JOC Article

5,5-Dimethyl-1,4,2-dioxazoles as Versatile Aprotic Hydroxamic Acid Protecting Groups

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5,5-Dimethyl-1,4,2-dioxazoles are readily installed by transketalization of 2,2-diethoxypropane, where both the NH and OH moieties are protected in a nonprotic form. The dioxazoles are stable to a wide variety of reaction conditions and readily revert back to the hydroxamic acid by treatment with Nafion-H in 2-propanol. The method is applicable to primary, secondary, tertiary, and aromatic hydroxamic acids, and the acidity of the protons adjacent to the dioxazole allows α-functionalization.

Introduction

Matrix metalloproteinases (MMPs) are a family of zinc metalloenzymes that mediate the degradation of connective tissues and have become targets for therapeutic inhibitors in several inflammatory, malignant, and degenerative diseases.[1] Considerable efforts in the pharmaceutical industry have been devoted toward perturbing the endogenous zinc metal that is vital to the enzymatic activity. In this context, the ability of hydroxamic acids to act as bidentate ligands has made this functional group a key component in the design of most MMP inhibitors. The associated metal chelation and acquisition properties of hydroxamic acids have also attracted much attention in a broad range of disciplines.[2]

Due to its labile and diprotic nature, the hydroxamate is typically installed in its protected form at the end of the synthetic sequence.[3] In general, only the alcohol proton is derivatized, and examples include *O*-Bn,[4] *O*-*t*-Bu,[5] *O*-Bz,[6] *O*-TMS,[7] *O*-TBS,[8] *O*-TBDPS,[9] *O*-Tr,[10] and *O*-SEM.[11] In rare occasions, both differentially protected devices can be cleaved in a single operation: *N*,*O*-bis-(BOC),[12] *N*-BOC-*O*-THP, and *N*-BOC-*O*-TBS.[13] In the course of developing a drug candidate, we investigated the possibility of using a dioxazole as an aprotic hydroxamic acid protective group. In this context, the masked hydroxamic acid could be introduced earlier in the synthesis and could perhaps be released in a single operation at the end of the sequence.

Dioxazolines are generally produced from the 1,3-cycloaddition reaction of nitrile *N*-oxides[14] with aldehydes and ketones via the corresponding oximes,[15] imidoyl chlorides,[16] nitro-[17] and furoxanes.[18] They can also be

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(2) For some recent literature on different uses of hydroxamic acid derivatives, see: (a) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563. (b) Miller, M. J.; Malouin, F. *Acc. Chem. Res.* **1993**, *26*, 241. (c) Roosenberg, J. M., II.; Lin, Y.-M.; Lu, Y.; Miller, M. J. *Curr. Med. Chem.* **2000**, *7*, 159. (d) Bodwin, J. J.; Cutland, A. D.; Malkani, R. G.; Pecoraro, V. L. *Coord. Chem. Rev.* **2001**, *216*−*217*, 489. (e) Kikugawa, Y. *Rev. Heteroatom. Chem.* **1996**, *15* 263. (f) Luterotti, S. *Rev. Anal. Chem.* **1992**, *11*, 195. (g) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452. (h) Weizman, H.; Libman, J.; Shanzer, A. *J. Am. Chem. Soc.* **1998**, *120*, 2188.

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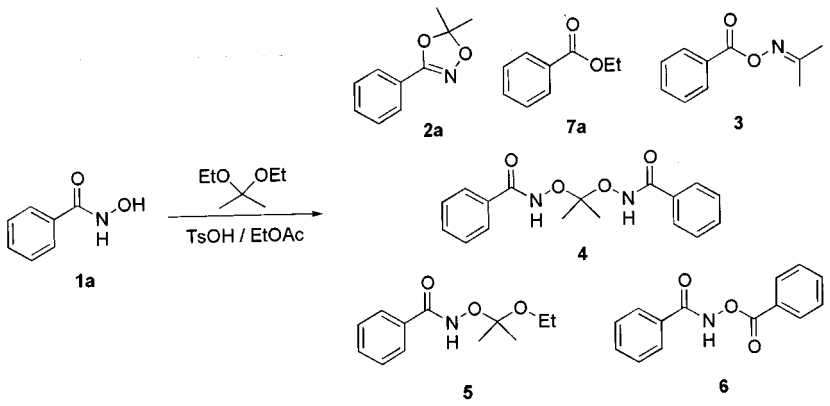
SCHEME 1



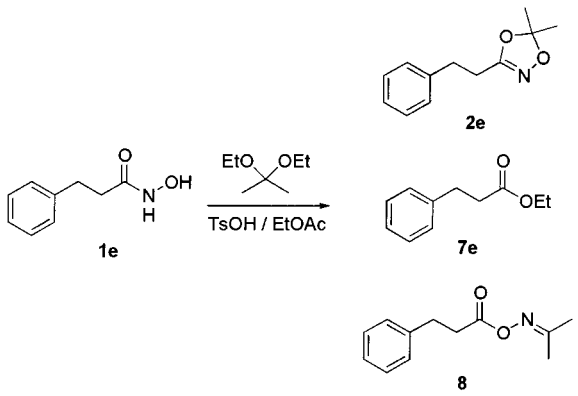
prepared by photolysis of acyl azides in the presence of ketones,[19] addition of hydroxamic acids onto acetylenic esters[20] and furans,[21] and observed in the rearrangement of *N*-acyloxaziridines.[22] In the study of the thermal decomposition of dioxazoles to isocyanates and ketones, Mukaiyama has reported the preparation of aryl derivatives through trans-acetalization.[23] In this paper, the examples were limited to aryl derivatives with variable yields (%) ranging from mid 20's to low 70's. Cyclization of *N*-acylated *O*-(2-methoxypropyl)hydroxylamine, a likely intermediate in the previous reaction, has also been shown to produce dioxazolines.[24] With the exception of a few isolated examples,[25] a general deprotection procedure of dioxazolines back to hydroxamic acids is not precedented in the literature. Hence, we wish to demonstrate herein the generality of the protection by broadening the scope to include aliphatic systems, assess whether the dioxazoles can be cleaved without alcoholysis to the corresponding ester, and evaluate the dioxazoline stability under various reaction conditions. We also wish to further broaden the scope of dioxazolines through α-deprotonation and functionalization of the resulting carbanion.

Results and Discussion

Initial attempts to convert benzohydroxamic acid (**1a**) to the dioxazole **2a** under a wide variety of reaction conditions, including the original Mukaiyama procedure, generates a wide variety of byproducts identified as the known *O*-benzoylacetoneoxime (**3**),[26] bis(hydroxamic acid)-isopropylidene ketal (**4**),[27] *N*-acylated *O*-(2-methoxypropyl)hydroxyl-amine (**5**), *N*,*O*-dibenzoylhydroxylamine (**6**),[28] and the corresponding ethyl ester **7a** (Scheme 1).

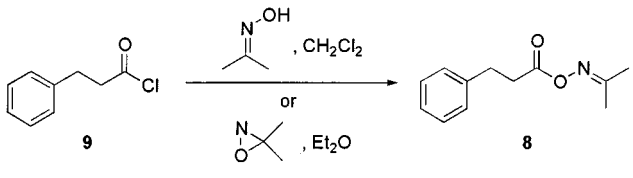
Application of the Mukaiyama procedure to the aliphatic hydroxamic acid **1e** was even more problematic since it provided only 4% of dioxazoline **2e** along with the ethyl ester **7e** and the rearranged acylated acetoneoxime **8** in 43% yield each (Scheme 2).

SCHEME 2



The structure of the latter was confirmed through independent synthesis by coupling the acid chloride **9** with acetoneoxime in 59% yield (Scheme 3). The ethyl ester is most likely formed via the oxime ester since these have been utilized as coupling agents.[29,30]

SCHEME 3



The postulated mechanism for generation of this impurity is similar to the one proposed by Geffken

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(20) (a) Heindel, N. D.; Fives, W. P.; Carrano, R. A. *J. Pharm. Sci.* **1977**, *66*, 772. (b) Chen, F. M. F.; Forrest, T. P. *Can. J. Chem.* **1973**, *51*, 1368.

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(26) Nishiyama, K.; Miyata, I. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2419.

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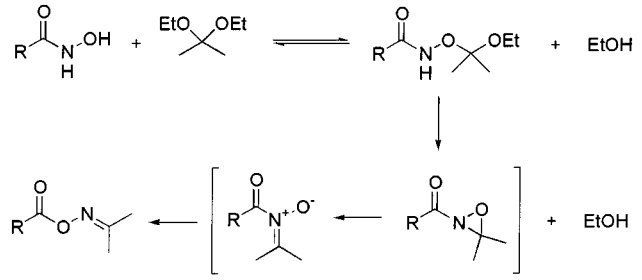
(28) Freeman, J. P. *J. Am. Chem. Soc.* **1960**, *82*, 3869.

(29) Fernandez, S.; Menendez, E.; Gotor, V. *Synthesis* **1991**, 713.

(30) Upon prolonged reaction times, increased ester **7e** formation was observed at the expense of the oxime **8**.

(Scheme 4).[31] To corroborate this mode of formation, the acid chloride was allowed to react with dimethyloxaziridine generated in situ, and this reaction also led to the formation of *O*-acyl acetoneoxime **8** in 11% yield.

SCHEME 4



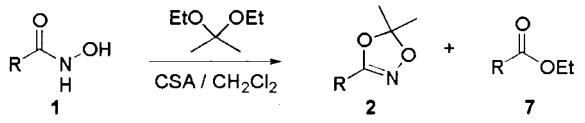
By carefully considering the source of the various impurities generated in the process, we reasoned that employing higher dilution would minimize the formation of dimers. Also, since initial screens revealed that a full equivalent of acid was required to ensure reasonable rate, it is preferable to utilize an anhydrous acid source. This is especially important due to the fact that hydrolysis of ketal produces ethanol, which eventually leads to increased ethyl ester formation. With these considerations, we sought to develop a general, high-yielding procedure applicable for both aromatic and aliphatic systems.

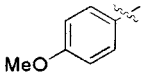
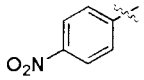
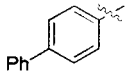
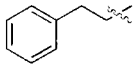
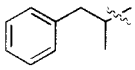
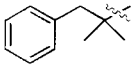
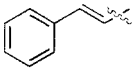
Finding the right conditions to convert the primary hydroxamic acid **1e** to the corresponding dioxazoline **2e** would not prove to be an easy task. After screening a wide variety of various acid/solvent combinations, we found that the use of camphorsulfonic acid (CSA) in methylene chloride offered the best reaction profile. Gratifyingly, this procedure led to the desired protected hydroxamic acid **2e** in 73% yield admixed with only 11% of the rearranged *O*-acyl acetoneoxime **8** (Table 1).[32] It is noteworthy that application of this procedure to all other hydroxamic acids tested herein led to no observed rearranged product. Furthermore, the amount of the major ester byproduct was in the range of 3−6%. This procedure was consistently high yielding for the aromatic series as well as for the olefinic system.

Deprotection was best performed in refluxing 2-propanol, which minimized transesterification. Unfortunately, the camphorsulfonic acid utilized in this process could not be separated by extractive workup, or by chromatography, and yields were rather low due to high water solubility. This matter was easily resolved by employing Nafion-H resin. The yields using this procedure were consistently high, with trans-esterification occurring in the range of 0−4% (Table 2).

To test the chemical compatibility of the dioxazoline protective group with various reagents, the primary and aromatic systems were subjected to a wide variety of reaction conditions (Table 3) at room temperature for a period of 24 h. In most cases, the dioxazolines were found

TABLE 1. Protection of Selected Hydroxamic Acids

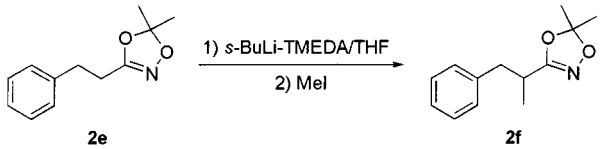


1(a-h)	R =	2:7 ratio	isolated yield of 2
a		25:1	89%
b		30:1	92%
c		22:1	83%
d		15:1	92%
e		8.0:1	74%
f		16:1	78%
g		26:1	91%
h		26:1	75%

to be resistant to those reaction conditions tested, except in the cases of sodium hydroxide in methanol, which led to the opened methyl ketal, and basic bleach, which affected the deprotection of dioxazole **2e** back to the hydroxamic acid. However, these may be regarded as only moderately reactive. Not unexpectedly, hydrogenation conditions led the corresponding amides.

We further explored the versatility of dioxazolines through α-functionalization. Gratifyingly, deprotonation of **2e** could be achieved using *sec*-butyllithium−TMEDA in THF, and the resulting anion was reacted with methyl iodide to produce the dioxazoline **2f** in an unoptimized yield of 68% (Scheme 5).

SCHEME 5

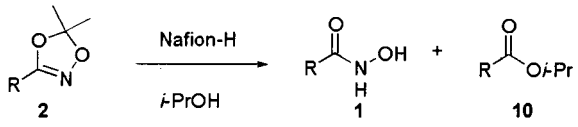


In summary, we have developed a general, high-yielding procedure to protect hydroxamic acids as 5,5-dimethyl-1,4,2-dioxazoles where both NH and OH are derivatized in a nonprotic form. We further demonstrated that they are stable to a wide variety of reaction conditions and readily revert back to the hydroxamic acid by Nafion-H in 2-propanol. The method is applicable to primary, secondary, tertiary, and aromatic hydroxamic acids, and the dioxazole provides a handle that allows

(31) Geffken, D.; Froböse, J. *J. Prakt. Chem.* **1993**, *335*, 555.

(32) The reaction was performed on a 50 mmol scale. It was noted that this reaction is scale-dependent as a smaller scale experiment on 5 mmol led to a lower yield of 53%. However, the yield on the latter scale could be further increased to 74% by utilizing the diisopropyl ketal.

TABLE 2. Deprotection of Selected Hydroxamic Acids



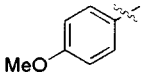
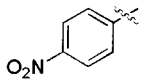
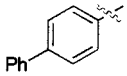
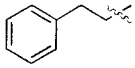
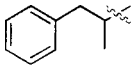
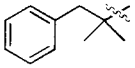
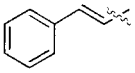
2(a-h)	R =	1:10 ratio	isolated yield of 1
a		50:1	98%
b		24:1	88%
c		<50:1	99%
d		<50:1	97%
e		10:1	85%
f		<50:1	99%
g		<50:1	90%
h		50:1	94%

TABLE 3. Chemical Stability of Dioxazoles 2a and 2e under Various Reaction Conditions

dioxazole	reaction conditions[a]	byproduct	dioxazole/ byproduct[b]
2a	$NaOH/H_2O$	none	
2e		none	
2a	NaOH/MeOH	ketal	4.3:1
2e		hydroxamic acid	2.4:1
2a	NaOMe/THF	none	
2e		none	
2a	*t*-BuOK/THF	none	
2e		none	
2a	EtMgBr/THF	none	
2e		none	
2a	$NaBH_4$/THF	none	
2e		none	
2a	BH_3·THF	none	
2e		none	
2a	$KMnO_4/MeCN/H_2O$	none	
2e		none	
2a	NaOCl/1 M aq NaOH	none	
2e		hydroxamic acid	8.6:1
2a	MeI/THF	none	
2e		none	
2a	H_2/Pd−C	amide	<1:50
2e		amide	<1:50

[a] Unless otherwise noted, all the experiments were performed using equimolar amounts of reagents and dioxazoline at a concentration of 0.1 M for 24 h. [b] Determined by ^{1}H NMR.

α-functionalization. Due to the wide use of hydroxamates in the design of MMPs, this concept should be of utility for preparing these inhibitors, in addition to other hydroxamic acids of interest.

Experimental Section

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc. (Woodside, NY). Melting points were obtained from a capillary apparatus and are uncorrected. Reactions were monitored by TLC using ethyl acetate in hexanes as eluant, followed by visualization with *p*-anisaldehyde stain (prepared from anisaldehyde (9.2 mL), acetic acid (3.75 mL), ethanol (338 mL, 95%), and sulfuric acid (12.5 mL)). Column chromatography purifications were carried out on silica gel 40 μm flash chromatography packing (60 Å pore diameter). Hydroxamic acids **1a**−**f**,**h** were prepared according to known literature procedures.[33]

2,2-Dimethyl-3-phenylpropionohydroxamic Acid (1g). To a solution of 2,2-dimethyl-3-phenylpropionic acid[34] (1.00 g, 5.61 mmol) and *N*,*N*-dimethylformamide (500 μL) in dichloromethane (10 mL) was added oxalyl chloride (540 μL, 6.17 mmol) dropwise over 10 min. After additional stirring for 15 min, hydroxylamine hydrochloride (430 mg, 6.17 mmol) was added, and the mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and quenched in saturated aqueous sodium bicarbonate. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residual material was purified by recrystallization using dichloromethane/hexanes to provide the title compound (510 mg, 47%) as a white solid: mp 127−130 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.25−7.12 (m, 5H), 2.81 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 175.53, 138.03, 130.02, 127.85, 126.26, 46.23, 42.13, 23.96. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.51; H, 8.04, N, 7.23.

Preparation of *O*-Hydrocinnamoyl Acetone Oxime (8) from Acetone Oxime. To an ice-cold solution of acetone oxime (1.30 g, 17.79 mmol) and triethylamine (3.30 mL, 23.7 mmol) in dichloromethane (20.0 mL) was added hydrocinnamoyl chloride (880 μL, 5.93 mmol). The resulting mixture was heated to reflux for 5 h. The reaction was cooled to 0 °C and quenched with water, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residual material using ethyl acetate/hexane (1:4) provided the *O*-acylacetone oxime **8** (850 mg, 59%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H), 3.02 (t, J = 7.5 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 2.03 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.2, 140.5, 128.8, 128.5, 126.6, 34.9, 31.2, 22.2, 17.1. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.32; H, 7.27, N, 6.62.

Preparation of *O*-Hydrocinnamoyl Acetone Oxime (8) from 3,3-Dimethyloxaziridine. To an ice-cold solution of acetone (1.47 mL, 20.0 mmol) in diethyl ether (10 mL) was added an aqueous solution of sodium hydroxide (2 M, 20 mL). The resulting mixture was treated with an aqueous solution of sodium hydroxide (2 M, 10 mL) and hydroxylamine-*O*-sulfonic acid (2.30 g, 20.0 mmol) in water (20 mL) was added to the above mixture, immediately followed by hydrocinnamoyl chloride (3.37 g, 20.0 mmol). The temperature of the reaction mixture was maintained below 10 °C by addition of crushed ice. After 10 min, the mixture was washed with an aqueous solution of hydroxylamine-*O*-sulfonic acid (1 g) in water (5 mL) to remove unreacted acetone followed by another solution of hydroxylamine-*O*-sulfonic acid (0.8 g) in aqueous sodium carbonate (2 M, 8 mL) to remove residual acid chloride. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residual material using ethyl acetate/hexane (1:9) provided the *O*-acylacetone oxime **8** (451 mg, 11%) as colorless oil.

(33) (a) Liguori, A.; Sindona, G.; Romeo, G.; Uccella, N. *Synthesis* **1987**, 168. (b) Ngu, K.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 7088. (c) Campbell, J. J.; Glover, S. A.; Hammond, G. P.; Rowbottom, C. A. *J. Chem Soc., Perkin Trrans. 2* **1991**, 2067. (d) Potapov, V. M.; Dem'yanovich, V. M.; Khlebnikov, V. A. *J. Org. Chem. USSR* **1982**, 1041.

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General Protection Procedure. To a solution of hydroxamic acid (5.0 mmol) and 2,2-diethoxypropane (15.0 mmol) in dichloromethane (100 mL) was added camphorsulfonic acid (5.0 mmol), and the resulting mixture was stirred at room temperature. Upon reaction completion, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous layer was repeatedly extracted with diethyl ether, and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated under vaccuo. The residual material was purified by chromatography to yield the 5,5-dimethyl-1,4,2-dioxazole.

5,5-Dimethyl-3-phenyl-1,4,2-dioxazole (2a).[23] Reaction time: 3 h. Column chromatography (2% ether in pentane) yielded **2a** (789 mg, 89%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.5 Hz, 2H), 7.49−7.41 (m, 3H), 1.68 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 131.5, 128.9, 126.9, 123.9, 115.8, 25.1. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.55; H, 6.27, N, 7.68.

5,5-Dimethyl-3-(*p*-methoxyphenyl)-1,4,2-dioxazole (2b). Reaction time: 3 h. Column chromatography (5% ether in pentane) yielded **2b** (952 mg, 92%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.4, 128.6, 116.2, 115.3, 114.3, 55.6, 25.0. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.69; H, 6.22, N, 6.73.

5,5-Dimethyl-3-(*p*-nitrophenyl)-1,4,2-dioxazole (2c).[23] Reaction time: 25 h. Column chromatography (10% ether in pentane) yielded **2c** (920 mg, 83%) as a white crystalline solid: mp 146−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 130.9, 129.8, 127.7, 124.1, 117.4, 25.2. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.44; H, 4.72, N, 12.27.

5,5-Dimethyl-3-(*p*-biphenyl)-1,4,2-dioxazole (2d). Reaction time: 4 h. Column chromatography (2% ether in pentane) yielded **2d** (1.15 g, 92%) as a white crystalline solid: mp 103−104 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.47−7.35 (m, 3H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 144.4, 139.9, 128.9, 128.0, 127.17, 126.9, 126.8, 122.3, 115.9, 23.7. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.83; H, 6.05, N, 5.27.

5,5-Dimethyl-3-(3-phenylpropyl)-1,4,2-dioxazole (2e). The reaction was performed on 50 mmol scale over 30 min. Column chromatography (2% ether in pentane) yielded **2e** (7.49 g, 73%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.20 (m, 5H), 2.93 (t, J = 8.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.54 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 139.9, 128.8, 128.6, 126.8, 114.9, 31.7, 25.9, 25.0. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.57; H, 7.44, N, 6.77.

5,5-Dimethyl-3-(1-methyl-3-phenylpropyl)-1,4,2-dioxazole (2f). Reaction time: 2 h. Column chromatography (2% ether in pentane) yielded **2f** (854 mg, 78%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H), 3.00 (dd, J = 6.5, 13.0 Hz, 1H) 2.84 (m, 1H), 2.69 (dd, J = 8.0, 13.0 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 138.9, 129.3, 128.7, 126.7, 114.7, 39.7, 32.0, 24.9, 16.9. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.20; H, 7.83, N, 6.33.

5,5-Dimethyl-3-(1,1-dimethyl-3-phenylpropyl)-1,4,2-dioxazole (2g). Reaction time: 3 h. Column chromatography (5% ether in pentane) yielded **2g** (1.07 g, 91%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.14 (m, 5H), 2.83 (s, 2H), 1.58 (s, 6H), 1.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 137.2, 130.6, 128.2, 126.9, 114.9, 45.7, 35.7, 25.2, 24.9. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.72; H, 7.92, N, 6.00.

5,5-Dimethyl-3-(cynnamyl)-1,4,2-dioxazole (2h). Reaction time: 1 h. Column chromatography (2% ether in pentane) yielded **2h** (765 mg, 75%) as a white crystalline solid: mp 81−83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 2H), 7.40−7.34 (m, 3H), 7.17 (d, J = 16.5 Hz, 1H), 6.60 (d, J = 16.5 Hz, 1H), 1.65 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.739, 138.0, 135.2, 129.8, 129.1, 127.5, 115.7, 109.7, 25.1. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.95; H, 6.62, N, 6.67.

General Deprotection Procedure. To a solution of 5,5-dimethyl-1,4,2-dioxazole (2.0 mmol) in isopropyl alcohol (11.0 mL) was added Nafion-H (400 mg), and the mixture was heated to relux. Upon reaction completion, the Nafion-H beads were removed and rinsed with 2-propanol (5.0 mL) followed by methanol (5.0 mL). The combined organic solutions were concentrated under vaccum, and the residual material was purified by chromatography (1% methanol in dichloromethane, then 10% methanol in dichloromethane) to yield the hydroxamic acid.

Benzoydroxamic Acid (1a). Reaction time: 30 h. Isolated (274 mg, 98%) as a white crystalline solid: mp 128−130 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, J = 7.0 Hz, 2H), 7.49 (t, J = 7.0 Hz, 1H), 7.41 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.22, 132.20, 131.78, 128.60, 127.04. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.27; H, 5.29, N, 10.05.

***p*-Methoxybenzohydroxamic Acid (1b).** Reaction time: 6 h. Isolated (290 mg, 88%) as a white crystalline solid: mp 153−155 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (d, J = 7.5 Hz, 2H), 6.95 (d, J = 7.5 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.95, 162.78, 128.72, 124.28, 113.68, 54.73. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.34; H, 5.58, N, 8.34.

***p*-Nitrobenzohydroxamic Acid (1c).** Reaction time: 20 h. Isolated (364 mg, 99%) as an off-white crystalline solid; ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.66, 149.89, 138.17, 128.34, 123.55.

***p*-Phenylbenzohydroxamic Acid (1d).** Reaction time: 48 h. Isolated (413 mg, 97%) as a white crystalline solid: mp 103−104 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.47−7.35 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.76, 144.60, 140.03, 128.87, 128.84, 127.93, 127.51, 126.94, 126.92. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.36; H, 4.85, N, 6.38.

3-Phenylpropionohydroxamic Acid (1e). Reaction time: 20 h. Isolated (280 mg, 85%) as a white crystalline solid: mp 79−80 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.26−7.14 (m, 5H), 2.89 (t, J = 8.0 Hz, 2H), 2.36 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.79, 140.72, 128.33, 128.22, 126.10, 34.55, 31.45. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.48; H, 6.82, N, 8.39.

2-Methyl-3-phenylpropionohydroxamic acId (1f). Reaction time: 20 h. Isolated (358 mg, 99%) as a white crystalline solid: mp 128−130 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.26−7.14 (m, 5H), 2.90 (dd, J = 8.5, 13.5 Hz, 1H), 2.62 (dd, J = 7.5, 13.5 Hz, 1H), 2.46 (m, 1H), 1.13 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.17, 139.69, 128.82, 128.18, 126.12, 40.00, 39.66, 16.86. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.65; H, 7.10, N, 7.88.

2,2-Dimethyl-3-phenylpropionohydroxamic Acid (1g). Reaction time: 48 h. Isolated (478 mg, 90%) as a white crystalline solid: mp 127−130 °C.

Cinnamohydroxamic Acid (1h). Reaction time: 13 h. Isolated (305 mg, 94%) as a white crystalline solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.58−7.52 (m, 3H), 7.39−7.32 (m, 3H), 6.46 (d, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.18, 140.52, 134.98, 129.72, 128.79, 127.60, 117.18.

Preparation of 2f from 2e. To a solution of dioxazole **2e** (410 mg, 2.0 mmol) and TMEDA (0.60 mL, 4.0 mmol) in anhydrous THF (40 mL) cooled at −100 °C, was added a solution of *sec*-butyllithium (1.3 M in cyclohexane, 3.1 mL, 4 mmol) dropwise over 5 min. Immediately following this addition, methyl iodide (0.62 mL, 10 mmol) was quickly added, and

the reaction mixture was allowed to warm to room temperature. After 40 min, the reaction mixture was poured into a saturated aqueous ammonium chloride solution (10 mL) and extracted several times with ethyl acetate. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the residual material using ethyl ether/pentane (1:19) provided the alkylated dioxazole **2f** (292 mg, 68%) as a colorless oil.

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