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Design, synthesis and utilization of a novel coupling reagent for the preparation of *O*-alkyl hydroxamic acids

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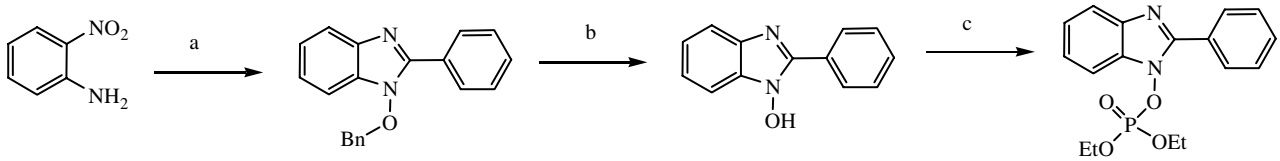
Abstract—An efficient novel reagent, phosphoric acid diethyl ester 2-phenyl-benzimidazol-1-yl ester, was designed, and synthesized and its applicability was demonstrated for the preparation of *O*-alkyl hydroxamic acids. The *O*-alkyl hydroxamic acids of N-protected amino acids were also synthesized. The enantiomeric purity of the synthesized compounds were measured using chiral HPLC and the degree of racemization was found to be negligible.

1. Introduction

Hydroxamic acids are important components of many chemotherapeutic agents such as the succinate-based matrix metalloproteinase (MMP) inhibitors,[1] class I/II histone deacetylase (HDAC) inhibitors[2] and iron-containing antibiotics.[3] Also, hydroxamic acid analogues are important targets for the medicinal chemist because of the intrinsic chelating properties of this functional group with Zn^{++} at the active site of metalloproteins.[4,5] Recently, various methods have been reported for the preparation of hydroxamic acids starting from carboxylic acids or their derivatives[6] and *N*-acyloxazolidinones.[7] The solution-phase hydroxyamination of esters is generally achieved via a two-step sequence; firstly, preparation of a salt of hydroxylamine followed by addition of the ester in alcohol as solvent[8] or activation of the acid by reaction with an acyl chloride or mixed anhydride and quenching with O-protected hydroxylamine analogues.[9] Although some of these methods are quite efficient for the preparation of substituted hydroxamic acids, there are drawbacks such as instability, toxicity, high volatility of some acylating agents, high cost and difficult purification which limit their applications. Thus, the development of a convenient method is important for the efficient preparation of hydroxamic acids from carboxylic acids. We have therefore designed and synthesized a novel reagent and demonstrated its applicability for the efficient preparation of hydroxamic acids.



1 **2** **3** **4**

Scheme 1. Synthesis of reagent **4**. Reagents and conditions: (a) NaH, BnBr, THF, 80 °C, 4 h; (b) 10% Pd/C, H_2, methanol, 15 min; (c) $(EtO)_2P(O)Cl$, Et_3N, dichloromethane, 30 min, 0 °C.

Keywords: Hydroxamic acid; *N*-Hydroxy-2-phenylbenzimidazole; *O*-Benzyl hydroxylamine; Amino acids.
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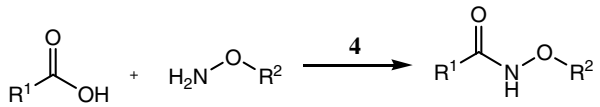
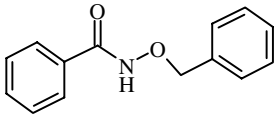
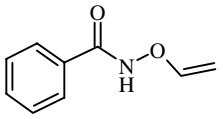
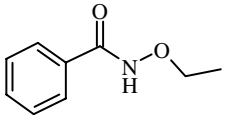
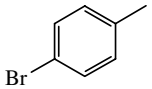
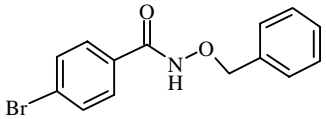
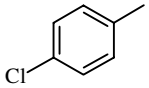
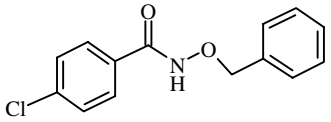
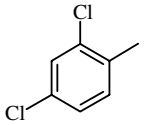
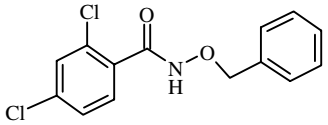
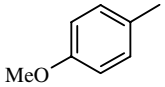
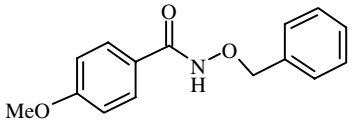
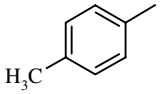
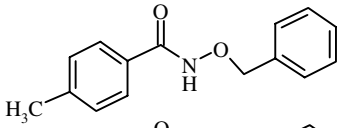
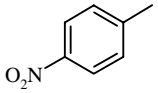
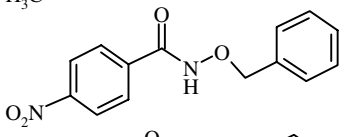
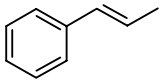
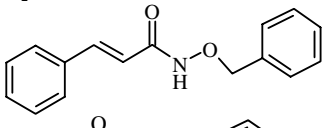
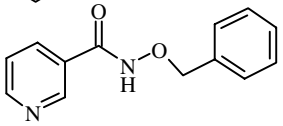
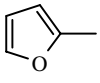
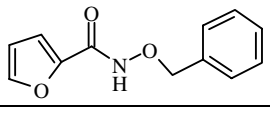
N-Hydroxy-2-phenylbenzimidazole **3** was synthesized according to the reported procedure[10] which involves the reaction of *o*-nitroaniline with benzyl bromide using sodium hydride as base, followed by benzyl deprotection using 10% Pd/C to give the desired product as a white crystalline solid. The coupling reagent **4** was synthesized by treating **3** with diethyl chlorophosphate and triethylamine in dichloromethane. The reagent was isolated as a

Table 1. Synthesis of different *O*-alkyl hydroxamic acids using reagent **4**



Entry	R^1	R^2	Product	Reaction time (min)	Yield (%)	Mp °C	
						Found	Reported
1		Bn		45	96	101–102	102–104[11]
2		Allyl		40	94	50–51	50[13]
3		Et		45	91	82–83	81–82[14]
4		Bn		35	93	134–135	136[11]
5		Bn		40	97	157–158	158[13]
6		Bn		35	96	140–141	142[13]
7		Bn		45	95	108–109	110–111[11]
8		Bn		50	91	125–126	128[13]
9		Bn		25	99	166–167	166–167[11]
10		Bn		50	93	98–99	99–100[11]
11		Bn		40	89	71–72	72–73[11]
12		Bn		35	92	98–99	99–101[11]

white crystalline solid and used for coupling several carboxylic acids with various *O*-alkyl hydroxylamines (Scheme 1).

Initially we studied the synthesis of *N*-hydroxybenzamide from benzoic acid and hydroxylamine hydrochloride, but all variations of solvent, temperature, base and equivalents were unsuccessful. *N*-Benzyloxybenzamide was isolated in 96% yield using 3.5 equiv of DIPEA in DMF. To improve the yield and minimize the problems in large-scale synthesis, a method was developed in which reagent **4** could be synthesized from **3** and used in situ for the synthesis of *O*-alkyl hydroxamic acids. An easy work-up is an advantage of this method, requiring only acid–base treatment and trituration with a suitable solvent to give sufficiently pure product. Also during the work-up, *N*-hydroxy-2-phenylbenzimidazole could be easily isolated by acid–base treatment and could be reused for the synthesis of reagent **4**.

Using similar reaction conditions, 12 different *O*-alkyl hydroxamic acids were synthesized and the results obtained are summarized in Table 1. All the synthesized hydroxamic acids were characterized by mass, IR and ^{1}H NMR measurements. Acids with electron-withdrawing substituents (e.g., nitro, entry 9) required a comparatively shorter reaction time than acids with electron-donating groups (e.g., methyl, entry 8) or those without substituents (entries 2 and 3). Compound **4** shows superiority over existing reagents regarding both yields and purification. In particular, 4-nitro-*N*-benzyloxybenzamide (entry 9) was isolated in higher yield (99%) than previously reported (37%).[11]

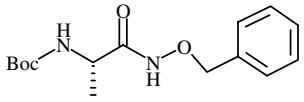
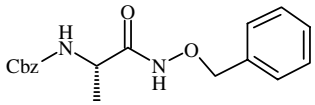
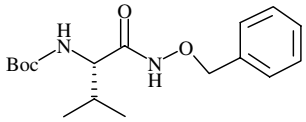
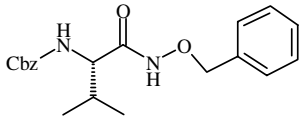
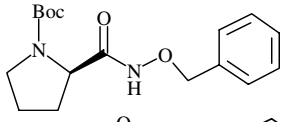
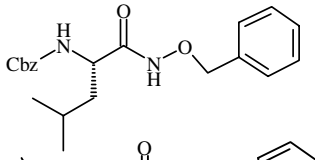
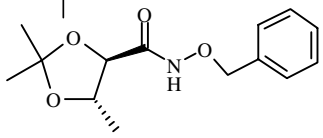
O-Benzylhydroxylamine was also coupled with N-protected amino acids (Table 2). For these reactions, moderate to good yields were obtained in the range 68–92%. The extent of racemization was measured using chiral HPLC. The enantiomeric excess obtained was in the range 94.1–98.3%, which proves the efficiency of coupling reagent **4** for optically active substrates.

The optical rotations of some of the synthesized compounds were measured and compared with the corresponding reported values. In the case of (1-benzyloxycarbamoyl-ethyl)carbamic acid *tert*-butyl ester (entry 1), the reported specific rotation was $[\alpha]_D$ −58.3 (*c* 0.1, $CHCl_3$)[12] whilst that for our product was $[\alpha]_D$ −58.1 (*c* 0.1, $CHCl_3$). For 2,2,5-trimethyl-[1,3]-dioxolane-4-carboxylic acid benzyloxy amide (entry 7), the reported specific rotation was $[\alpha]_D$ 25.6 (*c* 1.1, MeOH)[13] and we obtained $[\alpha]_D$ 25.9 (*c* 1.1, MeOH).

Intermediate **5** formed from the reaction of benzoic acid and *O*-benzylhydroxylamine was isolated and characterized by mass spectrometry and ^{1}H NMR spectroscopy. We suggest that firstly benzoic acid reacts with **4** to give the active ester **5** and this then reacts with *O*-benzylhydroxylamine (Scheme 2).

In conclusion, reagent **4** was easily synthesized from cheap starting materials and used in situ for the preparation of *O*-alkyl hydroxamic acids from carboxylic acids.

Table 2. Synthesis of different *O*-benzyl hydroxamic acids from N-protected amino acids using reagent **4**

Entry	Product	Yield[a] (%)	ee[b] (%)
1		89	98.3
2		92	96.8
3		68	94.1
4		74	95.2
5		91	95.8
6		87	96.7
7		76	94.6

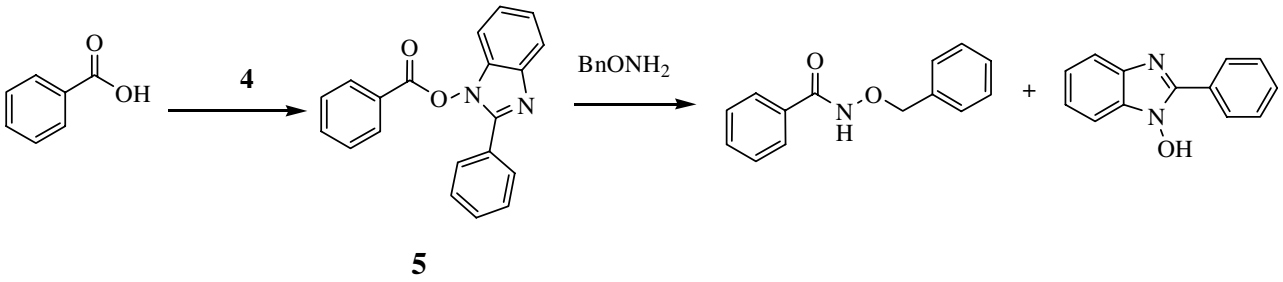
[a] Isolated yield.
[b] Enantiomeric excess determined by chiral HPLC.

The advantages of this coupling reagent are its scalability, and high yields of products. Also, for the preparation of *O*-benzyl-protected hydroxamic acids from amino acids, the observed racemization was minimal.

2. Preparation of phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester 4

A solution of *N*-hydroxy-2-phenylbenzimidazole (0.42 g, 0.02 mol) and triethylamine (0.7 ml, 0.05 mol) was stirred in DCM (2.5 ml) and diethyl chlorophosphate (0.21 ml, 0.024 mol) was added at 0 °C. The reaction mixture was stirred until completion of the reaction (TLC). Then, the DCM was evaporated and the residue was stirred with pentane and decanted. The remaining residue was stirred with diethyl ether and decanted three times. The combined extracts were concentrated to give the title compound **4** as a white solid.

Yield—462 mg, (67%); mp 112–116 °C (dec); IR (Nujol, cm^{-1}) 2985, 1298, 1036, 981; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.2 (t, $J = 6.2$ Hz, 6H), 4.1 (q, $J = 7.4$ Hz, 4H), 7.3 (m, 3H), 7.5 (d, $J = 8.1$ Hz, 2H), 7.8 (d, $J = 8.3$ Hz, 2H), 8.2 (d, $J = 8.3$ Hz, 2H); EIMS $m/z = 347$ $(M+H)^+$; Anal. Calcd for $C_{17}H_{19}N_2O_4P$: C, 58.96; H, 5.53; N, 8.06. Found: C, 59.23; H, 5.61; N, 8.11.



5

Scheme 2. Isolation of intermediate **5**.

3. General procedure for synthesis *O*-alkyl hydroxamic acids

A solution of *N*-hydroxy-2-phenylbenzimidazole (0.02 mol) and DIPEA (0.07 mol) was stirred in DMF and diethyl chlorophosphate (0.024 mol) was added with cooling. The reaction mixture was stirred for 10 min and carboxylic acid (0.016 mol) was added and the mixture was stirred for a further 10 min at 0 °C for active ester formation. Then, *O*-alkyl hydroxylamine (0.03 mol) was added and the mixture stirred at room temperature until completion of the reaction (TLC). Saturated aq NaCl (20 ml) solution was then added and the mixture was extracted with ethyl acetate (15 ml × 2). The organic layer was washed with 2 N HCl (15 ml), saturated $NaHCO_3$ (15 ml) and finally with water (2 × 20 ml). The organic layer was dried over sodium sulfate, filtered and evaporated to give the corresponding *O*-alkyl hydroxamic acid.

4. *N*-Benzyloxy-4-nitrobenzamide

Mp 166–167 °C (dec); IR (Nujol, cm^{-1}) 3196, 2932, 1671, 1524; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.03 (s, 2H), 7.36–7.48 (m, 5H), 7.9 (d, $J = 8.4$ Hz, 2H), 8.2 (d, $J = 8.4$ Hz, 2H); EIMS *m*/*z*—273 $(M+H)^+$; Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.92; H, 4.57; N, 10.13.

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References and notes

1. For a review see: (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735–2776; (b) Caldarrelli, M.; Habermann, J.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2049–2054.
2. (a) Finnin, M. S.; Doniggain, J. R.; Cohen, A.; Richon, V. M.; Rifkind, P. A. Marks; Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188–193; (b) Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097–5116; (c) Kim, D. K.; Lee, J. Y.; Kim, J. S.; Ryu, J. H.; Choi, J. Y.; Lee, J. W.; Kim, T. K.; Seo, J. W.; Park, H. J.; Yoo, J.; Park, J. H.; Kim, T. U.; Bang, Y. *J. Med. Chem.* **2003**, *46*, 5745–5754; (d) Lu, Q.; Yang, Y.-T.; Chen, C.-S.; Davis, M.; Byrd, J. C.; Etherton, M. R. *J. Med. Chem.* **2004**, *47*, 467–474.
3. (a) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563–1662; (b) Bergeron, R. J.; Wiegand, J.; McManis, J. S.; Perumal, P. T. *J. Med. Chem.* **1991**, *34*, 3182–3188.
4. Jung, M. *Curr. Med. Chem.* **2001**, *8*, 15065–15071.
5. Brown, P. D.; Davidson, A. H.; Gearing, A.; Whittakar, M. Hydroxamic acid matrix metalloproteinase inhibitors. In *Matrix Metalloproteinase Inhibitors in Cancer Chemotherapy*; Clendeninn, N. J., Appelt, K., Eds.; Humana Press: Totowa, NJ, 2001, pp 113–142.
6. (a) Koshiti, N.; Reddy, G. V.; Jacobs, H.; Gopalan, A. *Synth. Commun.* **2002**, *32*, 3779–3790; (b) Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. *Tetrahedron Lett.* **2001**, *42*, 5013–5016; (c) Fray, M. J.; Burslm, M. F.; Dickenson, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 567–570; (d) Dankwardt, S. M.; Billedeau, R. J.; Lawley, L. K.; Abbot, S. C.; Martin, R. L.; Chan, C. S.; Van Wart, H. E.; Walker, K. A. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2513–2516; (e) Nikam, S. S.; Kronberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett.* **1995**, *36*, 197–200; (f) Altenburger, J. M.; Mioskowski, C.; d'Orchymont, H.; Schirlin, D.; Schalk, C.; Tarnus, C. *Tetrahedron Lett.* **1992**, *33*, 5055–5058; (g) Barlaam, B.; Harmon, A.; Maudet, M. *Tetrahedron Lett.* **1998**, *39*, 7865–7868; (h) Ando, W.; Tsumaki, H. *Synth. Commun.* **1983**, *13*, 1053–1056; (i) King, F. D.; Pike, S.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1978**, 351–356.
7. Sibi, M. P.; Hasegawa, H.; Ghorphade, S. R. *Org. Lett.* **2002**, *4*, 3343–3346.
8. Hauser, C. R.; Renfrow, W. B. In *Organic Synthesis*; Wiley: New York, 1943; Collect Vol. II, pp 67–68.
9. (a) Burns, C. J.; Groneberg, R. D.; Salvino, J. M.; McGeehan, G.; Condon, S. M.; Morris, R.; Morrissette, M.; Mathew, R.; Darnbrough, S.; Neuenschwander, K.; Scotese, A.; Djuric, S.; Ullrich, J.; Labaudiniere, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2848–2850; (b) Mori, K.; Koseki, K. *Tetrahedron* **1988**, *44*, 6013–6020.
10. Gardiner, J. M.; Procter, J. *Tetrahedron Lett.* **2001**, *42*, 5109–5111.
11. Arnaud, G.; Alessandro, V.; Matteo, Z. *J. Org. Chem.* **2005**, *70*, 6925–6928.
12. Ramasamy, K.; Olsen, R. K.; Emery, T. *J. Org. Chem.* **1981**, *46*, 5438–5441.
13. Jeum-Jong, J.; Young-Dae, P.; Ho-Kyun, K.; Su-dong, C.; Ju-Kyeon, K. *Synth. Commun.* **2005**, *35*, 731–738.
14. Alan, R. K.; Nataliya, K.; Boris, V. R. *Synthesis* **2003**, 2777–2780.