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Site Selectivity in the Synthesis of *O*-Methylated Hydroxamic Acids with Diazomethane

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In this paper we report the results obtained by treating some selected hydroxamic acids with diazomethane in ethereal media. The multitask reagent diazomethane was used either as a base to induce deprotonation of the chosen hydroxamic acids or as conjugated acid which undergoes one-pot methylation processes of the generated anions. Product distributions clearly showed that a high site selectivity is expressed by the different deprotonated species in the alkylation processes. Under the adopted conditions, the prevalent site of methylation is in all the cases the oxygen of the hydroxamic acid. While in aliphatic hydroxamic acids only *O*-alkylation is observed, in the aromatic substrates, the NH group competes with the OH function as the nucleophilic site, although the OH reactivity still dominates.

Introduction

Hydroxamic acids belong to an important class of reagents in organic and inorganic chemistry,[1] also being valuable intermediates in pharmaceutical applications.[2] In fact, they are used as siderophores, antibiotics, powerful chelating agents, and protease inhibitors.[3] In this context, methylated derivatives of hydroxamic acids are active inhibitors of cyclooxygenase- and lypooxygenase-mediated processes.[4] More recently, great interest has been addressed by theoretical studies dealing with the determination of the proton affinities and the gas-phase basicities of simple hydroxamic acids in order to elucidate the solution behavior of more complex similar systems having biological applications.[5]

The structure−function relationships of hydroxamic acids still present some unresolved questions[6] related to the understanding of their exceptionally low pK_a values, if compared with structurally similar amide derivatives, and to the evaluation of the structural features of their conjugated bases.[7] In fact, the identification of the deprotonation sites has not yet been clearly performed either in solution or in the gas phase. Past and recent reports have shown that both OH and NH groups are possible ionization sites in solution.[8]

A study of the oxidation potentials[9] and cation complexation experiments in alkaline media[10] of the hydroxamate ions have proposed the NH group to be the preferred ionization site in polar solvents, such as dimethyl sulfoxide, whereas the hydroxylic function acts as proton donor in protic solvents.[11] On the other hand, the NH moiety seems to be able to furnish predominant deprotonation with respect to the OH group under gas-phase conditions.[12] Moreover, extended spectroscopic experiments (^{14}N, ^{15}N, and ^{17}O heteronuclear NMR relaxation with the aid of NOE evaluation)[6,13] and theoretical calculations (ab initio methods)[14] have demonstrated that the acidity of both NH and OH functions

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Scheme 1. Methylation of Hydroxamic Acids 1a−e

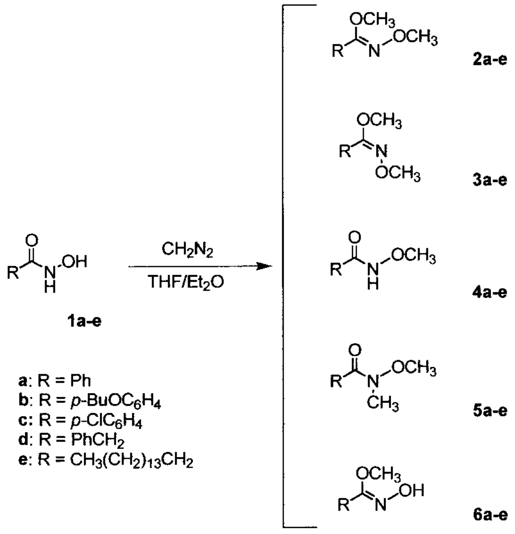


Table 1. Product Distributions Obtained in the Methylation of Hydroxamic Acids 1a−e

entry	hydroxamic acid	products	yields (%)
1	**1a**	**2a**, **5a**, **6a**	70, 3, 22
2	**1b**	**2b**, **3b**, **5b**, **6b**	72, 5, 8, 10
3	**1c**	**2c**, **5c**, **6c**	69, 9, 18
4	**1d**	**2d**, **3d**, **4d**	85, 10, 3
5	**1e**	**2e**, **3e**, **4e**	81, 8, 5

is strongly affected by the structural characteristics of the substrate, also depending on the solvent used in the experimental investigations.[15]

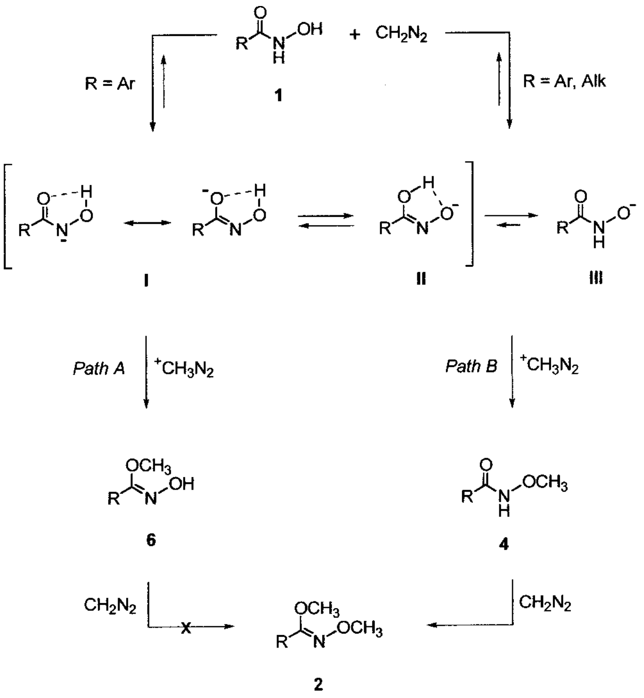
Results and Discussion

To achieve the aim of a more profound evaluation either of the acidic properties or the nucleophilic reactivities of both NH and OH functions, we now propose a novel tool based on the use of diazomethane. This multitask reagent behaves as a base,[16] generating the methyldiazonium ion which can perform a selective alkylation of the hydroxamate ions produced in an ethereal solvent. Diazomethane might also prove useful to open short and convenient synthetic routes to methylated derivatives of structurally complex hydroxamic acids having biological importance. Finally, the availability of a one-pot selective methylation of hydroxamic acid models might represent a remarkable tool to improve the understanding of the structures and the reactivity of their charged conjugated bases.

To evaluate the reaction with diazomethane, benzohydroxamic acid **1a** was chosen as a model compound for its well-known ability to stabilize the negative charge on the nitrogen atom of the corresponding hydroxamate ion. Compound **1a** reacts with 3 equiv of diazomethane in a 1:3 (v/v) tetrahydrofuran/diethyl ether solution to afford methyl (*Z*)-*O*-methylbenzohydroximate **2a**, methyl *N*-methylbenzohydroxamate **5a**, and methyl (*Z*)-benzohydroximate **6a** (Scheme 1), whose respective overall yields are reported in Table 1.

The correct configuration of the oxime ether **2a**, the major product reaction, was assigned after its thermal isomerization at 150 °C into methyl (*E*)-*O*-methylbenzohydroximate **3a**. The latter provided ^{1}H NMR data which fully correlate with those reported in the literature[17] for the same compound. The two isomers **2a** and **3a** mainly differ for their ^{1}H NMR spectroscopic properties, showing well distinguishable frequencies for both *N*- and *C*-methoxy substituents. The electron impact mass spectrum and the ^{1}H NMR analysis of the side product **5a** were found to be identical to those obtained from an authentic sample of methyl *N*-methylbenzohydroxamate synthesized by treatment of *N*,*O*-dimethylhydroxylamine with benzoyl chloride. In the reaction of **1a** with diazomethane, the product distribution appears to be related to the hydrogen abstraction affording the charged species **I** and **II**, and more closely to the proton-transfer equilibria which could allow the interconversion between the same anions through an intramolecular hydrogen bond (Scheme 2). The formation of dimethylated oximes of the type **2** could be attributed to the reaction of the charged intermediates **II** and **III** which are preliminary methylated at the anionic site to generate **4**. Subsequent alkylation of the *O*-methyl derivative **4** gives the final dimethylated product **2**. Instead, the hydroxamic acid anion **I**, formally originated from a deprotonation process occurring at the NH site, is believed to be responsible for the formation of the monoalkylated oxime derivatives **6**.

Scheme 2. Equilibria and Reaction Pathways in the Methylation of Hydroxamic Acids 1a−e



When **6a** was treated with diazomethane, no reaction was observed, and the monomethylated oxime precursor was quantitatively recovered unchanged. The unsuccessful alkylation of **6a** to give the corresponding dimethylated product excludes the formation of **2a** by the intermediates involved in the path A. Furthermore, the hypothesis that the conversion of **1a** into **2a** could occur through the mechanism depicted in the path B is supported by the evidence that the methyl benzohydrox-

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amate **4a** is a real reaction intermediate, the existence of which was confirmed by performing GC/MS analysis of the crude mixture. The collected data clearly show that paths A and B are competitively active in the reaction of **1a** with diazomethane. The observed product distribution could thus be explained on the basis of a comparable reactivity of the anions **I** and **II**, determined by the presence of a charge delocalization involving the nitrogen atom in the former species and the phenyl group in the latter charged structure.

The reaction of **1a** with diazomethane also showed total stereoselection. The exclusive formation of the (*Z*) oxime **6a** can be attributed to its higher stability with respect to the (*E*) isomer. This difference is probably due to a minimization of the steric hindrance between the phenyl substituent and the OH group in the (*E*) oxime and to the possible formation of an intramolecular hydrogen bond involving the oxygenated parts in the same isomer. Finally, despite the previously reported procedure,[18] methylation of benzohydroxamic acid **1a** did not afford other side products. In fact, the literature method gave methyl *O*-methylbenzohydroximate, as a mixture of **2a** and **3a** (45% total yield), 3,4-diphenyl-1,3,5-oxadiazolin-2-one (42%), and traces of methyl benzoate, the last ones probably arising from thermal degradation processes operating when the reaction crude mixture is submitted to distillation. The thermal effects on the stability of mono- and dimethylated products were confirmed by warming a crude mixture of **2a**, **5a**, and **6a** in a screw-capped vial at 150 °C for 24 h. Under the adopted conditions, the formation of 3,4-diphenyl-1,3,5-oxadiazolin-2-one and methyl benzoate was observed as detected by GC/MS analysis.

The introduction of a substituent on the aromatic ring of the hydroxamic acid structure does not alter the course of the methylation. *p*-Butoxyphenylhydroxamic acid **1b** showed the same general behavior of **1a**. In this case, the electron-releasing group placed on the aryl moiety introduces only a slight change in the product distribution with respect to that obtained from the treatment of **1a** with the methylating agent. In fact, when **1b** was allowed to react with diazomethane under the usual conditions (Scheme 1), methyl (*Z*)-*O*-methyl-*p*-butoxyphenylhydroximate **2b** was recovered as the prevalent product in 72% total yield (Table 1). Only traces of the (*E*) isomer **3b** were also isolated (5%), whereas the side products **5b** and **6b** were obtained in scarce overall yields (8 and 10%, respectively). Moreover, alkylation of *p*-chlorophenylhydroxamic acid **1c** gave a product distribution analogous to that observed in the case of benzohydroxamic acid **1a**. In fact, methyl (*Z*)-*O*-methyl-*p*-chlorophenylhydroximate **2c**, *N*-methyl-*p*-chlorophenylhydroxamate **5c**, and methyl (*Z*)-*p*-chlorophenylhydroximate **6c** were recovered by chromatographic purification in 69, 9, and 18% overall yields, respectively. Thus, the product distributions observed in the treatment of aryl hydroxamic acids **1a**, **1b**, and **1c** with diazomethane do not closely depend on the electronic effects exerted by the substituent present on the aromatic ring of the hydroxamic acid.

To explain the role played by the substituent R on the competitive alkylation of both NH and OH functionalities, the behavior of some alkyl hydroxamic acids was finally investigated. In particular, phenylaceto- and palmitohydroxamic acids (**1d** and **1e**, respectively; Scheme 1) were chosen as suitable models for the fulfillment of our purpose. When **1d** and **1e** were allowed to react under the experimental conditions adopted to carry out the methylation, methyl *O*-methylphenylaceto- and methyl *O*-methylpalmitohydroximate were obtained, each one as a mixture of the corresponding (*Z*) and (*E*) isomers (**2d**, **3d** and **2e**, **3e**, respectively; Scheme 1), in appreciable to good total yields (Table 1). In this case also, all the examined reactions showed a preference toward the formation of the oxime derivative having the (*Z*) configuration. Moreover, the observed results are consistent with the assumption that the reactivity of the alkyloxyanion **III**, in which the negative charge is localized on the hydroximate oxygen, is remarkably increased with respect to the corresponding aryl analogue, stabilized by a charge conjugation involving the substituent group. Hence the formation of the recovered products could be exclusively rationalized on the basis of the path B (Scheme 2), as also confirmed by the isolation and fully characterization of the respective reaction intermediates of the type **4**.

Treatment of alkyl hydroxamic acids **1d** and **1e** with diazomethane did not afford the corresponding *N*,*O*-dimethylhydroxamates. The ambident nucleophile **I** is probably the reactive species involved in the formation of the dimethylated products **5a**, **5b**, and **5c**. The nitranion **I**, in fact, initially reacts with the methyldiazonium ion to give the *N*-methylated intermediates which, in turn, are subjected to a second alkylation step affording the *N*,*O*-dimethylhydroxamates. When the substituent R on the hydroxamic acid structure is an aryl group (as in **1a**, **1b**, and **1c**), the nitranion **I** also generate (*O*)-methylhydroximates **6a**, **6b**, and **6c**, which are prevalently obtained respect to the *N*,*O*-dimethylated derivatives **5a**, **5b**, and **5c**. This preferred *O*-methylation (path A, Scheme 2), could be justified by a fast hard−hard reaction driven by the presence of a preformed positive charge on the methyldiazonium ion.

In all the examined cases the reaction between hydroxamic acids and diazomethane results in prevalent formation of methyl *O*-methyl hydroxymates through a process characterized by high site selectivity. The studied methylations appear also to be stereocontrolled since the Z isomer of each generated hydroxymate is recovered as the major product of any process. Under the adopted conditions, the conjugated acid methyldiazonium ion was able to react with the obtained *N*- or *O*-hydroxamates leading to processes whose reaction rates are determined by the peculiar reactivity of each hydroxamic acid anion.

Proton abstraction and transfer equilibria generating the anions from the respective hydroxamic acid are not directly implicated in the control of the product distributions observed in the methylation processes. If the N_2 loss from methyldiazonium ion (paths A and B; Scheme 2) was not considered as the rate-determining step of the entire methylation processes, the charged electrophile would be able to quench the conjugated bases derived from the hydroxamic acids. Consequently, the observed site selectivity in the product distributions should be considered a valuable evidence of only the different acidic properties of both NH and OH functionalities. On the contrary, as reported for some model compounds in a considerable study,[19] the rate-determining step of the

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alkylation of the generated ions is considered to be the reactive event occurring between the methyldiazonium ion and the different nucleophiles involved in the abovementioned equilibria. Previous reports have been focused on the possibility either of *N* or *O* deprotonation; however, the relative reactivity of each conjugated base seems to drive the product distribution in the methylation, rather than the preferred H-extraction. In fact, all the hydroxamic acid anions react in a competitive manner with the charged methyldiazonium ion, leading to a significant shift of the ionization equilibria which, in turn, move to the formation of the most reactive nucleophiles, affording the prevalent reaction products.

Experimental Section

Commercially available reagents were purchased from Aldrich Chemical Co. and used as supplied unless stated otherwise. Solvents were purified and dried by the standard procedures and distilled prior to use. ^{1}H NMR were recorded at 300 MHz using diluted solutions of each compound in $CDCl_3$ as solvent and tetramethylsilane as internal standard. GC/MS analyses were carried out using a 30 m HP-5MS capillary column with a 0.25 mm internal diameter and a 0.25 μm film thickness, purchased from Hewlett-Packard. Gas chromatographic conditions for the analyses were as follows: the initial oven temperature was 60 °C for 2 min and then programmed to 280 °C at a rate of 8 °C/min with a 10 min final hold time; the injection port temperature was set at 250 °C, and the carrier gas (He) was maintained at a flow rate of 1.2 mL/min. The mass detector was held at 280 °C and was operated in the electron impact ionization mode (EIMS) at an electron energy of 70 eV. Reaction mixtures were monitored by TLC using Merck silica gel 60-F_{254} precoated glass plates. Short-column flash chromatography (SCFC) was performed on Merck Kieselgel 60H without gypsum. Elemental analysis were performed on a Perkin-Elmer Elemental Analyzer. Hydroxamic acids **1a**−**e** were prepared by treating the corresponding ethyl ester with hydroxylamine hydrochloride in a methanolic potassium hydroxide solution, as described in the literature.[20] The diethyl ether solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea using a classical procedure.[21] The concentration of the diazomethane solution (0.66 M) was obtained by a back-titration performed with a standard benzoic acid solution. Caution: diazomethane is highly toxic. Hence, this reagent must carefully be handled.[21] Diethyl ether solutions of diazomethane are stable also for long periods if stored on KOH pellets at −20 °C. All reactions were carried out under inert atmosphere (N_2).

Methylation of Hydroxamic Acids 1a−e. *General Procedure.* A 0.66 M solution of diazomethane in diethyl ether (3 mmol) was added to a solution of the appropriate hydroxamic acid **1a**−**e** (1 mmol) in dry tetrahydrofuran. The reaction mixture was stirred for 24 h at room temperature. After this time, TLC analysis showed complete conversion of the precursor. Evaporation of the solvent under reduced pressure gave crude product which was chromatographed to afford a mixture of the corresponding methyl (*Z*)-*O*-methylhydroximate **2**, methyl (*E*)-*O*-methylhydroximate **3**, methyl hydroxamate **4**, methyl *N*-methylhydroxamate **5**, and methyl (*Z*)-hydroximate **6**.

Methylation of Benzohydroxamic Acid (1a). A solution of **1a** (2.0 g, 14.6 mmol) in dry tetrahydrofuran (20 mL) was allowed to react with a diethyl ether solution of diazomethane (66.3 mL, 43.8 mmol) to give a crude oil (2.4 g). SCFC of the recovered material using light petroleum (bp 40−60 °C)/diethyl ether (7:3, v/v) as eluent afforded **2a** (1.69 g, 70%), **5a** (73 mg, 3%), and **6a** (0.49 g, 22%), each one as colorless oil.

2a. IR (film): ν 3066 cm^{-1}, 2939, 1613, 1573, 1320, 1054, 773, 649. ^{1}H NMR: δ 3.91 ppm (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 7.35−7.49 (m, 3 H, ArH), 7.60−7.72 (m, 2 H, ArH). GC/MS: *m*/*z*, (%) 165 (57) [M$^+$], 164 (67), 119 (39), 104 (100), 91 (38), 77 (62). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.35; H, 6.70; N, 8.50. **5a**. IR (film): ν 3060 cm^{-1}, 2964, 1640, 1448, 1380, 786, 706. ^{1}H NMR: δ 3.35 ppm (s, 3 H, NCH_3), 3.53 (s, 3 H, OCH_3), 7.35−7.48 (m, 3 H, ArH), 7.61−7.71 (m, 2 H, ArH). GC/MS: *m*/*z*, (%) 165 (2) [M$^+$], 105 (100), 77 (51). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.40; H, 6.72; N, 8.49. **6a.** IR (film): ν 3321 cm^{-1}, 3070, 2948, 1638, 1325, 982, 773, 695. ^{1}H NMR: δ 3.97 ppm (s, 3 H, OCH_3), 7.36−7.49 (m, 3 H, ArH), 7.61−7.73 (m, 2 H, ArH), 8.70 (s, 1 H, OH). GC/MS: *m*/*z*, (%) 151 (14) [M$^+$], 150 (19), 134 (22), 119 (11), 103 (100), 91 (10), 77 (31). Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.60; H, 5.98; N, 9.28.

Isomerization of Methyl (*Z*)-*O*-Methylbenzohydroximate (2a). Pure **2a** (0.5 g, 3.03 mmol) was warmed at 150 °C in a tightly sealed screw-capped vial. After 48 h GC/MS analysis of the recovered residue showed the presence of two products corresponding to the isomers methyl (*Z*)-*O*-methylbenzohydroximate **2a** (56%) and methyl (*E*)-*O*-methylbenzohydroximate **3a** (44%). The obtained isomers were then separated by SCFC using light petroleum (bp 40−60 °C)/diethyl ether (9:1, v/v) as eluent.

3a. Colorless oil (0.2 g, 40% recovered yield). IR (film): ν 3056 cm^{-1}, 2962, 1630, 1592, 1262, 1101, 798, 700. ^{1}H NMR: δ 3.80 ppm (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 7.37−7.43 (m, 3 H, ArH), 7.68−7.73 (m, 2 H, ArH). GC/MS: *m*/*z*, (%) 165 (68) [M$^+$], 164 (61), 119 (36), 104 (100), 91 (33), 77 (58). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.46; H, 6.67; N, 8.50.

Synthesis of 5a. Benzoyl chloride (0.281 g, 2 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (0.214 g, 2.2 mmol) was dissolved in ethanol free chloroform (20 mL). The resulting mixture was cooled to 0 °C, and dry triethylamine (0.31 mL, 2.2 mmol) was added. The homogeneous solution was stirred at room temperature until complete conversion of the starting chloride. Saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL) were then added, and the mixture was extracted twice with diethyl ether. The organic layer was dried (Na_2SO_4) and evaporated to dryness to afford crude **5a** which was purified by SCFC using light petroleum (bp 40−60 °C)/diethyl ether (7:3, v/v) as eluent (0.297 g, 90%).

IR (film): ν 3060 cm^{-1}, 2964, 1640, 1448, 1380, 786, 706. ^{1}H NMR: δ 3.35 ppm (s, 3 H, NCH_3), 3.53 (s, 3 H, OCH_3), 7.41 (m, 3 H, ArH), 7.68 (m, 2 H, ArH). GC/MS: *m*/*z*, (%) 165 (12) [M$^+$], 134 (18), 105 (100), 77 (51). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.49; H, 6.67; N, 8.52.

Treatment of 6a with Diazomethane. A solution of **6a** (0.305 g, 2 mmol) in dry tetrahydrofuran (1.1 mL) was allowed to react with a diethyl ether solution of diazomethane (3.3 mL, 2.2 mmol) at room temperature for 24 h. After evaporation of the volatiles, unreacted **6a** was quantitatively recovered.

Thermal Degradation of 2a, 5a, and 6a. A 0.5 g amount of a crude mixture obtained from the reaction of **1a** with diazomethane was warmed at 150 °C for 24 h in a tightly sealed screw-capped vial. The mixture was then cooled at room temperature and fractionated by SCFC using light petroleum (bp 40−60 °C)/diethyl ether (9:1, v/v) as eluent. Purification afforded the two isomers **2a** and **3a**, and methyl benzoate, in 18, 30, and 36% yield, respectively. GC-MS analysis performed on the crude mixture also revealed the presence of 3,4-diphenyl-1,3,5-oxadiazolin-2-one. GC/MS: *m*/*z*, (%) 238 (8) [M$^+$], 194 (10), 119 (35), 103 (100), 91 (18), 76 (33).

Methylation of *p*-Butoxyphenylhydroxamic Acid (1b). A solution of **1b** (0.5 g, 2.39 mmol) in dry tetrahydrofuran (5 mL) was allowed to react with a diethyl ether solution of diazomethane (11 mL; 7.26 mmol) to give a crude oil (0.55 g) which was fractioned by SCFC using chloroform/methanol (9:1, v/v) as eluent. Chromatographic purification afforded **2b** (0.41 g, 72%), **3b** (28 mg, 5%), **5b** (46 mg, 8%), and **6b** (54 mg; 10%), each compound as a colorless oil.

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2b. IR (film): ν 3062 cm^{-1}, 2961, 1613, 1560, 1320, 1250, 773. ^{1}H NMR: δ 0.97 ppm (t, J = 7.3 Hz, 3 H, $\mathrm{OCH_2CH_2CH_2C}H_3$), 1.48 (m, 2 H, $\mathrm{OCH_2CH_2C}H_2\mathrm{CH_3}$), 1.75 (m, 2 H, $\mathrm{OCH_2C}H_2\mathrm{CH_2CH_3}$), 3.89 (s, 3 H, $\mathrm{OCH_3}$), 3.90 (s, 3 H, $\mathrm{OCH_3}$), 3.95 (t, J = 6.5 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_2CH_2CH_3}$), 6.87 (d, J = 9.0 Hz, 2 H, ArH), 7.75 (d, J = 9.0 Hz, 2 H, ArH). GC/MS: m/z, (%) 237 (77) [M$^+$], 180 (100), 150 (11), 135 (47), 120 (95), 107 (21). Anal. Calcd for $\mathrm{C_{13}H_{19}NO_3}$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.75; H, 8.09; N, 5.91. **3b.** IR (film): ν 3062 cm^{-1}, 2961, 1607, 1510, 1320, 1259, 773. ^{1}H NMR: δ 0.99 ppm (t, J = 7.4 Hz, 3 H, $\mathrm{OCH_2CH_2CH_2C}H_3$), 1.50 (m, 2 H, $\mathrm{OCH_2CH_2C}H_2\mathrm{CH_3}$), 1.76 (m, 2 H, $\mathrm{OCH_2C}H_2\mathrm{CH_2CH_3}$), 3.80 (s, 3 H, $\mathrm{OCH_3}$), 3.81 (s, 3 H, $\mathrm{OCH_3}$), 3.97 (t, J = 6.6 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_2CH_2CH_3}$), 6.87 (d, J = 9.0 Hz, 2 H, ArH), 7.75 (d, J = 9.0 Hz, 2H, ArH). GC/MS: m/z, (%) 237 (79) [M$^+$], 180 (100), 150 (12), 135 (47), 120 (90), 107 (21). Anal. Calcd for $\mathrm{C_{13}H_{19}NO_3}$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.77; H, 8.06; N, 5.89. **5b.** IR (film): ν 3024 cm^{-1}, 2956, 1718, 1606, 1560, 1435, 1250, 790. ^{1}H NMR: δ 0.96 ppm (t, J = 7.3, 3 H, $\mathrm{OCH_2CH_2CH_2C}H_3$), 1.48 (m, 2 H, $\mathrm{OCH_2CH_2C}H_2\mathrm{CH_3}$), 1.76 (m, 2 H, $\mathrm{OCH_2C}H_2\mathrm{CH_2CH_3}$), 3.33 (s, 3 H, $\mathrm{NCH_3}$), 3.54 (s, 3 H, $\mathrm{OCH_3}$), 3.98 (t, J = 6.5 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_2CH_2CH_3}$), 6.87 (d, J = 8.9 Hz, 2 H, ArH), 7.69 (d, J = 8.9 Hz, 2 H, ArH). GC/MS: m/z, (%) = 237 (77) [M$^+$], 177 (95), 150 (5), 121 (100), 93 (9), 65 (7). Anal. Calcd for $\mathrm{C_{13}H_{19}NO_3}$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.78; H, 8.07; N, 5.88. **6b.** IR (film): ν 3330 cm^{-1}, 3060, 2950, 1620, 1350, 987, 773. ^{1}H NMR: δ 0.96 ppm (t, J = 7.4 Hz, 3 H, $\mathrm{OCH_2CH_2CH_2C}H_3$), 1.47 (m, 2 H, $\mathrm{OCH_2CH_2C}H_2\mathrm{CH_3}$), 1.74 (m, 2 H, $\mathrm{OCH_2C}H_2\mathrm{CH_2CH_3}$), 3.87 (s, 3 H, $\mathrm{OCH_3}$), 3.98 (t, J = 6.6 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_2CH_2CH_3}$), 7.55 (d, J = 8.8 Hz, 2 H, ArH), 7.98 (d, J = 8.8 Hz, 2 H, ArH), 8.30 (s, 1 H, OH). GC/MS: m/z, (%) 223 (33) [M$^+$], 191 (3), 175 (15), 166 (55), 150 (25), 119 (100). Anal. Calcd for $\mathrm{C_{12}H_{17}NO_3}$: C, 64.56; H, 7.67; N, 6.27. Found: C, 64.52; H, 7.69; N, 6.29.

Methylation of *p*-Chlorophenylhydroxamic Acid (1c). A solution of **1c** (0.8 g, 4.7 mmol) in dry tetrahydrofuran (7 mL) was allowed to react with a diethyl ether solution of diazomethane (21.3 mL, 14.1 mmol) to give a crude oil (0.92 g). The recovered material was fractioned by SCFC performed using light petroleum (bp 40−60 °C)/diethyl ether (1:1, v/v) as eluent to afford **2c** (0.65 g, 69%), **5c** (84.4 mg, 9%), and **6c** (0.16 g, 18%), each compound as colorless oil.

2c. IR (film): ν 3063 cm^{-1}, 2942, 1612, 1568, 1320, 1094, 773. ^{1}H NMR: δ 3.92 ppm (s, 3 H, $\mathrm{OCH_3}$), 3.96 (s, 3 H, $\mathrm{OCH_3}$), 7.33 (d, J = 9.1 Hz, 2 H, ArH), 7.58 (d, J = 9.1 Hz, 2 H, ArH). GC/MS: m/z, (%) 201 (21), 200 (24), 199 (64) [M$^+$], 198 (75), 153 (47), 140 (30), 138 (100), 125 (27), 111 (29), 75 (19). Anal. Calcd for $\mathrm{C_9H_{10}ClNO_2}$: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 54.18; H, 5.03; Cl, 17.75; N, 7.02. **5c.** IR (film): ν 3072 cm^{-1}, 2970, 1645, 1440, 1360, 1096, 780. ^{1}H NMR: δ 3.48 ppm (s, 3 H, $\mathrm{NCH_3}$), 3.51 (s, 3 H, $\mathrm{OCH_3}$), 7.38 (d, J = 8.8 Hz, 2 H, ArH), 7.65 (d, J = 8.8 Hz, 2 H, ArH). GC/MS: m/z, (%) = 201 (1), 199 (4) [M$^+$], 141 (42), 139 (100), 113 (35), 111 (37), 75 (16). Anal. Calcd for $\mathrm{C_9H_{10}ClNO_2}$: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 54.15; H, 5.06; Cl, 17.74; N, 7.01. **6c.** IR (film): ν 3325 cm^{-1}, 3072, 2945, 1648, 1332, 1094, 980, 773. ^{1}H NMR: δ 4.00 ppm (s, 3 H, $\mathrm{OCH_3}$), 7.32 (d, J = 10.0 Hz, 2 H, ArH), 7.60 (d, J = 10.0 Hz, 2 H, ArH), 8.27 (s, 1 H, OH). GC/MS: m/z, (%) 189 (5), 187 (17) [M$^+$], 186 (22), 185 (56), 184 (72), 168 (20), 155 (13), 153 (56), 141 (11), 140 (34), 139 (56), 138 (100), 137 (52), 125 (20), 113 (11), 111 (36), 102 (23), 90 (11), 75 (28). Anal. Calcd for $\mathrm{C_8H_8ClNO_2}$: C, 51.77; H, 4.34; Cl, 19.10; N, 7.55. Found: C, 51.76; H, 4.35; Cl, 19.08; N, 7.55.

Methylation of Phenylacetohydroxamic Acid (1d). A solution of **1d** (2 g, 13.2 mmol) in dry tetrahydrofuran (18 mL) was allowed to react with a diethyl ether solution of diazomethane (60 mL, 39.6 mmol) to give a crude oil (2.35 g). The recovered material was fractioned by SCFC performed using light petroleum (bp 40−60 °C)/diethyl ether (1:1, v/v) as eluent to afford **2d** (2.0 g, 85%), **3d** (0.24 g, 10%), and **4d** (67 mg, 3%), each compound as a colorless oil.

2d. IR (film): ν 3030 cm^{-1}, 2946, 1638, 1495, 1310, 1259, 1088, 701. ^{1}H NMR: δ 3.30 ppm (s, 2H, $\mathrm{C}H_2\mathrm{Ph}$), 3.58 (s, 3H, $\mathrm{OCH_3}$), 3.78 (s, 3H, $\mathrm{OCH_3}$), 7.20−7.38 (m, 5H, ArH). GC/MS: m/z, (%) 179 (24) [M$^+$], 148 (13), 132 (100), 105 (16), 91 (68), 77 (18). Anal. Calcd for $\mathrm{C_{10}H_{13}NO_2}$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.98; H, 7.29; N, 7.84. **3d.** IR (film): ν 3020 cm^{-1}, 2950, 1628, 1450, 1315, 1260, 1060, 705. ^{1}H NMR: δ 3.30 ppm (s, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 3.34 (s, 3 H, $\mathrm{OCH_3}$), 3.41 (s, 3 H, $\mathrm{OCH_3}$), 7.22−7.41 (m, 5 H, ArH). GC/MS: m/z, (%) 179 (34) [M$^+$], 148 (12), 132 (100), 105 (16), 91 (70), 77 (18). Anal. Calcd for $\mathrm{C_{10}H_{13}NO_2}$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.05; H, 7.33; N, 7.80. **4d.** IR (film): ν 3356 cm^{-1}, 3029, 2952, 2361, 1663, 1602, 720. ^{1}H NMR: δ 3.20 ppm (s, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 3.62 (s, 3 H, $\mathrm{OCH_3}$), 5.54 (s, 1 H, NH), 7.21−7.43 (m, 5 H, ArH). GC/MS: m/z, (%) 165 (27) [M$^+$], 148 (18), 118 (37), 91 (100), 77 (38). Anal. Calcd for $\mathrm{C_9H_{11}NO_2}$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.43; H, 6.69; N, 8.41.

Methylation of Palmitohydroxamic Acid (1e). A solution of **1e** (0.8 g, 2.95 mmol) in dry tetrahydrofuran (18 mL) was allowed to react with a diethyl ether solution of diazomethane (14 mL, 9.24 mmol) to give a crude oil (0.8 g). The recovered material was fractioned by SCFC performed using chloroform/methanol (1:1, v/v) as eluent to afford **2e** (0.72 g, 81%), **3e** (70 mg, 8%), and **4e** (42 mg, 5%), each compound as a colorless oil.

2e. IR (film): ν 2924 cm^{-1}, 2853, 1640, 1465, 1310, 1064. ^{1}H NMR: δ 0.88 ppm [t, J = 6.5 Hz, 3 H, $\mathrm{CH_2(CH_2)_{13}C}H_3$], 1.05−1.28 [m, 26 H, $\mathrm{CH_2(C}H_2)_{13}\mathrm{CH_3}$], 2.22 [t, J = 6.6 Hz, 2 H, $\mathrm{C}H_2\mathrm{(CH_2)_{13}CH_3}$], 3.75 (s, 3 H, $\mathrm{OCH_3}$), 3.83 (s, 3 H, $\mathrm{OCH_3}$). GC/MS: m/z, (%) 268 (1), 253 (68), 130 (7), 116 (24), 103 (100), 43 (77). Anal. Calcd for $\mathrm{C_{18}H_{37}NO_2}$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.22; H, 12.48; N, 4.67. **3e.** IR (film): ν 2930 cm^{-1}, 2845, 1636, 1450, 1320, 1060. ^{1}H NMR: δ 0.88 ppm [t, J = 6.5 Hz, 3 H, $\mathrm{CH_2(CH_2)_{13}C}H_3$], 1.04−1.27 [m, 26 H, $\mathrm{CH_2(C}H_2)_{13}\mathrm{CH_3}$], 2.32 [t, J = 6.5 Hz, 2 H, $\mathrm{C}H_2\mathrm{(CH_2)_{13}CH_3}$], 3.64 (s, 3 H, $\mathrm{OCH_3}$), 3.71 (s, 3 H, $\mathrm{OCH_3}$). GC/MS: m/z, (%) 268 (1), 253 (81), 130 (7), 116 (24), 103 (100), 43 (64). Anal. Calcd for $\mathrm{C_{18}H_{37}NO_2}$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.21; H, 12.47; N, 4.67. **4e.** IR (film): ν 3310 cm^{-1}, 2920, 2852, 1672, 1467, 984. ^{1}H NMR: δ 0.88 ppm [t, J = 6.0 Hz, 3 H, $\mathrm{CH_2(CH_2)_{13}C}H_3$], 1.10−1.28 [m, 26 H, $\mathrm{CH_2(C}H_2)_{13}\mathrm{CH_3}$], 2.42 [t, J = 6.6 Hz, 2 H, $\mathrm{C}H_2\mathrm{(CH_2)_{13}CH_3}$], 3.65 (s, 3 H, $\mathrm{OCH_3}$), 5.62 (s, 1 H, NH). GC/MS: m/z, (%) 239 (100), 103 (28), 85 (36), 71 (56), 57 (84), 43 (76). Anal. Calcd for $\mathrm{C_{17}H_{35}NO_2}$: C, 71.52; H, 12.36; N, 4.91. Found: C, 71.48; H, 12.37; N, 4.92.

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