conversion of a Primary Amine to a Hydroxamic Acid



Scheme 2. Oxidation of Phenethylamine with BPO



tures as found in the siderophores **2** and **3**. The unsaturated hydroxamic acids are not readily accessible via the commonly used *O*-benzyl protected hydroxamates. Deprotection of an *O*-benzyl protected α,*β*-unsaturated hydroxamate via hydrogenation would compromise the appended double bond. In short, progress in this area would allow for rapid access to new iron binding ligands for further clinical evaluation.

Results and Discussion

The early studies by Milewski used benzoyl peroxide as the oxidant and identified two competing pathways: *N*-oxidation and *N*-acylation.[12] Our first attempt was to apply their method to a primary amine model system (i.e., phenethylamine). Phenethylamine contains an appended aromatic ring system, which is easily monitored by UV detection. Unfortunately, in our hands their procedure (CH_2Cl_2 and solid Na_2CO_3) gave low yields of the desired (benzoyloxy)amine and instead gave mostly the benzamide byproduct (i.e. structures **4** and **5** in Scheme 2, respectively).

Using a more biomimetic approach,[13] we discovered that the presence of water significantly altered the outcome of this reaction. Using an aqueous carbonate buffer/CH_2Cl_2 mixture sharply increased the yield of the *N*-oxidized product **4** at the expense of the amide **5** (see Scheme 2). Encouraged by these results, we embarked on a detailed study of the benzoyl peroxide-mediated oxidation of phenethylamine using biphasic conditions.

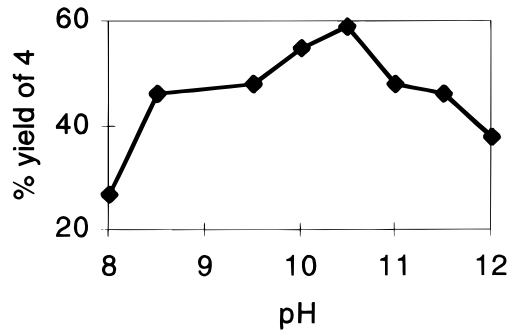


Figure 2. Yield of **4** at various pH.

Table 1. Yields of 4 and 5 at Various pH

pH	**4** (%)	**5** (%)	**4/5**
8	27	21	1.3
8.5	46	17	2.7
9.5	48	16	3
10	55	15	3.7
10.5	59	14	4.2
11	48	19	2.5
11.5	46	22	2.1
12	38	23	1.7

Reverse-phase HPLC was used to quantify the yields of the desired product **4** and the byproduct **5**. The analysis was based on the respective molar absorptivity ratios of **4** and **5** versus a diphenylmethane standard. Diphenylmethane was chosen as the internal standard as it was stable to the oxidation conditions.

Since our process was biphasic, we were interested in finding the optimal pH of the aqueous phase to obtain the maximum yield of the *N*-oxidation product. Different pH buffer solutions were prepared by combining 0.75 M $NaHCO_3$ and 1.5 M NaOH solutions at certain ratios. To neutralize the benzoic acid as it formed, at least 0.5 mL of buffer solution per 0.1 mmol phenethylamine was needed to maintain the pH throughout the entire reaction time. The pH experiments were conducted at room temperature with 1 equiv of BPO (0.4 mmol), 1 equiv of phenethylamine (0.4 mmol), 3 mL of methylene chloride, and 3 mL of aqueous buffer solution. The data from the pH study are listed in Table 1. The pH/yield profile for the oxidation of phenethylamine (see Figure 2) suggested that a pH of 10.5 was optimal for this reaction.

Using a pH 10.5 buffer, we varied the molar ratios of phenethylamine and BPO in order to observe their respective concentration effects. Reactions were conducted at room temperature with 1 equiv of phenethylamine (0.4 mmol), 3 mL of methylene chloride, 3 mL of pH 10.5 aqueous buffer solution, and varying concentrations of BPO. This concentration study (see Table 2) indicated that 2 equivalents of BPO and 1 equiv of phenethylamine provided good yields of **4**.

To date, the highest yields of **4** were obtained with equal volumes of a pH 10.5 carbonate buffer solution and 0.1 M phenethylamine in CH_2Cl_2 using 2 equiv of benzoyl peroxide (vs the amine) at room temperature.

The (benzoyloxy)amine **4** could be separated from the benzamide **5** by column chromatography or the mixture

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Table 2. Yields of 4 and 5 with Various Equivalents of BPO

BPO:amine	**4** (%)	**5** (%)	**4/5**
1	59	14	4.2
2	60	11	5.4
3	41	22	1.9
4	14	39	0.4

simply acetylated (with CH_3COCl) in the same pot to give the corresponding *O*-benzoyl protected hydroxamate **6** and recovered **5**, which were readily separated by column chromatography (see Experimental Section).

To evaluate the scope of this new procedure, a variety of primary amines (R-NH_2) were oxidized to their corresponding (benzoyloxy)amines. Each intermediate **B** was subsequently acylated to the respective *O*-benzoylhydroxamate **C** (see Scheme 1). The results are summarized in Table 3.

In general, the product yield for the one-pot−two-step process increased as the steric bulk of the R-group increased. The reaction time of the acylation step (i.e. **B** to **C** in Scheme 1) was also dependent on the steric bulk of the R group. In particular, acylation became quite slow with the hindered (benzoyloxy)amine precursor to **12**.

The mild conditions of this "one-pot" synthesis (room temperature, pH 10.5) make it ideally suited for converting a primary amine to the corresponding *O*-benzoyl protected hydroxamate. In general, *O*-benzoyl groups can be deprotected with 10% NH_3/CH_3OH at −23 °C to give high yields of the corresponding hydroxamic acids.[6]

While the benzoyl peroxide oxidant has been used previously, our biphasic method is novel. Our discovery is significant as it allows facile entry to α,β-unsaturated hydroxamic acids via masked systems such as **8**. This technology should be of immense value to medicinal chemists interested in synthesizing functionalized hydroxamic acids for iron chelation therapy and metalloenzyme inhibition.[14,15]

Experimental Section

Materials and Methods. Reagents were purchased from the ACROS Chemical Company. All commercially available amines were distilled prior to use. ^{1}H NMR spectra were recorded at 200 MHz on Varian XL-200 spectrometer. Different pH buffer solutions were prepared by combining 0.75 M $NaHCO_3$ and 1.5 M NaOH solutions at certain ratios.

General Procedure for the Oxidation of Phenethylamine at Various pH. A solution of BPO (0.096 g, 0.4 mmol) in 3 mL of CH_2Cl_2 was added quickly to a mixture of phenethylamine (0.048 g, 0.4 mmol) and diphenylmethane (0.067 g, 0.4 mmol) in 3 mL of an aqueous buffer solution (pH = 8, 8.5, 9.5, 10, 10.5, 11, 11.5, and 12, respectively) at room temperature. The disappearance of the starting material was monitored by TLC (2% NH_3/MeOH, R_f = 0.39). After the reaction was complete, the water layer was extracted twice with 10 mL of CH_2Cl_2. The organic layers were combined and concentrated to give the crude product.

General Procedure for the Oxidation of Phenethylamine by Using Various Equivalents of Benzoyl Peroxide. A solution of BPO (1, 2, 3, 4 equiv, respectively) in 3 mL of CH_2Cl_2 was added quickly to a mixture of phenethylamine (0.048 g, 0.4 mmol) and diphenylmethane (0.067 g, 0.4 mmol) in 3 mL of pH 10.5 aqueous buffer solution at room temperature. The disappearance of the starting material was monitored by TLC (2% NH_3/MeOH, R_f = 0.39). After the reaction was complete, the water layer was extracted twice with 10 mL of CH_2Cl_2. The organic layers were combined and concentrated to give the crude product.

Chromatographic Procedure. Instrument: UV spectroscopy revealed that both **4** and **5** absorbed strongly near 224 nm. Therefore, the wavelength of 224 nm was selected for UV detection. Analyses were carried out by using a Gilson HPLC system equipped with a reversed-phase C-18 column and a UV detector measuring absorbency at 224 nm. Crude reaction mixtures were eluted using 70% acetonitrile/water with a flow rate of 1 mL/min. The retention times for **5**, **4**, BPO, and diphenylmethane were 3.91, 6.98, 8.86, and 11.22 min, respectively.

Calibration: *N*-(Benzoyloxy)phenethylamine (26 mg, 0.108 mmol), *N*-(2-phenylethyl)benzamide (12.5 mg, 0.056 mmol), and diphenylmethane (0.0715 g, 0.43 mmol) were combined and dissolved in 25 mL of 70% acetonitrile/water. An aliquot of this solution was injected into the HPLC and gave the molar absorptivity ratios of **4** versus diphenylmethane (2.39) and **5** versus diphenylmethane (2.83), respectively.

Determination of the Yields of Product 4 and Byproduct 5. The crude product of the model study was dissolved in 10 mL of 100% acetonitrile. The crude product solution (1 mL) was added to 5 mL of a 70% acetonitrile/water solution. An aliquot of this solution was injected into the HPLC to give the corresponding absorbency expressed in area %. The yields were calculated using the above calibration data and the moles of standard added (i.e., 0.4 mmol).

General Procedure for the Sequential Oxidation and Acylation of a Primary Amine. A solution of BPO (1.92 g, 8 mmol) in 40 mL of CH_2Cl_2 was added quickly to a mixture of the amine (4 mmol) in 40 mL of pH 10.5 buffer solution at room temperature. In general, TLC (2% NH_3/MeOH) was used to monitor the consumption of the starting material. A solution of the acid chloride (4 mmol) in 5 mL of CH_2Cl_2 was added to the reaction mixture after all the starting amine was consumed. After the acylation reaction was complete, the water layer was extracted twice with 20 mL of CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The product mixture was subjected to flash column chromatography, eluting with 20% ethyl acetate/hexane to isolate the masked *O*-benzoyl hydroxamate. The yields are listed in Table 3.

***N*-(Benzoyloxy)-2-phenethylamine (4) and *N*-(2-Phenylethyl)benzamide (5).** Oxidation of phenethylamine (0.484 g, 4 mmol) was carried out as described in the general procedure. Column chromatography (20% EtOAc/hexane) gave **4** (0.70 g, 73%) and the *N*-(2-phenylethyl)benzamide (**5**) (0.09 g, 10%), respectively. **4**: R_f = 0.47 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, aromatic H), 7.35 (m, 8H, aromatic H), 3.45 (t, 2H, CH_2N), 2.98 (t, 2H, CH_2); high-resolution mass spectrum (FAB): theory for ($C_{15}H_{15}N_1O_2$) M + 1 = 242.1209, found M + 1 = 242.1204. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 75.04; H, 6.45; N, 5.86. **5**: R_f = 0.25 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 7.65 (d, 2H, aromatic H), 7.20 (m, 8H, aromatic H), 3.6 (q, 2H, CH_2), 2.82 (t, 2H, CH_2).

***N*-(Benzoyloxy)-*N*-(2-phenylethyl)acetamide (6).** The oxidation and acylation of phenethylamine (0.484 g, 4 mmol) were carried out as described in the general procedure to give 0.813 g of the protected hydroxamate **6** (72%). **6**: R_f = 0.20 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.01 (d, 2H, aromatic H), 7.67 (m, 1H, aromatic H), 7.51 (m, 2H, aromatic H), 7.25 (m, 5H, aromatic H), 4.07 (t, 2H, CH_2N), 2.99 (t, 2H, CH_2), 2.00 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.80; H, 6.09; N, 4.94.

***N*-(Benzoyloxy)-*N*-hexylacetamide (7).** The oxidation and acylation of hexylamine (0.404 g, 4 mmol) were carried out as described in the general procedure to give 0.74 g of the desired product **7** (70%). **7**: R_f = 0.19 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, 2H, aromatic H), 7.59 (m, 3H, aromatic H), 3.81 (t, 2H, CH_2N), 2.05 (s, 3H, CH_3),

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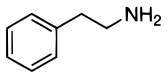
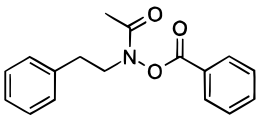
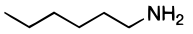
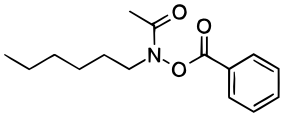
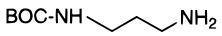
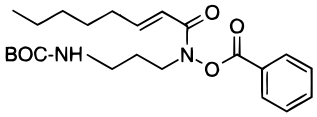
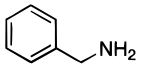
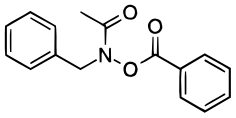
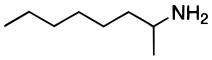
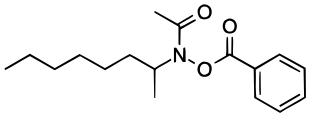
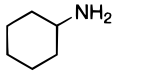
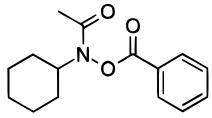
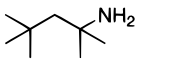
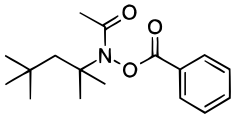
(15) Wright, S. W.; Harris, R. R.; Kerr, J. S.; Green, A. M.; Pinto, D. J.; Bruin, E. M.; Collins, R. J.; Dorow, R. L.; Mantegna, L. R.; Sherk, S. R.; Covington, M. B.; Nurnberg, S. A.; Welch, P. K.; Nelson, M. J.; Magolda, R. L. *J. Med. Chem.* **1992**, *35*, 4061−4068.

Table 3. Conversion of Primary Amines to *O*-benzoyl Protected Hydroxamates

Starting Primary Amine	Product	#, % isolated yield
		**6**, 72%
		**7**, 70%
		**8**, 68%
		**9**, 56%
		**10**, 85%
		**11**, 89%
		**12**, 89%

1.65 (m, 2H, CH_2), 1.31 (m, 6H, CH_2), 0.89 (t, 3H, CH_3). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.52; H, 8.03; N, 5.36.

***N*-(3-(*tert*-Butoxycarbonylamino)propyl)-*N*-(benzoyloxy)-2-(*E*)-octenamide 8.** A solution of BPO (14.52 g, 60 mmol) and CH_2Cl_2 (225 mL) was added dropwise at room temperature to a vigorously stirred mixture of N^1-BOC-propanediamine (5.22 g, 30 mmol) and 300 mL of a carbonate buffer solution (at pH = 10.5). The buffer solution was prepared by combining 222 mL of 0.75 N aqueous $NaHCO_3$ and 78 mL of 1.5 N aqueous NaOH. The starting material was consumed after 4 h as shown by TLC (4% NH_3/MeOH). Note: Column chromatography (40% ethyl acetate/hexane) can be used to separate the (benzoyloxy)amine intermediate (BOC-$NHCH_2CH_2CH_2NHOCOPh$) **13** and the benzamide (BOC-$NHCH_2CH_2CH_2NHCOPh$) **14** (e.g. R_f = 0.43 and 0.29, respectively). [The characterization of **13** is included for completeness. **13**: ^{1}H NMR ($CDCl_3$): δ 8.03 (d, 2H, aromatic H), 7.52 (m, 3H, aromatic H), 6.80 (broad m, 1H, NH), 4.81 (broad m, 1H, NH), 3.22 (m, 4H, CH_2), 1.82 (m, 2H, CH_2), 1.41 (s, 9H, *tert*-butyl); high-resolution mass spectrum (FAB): theory for ($C_{15}H_{23}N_2O_4$) M + 1 = 295.1658, found M + 1 = 295.1645]. A solution of *trans*-2-octenoyl chloride (4.81 g, 30 mmol) in 30 mL of CH_2Cl_2 was added dropwise to the mixture of **13** and **14** over 15 min. The disappearance of **13** was monitored by TLC (40% ethyl acetate/hexane). After the acylation was complete, the organic layer was separated, and the remaining water layer was washed twice with additional CH_2Cl_2 (100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. The crude hydroxamate was subjected to flash column chromatography and eluted with 30% ethyl acetate/hexane to give **8** (8.58 g: 68%) as a colorless oil. **8**: R_f = 0.33 in 30% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.12 (d, 2H, aromatic), 7.71 (t, 1H, aromatic H), 7.54 (t, 2H, aromatic H), 7.03 (dt, 1H, olefinic), 6.05 (d, 1H, olefinic), 5.20 (broad, 1H, NH), 3.92 (t, 2H, CH_2NO), 3.24 (q, 2H, CH_2), 2.15 (q, 2H, $CH_2C{=}C$), 1.82 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.53−1.15 (m, 13H, *tert*-butyl and 2 CH_2), 0.83 (t, 3H, CH_3); Anal. Calcd for $C_{23}H_{34}N_2O_5$: C, 66.01; H, 8.19; N, 6.69. Found: C, 65.83; H, 8.17; N, 6.61.

***N*-(Benzoyloxy)-*N*-benzylacetamide (9).** Oxidation and acylation of benzylamine (0.429 g, 4 mmol) were carried out as described in the general procedure to give 0.605 g of the desired product **9** (56%). **9**: R_f = 0.20 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, aromatic H), 7.64 (m, 1H, aromatic H), 7.46 (m, 3H, aromatic H), 7.34 (m, 4H, aromatic H), 4.99 (s, 2H, CH_2), 2.11 (s, 3H, CH_3). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.11; H, 5.59; N, 5.14.

***N*-(Benzoyloxy)-*N*-(1-methylheptyl)acetamide (10).** Oxidation and acylation of 1-methylheptylamine (0.517 g, 4 mmol) were carried out as described in the general procedure to give 0.99 g of the desired product **10** (85%). **10**: R_f = 0.20 in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 2H, aromatic H), 7.61 (m, 3H, aromatic H), 4.75 (broad s, 1H, CH), 2.06 (s, 3H, CH_3), 1.35 (m, 13H, CH_2 and CH_3), 0.90 (t, 3H, CH_3). Anal.

Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.64; N, 4.81. Found: C, 70.17; H, 8.66; N, 4.82.

***N*-(Benzoyloxy)-*N*-cyclohexylacetamide (11).** Oxidation and acylation of cyclohexylamine (0.397 g, 4 mmol) were carried out as described in the general procedure to give 0.93 g of the desired product **11** (89%). **11**: $R_f = 0.19$ in 20% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 2H, aromatic H), 7.60 (m, 3H, aromatic H), 4.50 (broad s, 1H, CH), 2.69 and 2.47 (dt, 2H, CH_2), 2.15−1.00 (m, 11H, CH_2 and CH_3). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.90; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.29; N, 5.42.

***N*-(Benzoyloxy)-*N*-(1,1,3,3-tetramethylbutyl)acetamide (12).** Oxidation and acylation of *tert*-octylamine (0.517 g, 4 mmol) were carried out as described in the general procedure to give 1.04 g of the desired product **12** (89%). **12**: $R_f = 0.20$ in 19% ethyl acetate/hexane; ^{1}H NMR ($CDCl_3$): δ 8.11 (d, 2H, aromatic H), 7.60 (m, 3H, aromatic H), 2.00 (s, 3H, CH_3), 1.69 (s, 5H, CH_2 and CH_3), 1.35 (m, 3H, CH_3), 1.09 (t, 9H, CH_3). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.64; N, 4.81. Found: C, 69.97; H, 8.68; N, 4.75.

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