Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Hydroxamic Acids by Activation of Carboxylic Acids with N,N′-Carbonyldiimidazole: Exploring the Efficiency of the Method

Natalija Usachova [a], Gundars Leitis [a], Aigars Jirgensons [a] & Ivars Kalvinsh [a]

[a] Latvian Institute of Organic Synthesis, Riga, Latvia

Version of record first published: 22 Feb 2010

To cite this article: Natalija Usachova, Gundars Leitis, Aigars Jirgensons & Ivars Kalvinsh (2010): Synthesis of Hydroxamic Acids by Activation of Carboxylic Acids with N,N′-Carbonyldiimidazole: Exploring the Efficiency of the Method, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:6, 927-935

To link to this article: http://dx.doi.org/10.1080/00397910903026723

Synthetic Communications®, 40: 927–935, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903026723

Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF HYDROXAMIC ACIDS BY ACTIVATION OF CARBOXYLIC ACIDS WITH *N,N′*-CARBONYLDIIMIDAZOLE: EXPLORING THE EFFICIENCY OF THE METHOD

Natalija Usachova, Gundars Leitis, Aigars Jirgensons, and Ivars Kalvinsh

Latvian Institute of Organic Synthesis, Riga, Latvia

Activation of carboxylic acids with* N,N′*-carbonyldiimidazole followed by the reaction with anhydrous or aqueous hydroxylamine hydrochloride was demonstrated to be an operationally simple method for the synthesis of hydroxamic acids in good yield and high purity after aqueous workup. The potential by-product,* N,O*-diacylhydroxylamine, is cleanly transformed to hydroxamic acid in these reaction conditions.

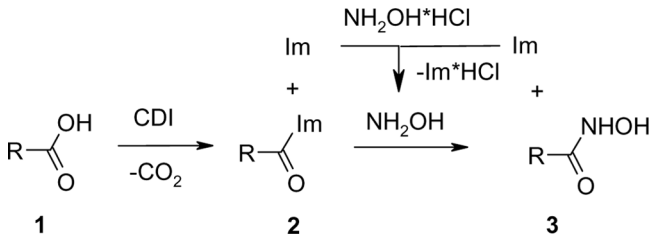
Keywords: Activation; *N,N*-carbonyldiimidazole; carboxylic acid; hydroxamic acid; hydroxylamine

Hydroxamic acid provides central functionality in a number of metalloproteinase inhibitors because of its ability to strongly coordinate with metal ions and as such has high relevance for the development of new pharmaceuticals.[1] Common methods of hydroxamic acid synthesis are the reaction of ester with hydroxylamine[2] or the activation of carboxylic acid followed by the reaction with *O*-protected, *N,O*-protected, or unprotected hydroxylamine.[3,4] Coupling of carboxylic acids with protected hydroxylamines is very often used despite the facts that these are relatively expensive reagents and an additional deprotection step is necessary to complete the synthesis. The reason for this is that there are drawbacks associated with competitive *N,O*-diacylation of unprotected hydroxylamine and difficulties in obtaining the product in pure form.

As a part of drug discovery program, we required a method for parallel synthesis of hydroxamic acids from carboxylic acids that provided the products in high purity without chromatographic purification or crystallization. We turned our attention to the activation of carboxylic acids with *N,N′*-carbonyldiimidazole (CDI), a well-known approach for the synthesis of carboxylic acid derivatives. It is attractive because of the simple separation of products from water-soluble by-products.[5] A literature search reveled surprisingly scant information regarding the use of unprotected hydroxylamine as a reaction partner for CDI-activated

Received April 7, 2009.

Address correspondence to Aigars Jirgensons, Latvian Institute of Organic Synthesis, Riga, LV-1006, Latvia. E-mail: aigars@osi.lv

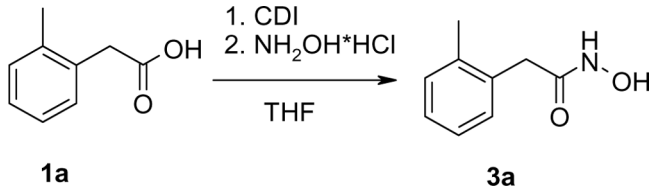


Scheme 1. Activation of carboxylic acid and the reaction with formed hydroxylamine in situ.

carboxylic acid. In early work, Staab et al. demonstrated the preparation of two simple hydroxamic acids from CDI-activated carboxylic acids and hydroxylamine hydrochloride.[6] No additional base was necessary because imidazole liberated during the reaction promoted deprotonation of hydroxylamine hydrochloride (Scheme 1). We were able to locate just a few other examples of this approach in the literature[7] and decided that additional investigation would be necessary to explore the efficiency of this method.[8]

Carboxylic acid **1a** was used as a test substrate to find the best reactant ratio for hydroxamic acid **3a** synthesis (Scheme 2, Table 1). The high-performance liquid chromatography (HPLC) purity and yield were determined after extractive workup. The best results can be achieved using slight excess of CDI over carboxylic acid and in turn slight excess of hydroxylamine hydrochloride over CDI (Table 1, entry 4). Care should be taken for the quality of CDI, which tends to decompose while storing. Typically, a reagent with >90% of CDI content (^{1}H NMR) was used for the experiments. When solid $NH_2OH \cdot HCl$ was added to the solution of activated carboxylic acid, a heterogeneous reaction mixture has formed. It was established that $NH_2OH \cdot HCl$ can be added as an aqueous solution, leading to a homogeneous reaction mixture, without significantly impairing yield and purity of the product **3a** (Table 2). This could be very useful for parallel synthesis, where the stock solutions of the reagents are preferred.

Structurally different carboxylic acids **1b–i** were transformed to the corresponding carboxylic acids **3b–i** at optimized conditions (Figure 1). Hydroxamic acids **3b–e** were obtained from carboxylic acids **1b–e** in excellent yield and high purity (Table 3). Hydroxamic acids ***R*-** and ***S*-3c** were obtained from corresponding *N*-Boc-protected phenylalanines ***R*-** and ***S*-1c** in high enantiomeric purity. Unsaturated acids **1f** and **1g** gave hydroxamic acids **3f** and **3g** in somewhat reduced yield but nevertheless high purity. Dihydroxamic acid **3h** was obtained in poor yield because



Scheme 2. Synthesis of hydroxamic acid **3a** from carboxylic acid using the CDI activation method.

Table 1. Optimization of the reactant ratio with the test substrate **1a** by adding solid $NH_2OH \cdot HCl$ to activated carboxylic acid

Entry	CDI (eq)	Solid $NH_2OH \cdot HCl$ (eq)	Yield (%)	HPLC purity (%)
1	1	1.5	100	90
2	1.5	1	87	35
3	1.5	1.5	82	98
4	1.5	2	96	98

Table 2. Yield and purity of hydroxamic acid **3a** by adding aqueous $NH_2OH \cdot HCl$ to activated carboxylic acid

		Aq. $NH_2OH \cdot HCl$			
Entry	CDI (eq)	Eq	M	Yield (%)	HPLC purity (%)
1	1.5	4	4	86	99
2	1.5	2	2	94	98
3	1.5	4	2	87	99
4	1.5	2	4	85	99

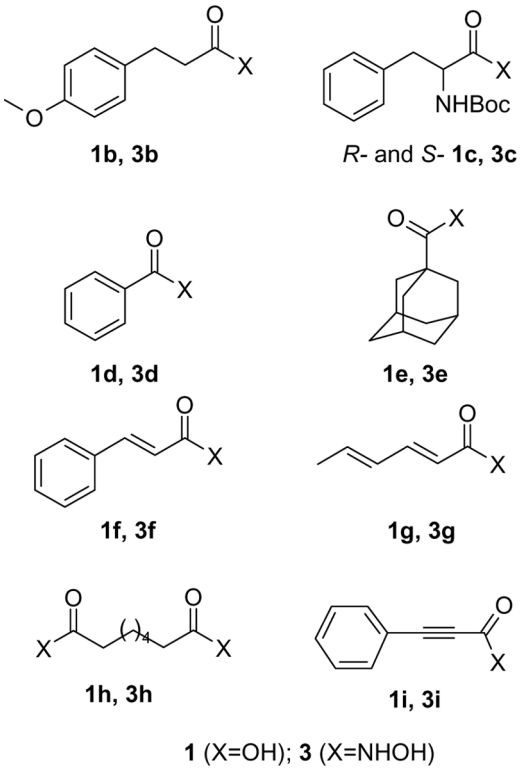


Figure 1. Carboxylic acids **1b–i** and the corresponding hydroxamic acids **3b–i**.

Table 3. Transformation of carboxylic acids **1b–i** to hydroxamic acids **3b–i**

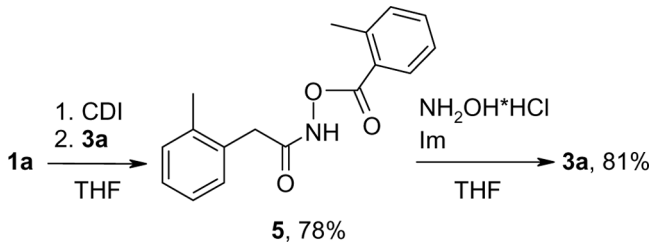
Entry	Hydroxamic acid	Method[a]	Yield (%)	Purity (%)
1	**3b**	A	93	99 (HPLC)
2	**3b**	B	88	97 (HPLC)
4	***R*-3c**	A	99	93 (HPLC), ee 93
5	***S*-3c**	A	99	>90 (^{1}H NMR), ee 93
6	**3d**	A	75	95 (HPLC)
7	**3e**	A	84	>85 (^{1}H NMR, EA)
8	**3f**	A	66	95 (LC/MS)
9	**3f**	B	70	93 (LC/MS)
10	**3g**	A	52	90 (LC/MS)
11	**3g**	B	60	84 (LC/MS)
12	**3h**	A	23[b]	>90 (^{1}H NMR)
13	**3i**	A	24	82 (LC/MS)
14	**3i**	B	13	27 (LC/MS)

[a]Method A: addition of solid $NH_2OH \cdot HCl$; method B: addition of aqueous 2 M $NH_2OH \cdot HCl$ (2 eq) after activation of carboxylic acid.
[b]Crystallized from water.

of its high water solubility, making extractive workup unproductive. Very poor yield of hydroxamic acid **3i** was obtained from propiolic acid (**1i**), likely due to the incompatibility of the conjugated triple bond with reaction conditions.

Because we were aware of potential *N,O*-diacylhydroxylamine formation in given reaction conditions, an experiment was done where carboxylic acid **1a** was activated with CDI and then subjected to the reaction with hydroxamic acid **3a** (Scheme 3). According to ^{1}H NMR spectra of the crude product, this led to almost quantitative formation of *N,O*-diacylhydroxylamine **5**, which was obtained in good isolated yield. However, the product of diacylation **5** cleanly converted to hydroxamic acid **3a** in the reaction with hydroxylamine hydrochloride and imidazole as a base. This indicated that *N,O*-diacylhydroxylamine likely forms as an intermediate or a by-product; however, it acylates hydroxylamine to give the required hydroxamic acid **3**.

In summary, we have demonstrated that activation of carboxylic acids with CDI followed by the reaction with anhydrous or aqueous hydroxylamine hydrochloride is an operationally simple method to obtain structurally different hydroxamic acids in high purity and is a method of choice for parallel synthesis. It was



Scheme 3. Synthesis of *N,O*-diacylhydroxylamine **5** and its reaction with hydroxylamine.

shown that potential by-product *N,O*-diacylhydroxylamine is cleanly transformed to hydroxamic acid in these reaction conditions.

EXPERIMENTAL

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. All reactions were performed under an argon atmosphere. Thin-layer chromatography (TLC) was performed on silica gel and was visualized by staining with $KMnO_4$. NMR spectra were recorded on a Varian Mercury spectrometer (200 MHz) with chemical shifts values (δ) in parts per million (ppm) relative to tetramethylsilane (TMS) using residual chloroform signal as internal standard. HPLC analysis was performed on SymmetryShield RP18, 5 μm, 4.6 × 150 mm, on Apollo C18 (5 M), 4.6 × 150-mm column, mobile phase MeCN–0.1% aq. H_3PO_4, gradient 15 min, 5/95–95/5%, flow rate 1 ml/min, column temperature 40 °C, detection UV-210 at 254 nm. Chiral HPLC was performed on Chiralpack IA, 4.6 × 250-mm mobile phase 100% isopropylalcohol (IPA), isocratic, flow rate 0.2 ml/min. LC/MS analysis was performed using Micromass Quatro Micro™ AP Phenomenex, Gemini 5u C18 11OA, 50 × 2 mm, 5 μm, mobile phase MeCN (0.1% aq. HCOOH)–H_2O (0.1% HCOOH). Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

General Procedures for the Synthesis of Hydroxamic Acids 1

Procedure A. CDI (4.5 mmol, 1.5 eq) was added to a solution of carboxylic acid **1** (3.0 mmol) in dry tetrahydrofuran (THF) (5 ml). The reaction mixture was stirred for 1 h. Powdered hydroxylamine hydrochloride (417 mg, 6 mmol) was added. The resulting mixture was stirred overnight (ca. 16 h). The mixture was diluted with 5% aq. $KHSO_4$ (30 ml) and extracted with EtOAc (2 × 30 ml). The combined organic phase was washed with brine (30 ml) and dried over Na_2SO_4. The extract was filtered and concentrated in vacuo to give the product **3**.

Procedure B. This was analogous to procedure A, but 2M aqueous hydroxylamine hydrochloride (3 mL, 6 mmol) was used instead of solid hydroxylamine hydrochloride.

N-Hydroxy-2-*o*-tolylacetamide (3a)

According to method A: 476 mg (96%). Colorless crystals, mp 157 °C. HPLC purity (UV 210 nm). According to method B: 466 mg (99%). Colorless crystals, mp 151 °C. HPLC purity 99% (UV 210 nm). MS: 166 (M + 1).^{1}H NMR (DMSO-d_6) δ: 2.25 (3H, s, CH_3), 3.28 (2H, s, partially overlapped with H_2O, CH_2), 7.0–7.2 (4H, m, Ar), 8.78 (1H, s, NH) and 10.59 ppm (1H, s, OH).

N-Hydroxy-3-(4-methoxyphenyl)propanamide (3b)[9]

According to method A: 545 mg (93%). Colorless crystals, mp 114 °C (lit. 113–115 °C). HPLC purity 99% (UV 210 nm). According to method B: 515 mg

(88%). Colorless crystals, mp 110 °C. HPLC purity 98% (UV 210 nm). MS: 196 (M + 1). ^{1}H NMR (DMSO-d_6) δ: 2.18 (2H, t, $J = 7.8$ and 15.6 Hz, 3-CH_2), 2.71 (2H, t, $J = 7.8$ and 15.6 Hz, 2-CH_2), 3.69 (3H, s, CH_3), 6.80 (2H, d, $J = 8.8$ Hz, 3′,5′-CH), 7.08 (2H, d, $J = 8.8$ Hz, 2′,6′-CH), 8.67 (1H, s, NH) and 10.32 ppm (1H, s, OH).

(*S*)-*N*-Hydroxy-2-*t*-butoxycarbonylamino-3-phenylpropanamide (*S*-3c)[4d]

According to method A: Colorless crystals 902 mg (~100%), mp > 132 °C (dec.), HPLC purity 93% (UV 210 nm), chiral HPLC ee 92%, $[\alpha]_D^{20} = +8.7^o$ (*c* 1, EtOH, 25 °C) (lit. $[\alpha]_D^{20} = +25.2^o$ (*c* 1, EtOH), MS: 281 (M + 1). ^{1}H NMR (DMSO-d_6) δ: 1.1–1.4 (9H, m, CH_3), 2.6–2.9 (2H, m, CH_2), 4.00 (1H, dd, $J = 8.8$ and 13.7 Hz, CH), 6.97 (1H, d, $J = 8.8$ Hz, carbamate NH), 7.1–7.4 (5H, m, Ar), 8.83 (1H, s, hydroxamic acid NH) and 10.60 ppm (1H, s, OH). *Note:* A notable difference in optical rotation value compared to that reported in the literature was observed.

(*R*)-*N*-Hydroxy-2-*t*-butoxycarbonylamino-3-phenylpropanamide (*R*-3c)

According to method A: 911 mg (~100%). Colorless crystals, mp > 138 °C (dec), HPLC purity 98% (UV 210 nm), chiral HPLC ee 92%, $[\alpha]_D^{20} = -9.7^o$ (*c* 1, EtOH, 25 °C) MS: 281 (M + 1). ^{1}H NMR identical to the compound ***S*-3c**.

N-Hydroxybenzamide (3d)[10]

According to method A: 307 mg (75%). Pale yellow crystals, mp 113 °C (>140 °C dec) (lit. 126–127 °C), HPLC 89% (UV 210 nm), MS: 138.1 (M + 1). ^{1}H NMR (DMSO-d_6) δ: 7.3–7.6 (3H, m, 3′,5′-CH and 4′-CH), 7.72 (1.5H, d, $J = 7.8$ Hz, 2′,6′-CH, tautomer), 7.92 (0.5H, d, $J = 7.81$ Hz, 2′,6′-CH tautomer), 9.02 (1H, s, NH) and 11.18 ppm (1H, s, OH).

N-Hydroxyadamantane-1-carboxamide (3e)[11]

According to method A: 581 mg (99%). Pale yellow crystals, mp 141 °C (>145 °C dec.) (lit. > 149 °C dec). ^{1}H NMR (DMSO-d_6) δ: 1.62 (6H, s, 4,6,10-CH_2), 1.73 (6H, s, 2,8,9-CH_2), 1.92 (3H, s, 3,5,7-CH), 8.48 (1H, s, NH), and 10.21 (1H, s, OH). Anal. calcd. for $C_{11}H_{17}NO_2$–$C_{11}H_{16}O_2$, (6:1): C, 68.4%; H, 8.8%; N, 6.2%. Found: C, 68.3%, H, 9.0%; N, 6.2%.

(*E*)-*N*-Hydroxy-3-phenylacrylamide (3f)[12]

According to method A: 321 mg (66%) pale pink crystals, mp 109 °C (>115 °C dec) (lit. 114–115 °C), LC/MS purity 96% (UV 210 nm). According to method B: pale pink crystals, 340 mg (70%), mp 107 °C (>115 °C dec), LC-MS purity 93% (UV 210 nm), MS: 164 (M + 1). ^{1}H NMR (DMSO-d_6) δ: 6.44 (1 H, d, $J = 16.1$ Hz,

2-CH), 7.3–7.6 (5H, m, Ar), 7.44 (1H, d, $J = 16.1$ Hz, 3-CH), 9.04 (1H, s, NH) and 10.75 ppm (1H, s, OH).

N-Hydroxy-2*E*,4*E*-hexa-2,4-dienoic Acid Amide (3g)[4c]

According to method **A:** 208 mg (54%). Pale yellow crystals, mp 118 °C (dec), LC/MS purity 85% (UV 210 nm). According to method B: 227 mg (60%) Pale yellow crystals, mp 120 °C (>130 °C dec), LC/MS purity 85% (UV 210 nm), MS: 128 (M + 1). ^{1}H NMR (DMSO-d_6) δ: 1.77 (3H, d, $J = 5.1$ Hz, CH_3), 5.72 (1H, d, $J = 15.4$ Hz, 2-CH), 5.9–6.4 (2H, m, 4-CH un 5-CH), 7.00 (1H, dd, $J = 9.5$ un 15.4 Hz, 3-CH), 8.87 (1H, s, NH) and 10.57 ppm (1H, s, OH).

N,N′-Dihidroxyoctanedioic Acid Diamide (3h)[12]

According to method A. When the reaction mixture was diluted with water a precipitate formed that could not be taken in organic phase. The precipitate was collected on a filter and dried *in vacuo* to give 143 mg (23%) as a colourless crystals with m.p. > 160 °C (dec.). ^{1}H NMR (DMSO-D_6) δ: 1.19 (4H, broad s, 4,5-CH_2); 1.44 (4H, m, 3,6-CH_2), 1.90 (4H, t, $J = 6.8$ Hz, 2,7-CH_2), 8.64 (2H, s, both NH) and 10.31 ppm (2H, s, both OH).

N-Hydroxy-3-phenylpropynoic Acid Amide (3i)[10]

According to method A: 114 mg (24%), Brown oil. LC/MS purity 82% (UV 210 nm). According to method B: 65 mg (13%). Brown oil. LC/MS purity 27% (UV 210 nm). MS: =162 (M + 1) ^{1}H NMR (DMSO-D_6) δ: 7.1–7.9 (5H, m, Ar); 9.33 (1H, s, NH) and 10.72 ppm (1H, s, OH).

2-*o*-Tolyl-*N*-(2-*o*-tolylacetoxy)acetamide (5)

CDI (730 mg, 4.5 mmol, 1.5 eq) was added to a solution of *o*-tolyl acetic acid (**1a**) (450 mg, 3 mmol) in dry THF (6 ml), and the mixture was stirred at room temperature for 3 h. *N*-Hydroxy-2-*o*-tolylacetamide (**3a**) was added to the mixture, and it was stirred at room temperature for ca. 12 h. The mixture was diluted with 5% aq. $KHSO_4$ (30 ml) and extracted with EtOAc (2 × 30 ml). The combined organic phase was washed with brine (2 × 30 ml), dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from MeCN to give *N,O*-diacylated hydroxylamine (695 mg, (78%) as colorless crystals with mp 154 °C and HPLC purity 99% (UV 210 nm). MS: 298 (M + 1). Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.7%; H, 6.4%; N, 4.7%. Found: C, 72.1%; H, 6.4%; N, 4.9%. ^{1}H NMR (DMSO-d_6) δ: 2.24 (6H, s, both CH_3), 3.47 [2H, s, $CH_2C(=O)$], 3.83 [1H, s, $CH_2C(=O)$], 7.1–7.3 (8H, m, Ar) and 11.91 ppm (1H, s).

N-Hydroxy-2-*o*-tolylacetamide (3a) from *N,O*-Diacylhydroxylamine 5

Powdered $NH_2OH \times HCl$ (76 mg, 1.1 mmol) and imidazole (75 mg, 1.1 mmol) were added to the suspension of *N,O*-diacylhydroxylamine **5** (297 mg, 1 mmol) in

THF (3 ml). The mixture was stirred at room temperature for 12 h and diluted with aqueous 5% $KHSO_4$ (30 ml). The product was taken in EtOAc (2×30 ml), and the combined organic phase washed with brine (30 ml) and dried over Na_2SO_4. Filtration and evaporation gave compound **3a** (268 mg, 81%). ^{1}H NMR spectra were identical to those of the compound prepared from carboxylic acid **1a**.

ACKNOWLEDGMENT

Partial financial support from the European Regional Development Fund (VPD1/ERAF/CFLA/05/APK/2.5.1/000029/014) is gratefully acknowledged.

REFERENCES

1. For a review, see (a) Marmion, C. J.; Griffith, D.; Nolan, K. B. Hydroxamic acids–An intriguing family of bioligands and enzyme inhibitors. *Eur. J. Inorg. Chem.* **2004**, 3003–3016; (b) Rao, B. G. Recent developments in the design of specific matrix metalloproteinase inhibitors aided by structural and computational studies. *Curr. Pharm. Design* **2005**, *11*, 295–322. For selected exmples, see (c) Tao, L.; Kapustin, G.; Etzkorn, F. A. Design and synthesis of a potent histone deacetylase inhibitor. *J. Med. Chem.* **2007**, *50*, 2003–2006; (d) Zhu, Z.; Mazzola, R.; Sinning, L.; McKittrick, B.; Niu, X.; Lundell, D.; Sun, J.; Orth, P.; Guo, Z.; Madison, V.; Ingram, R.; Beyer, B. M. Discovery of novel hydroxamates as highly potent tumor necrosis factor-α converting enzyme inhibitors, part I—discovery of two binding modes. *J. Med. Chem.* **2008**, *51*, 725–736.
2. From esters: (a) Devlin, J. P.; Ollis, W. D.; Thorpe, J. E. Studies concerning the antibiotic actinon, part V: Synthesis of structural analogues of actinonin by the anhydride-ester method. *J. Chem. Soc., Perkin Trans. 1* **1975**, 846–848; (b) Ho, C. Y.; Strobel, E.; Ralbovsky, J.; Galemmo, R. A. Improved solution- and solid-phase preparation of hydroxamic acids from esters. *J. Org. Chem.* **2005**, *70*, 4873–4875.
3. Using protected hydroxylamines: (a) Barlaam, B.; Hamon, A.; Maudet, M. New hydroxylamines for the synthesis of hydroxamic acids. *Tetrahedron Lett.* **1998**, *39*, 7865–7868; (b) Yang, S.-M.; Lagu, B.; Wilson, L. J. Mild and efficient Lewis acid–promoted detritylation in the synthesis of *N*-hydroxy amides: A concise synthesis of (−)-kobactin. *J. Org. Chem.* **2007**, *72*, 8123–8126; (c) Bailen, M. A.; Chinchilla, R.; Dodsworth, D. J.; Najera, C. Direct synthesis of hydroxamates from carboxylic acids using 2-mercaptopyridone-1-oxide-based thiouronium salts. *Tetrahedron Lett.* **2001**, *42*, 5013–5016.
4. Using unprotected hydroxylamine: (a) Koch, G.; Kottirsch, G.; Wietfeld, B.; Kusters, E. Process development of a dual MMP/TNF inhibitor (SDZ 242-484). *Org. Process Res. Dev.* **2002**, *6*, 652–659; (b) Sekar Reddy, A.; Suresh Kumar, M., Ravindra Reddy, G. A convenient method for the preparation of hydroxamic acids. *Tetrahedron Lett.* **2001**, *41*, 6285–6288; (c) Ech-Chahad, A.; Minassi, A.; Berton, L.; Appendino, G. An expeditious hydroxyamidation of carboxylic acids. *Tetrahedron Lett.* **2005**, *46*, 5113–5115; (d) Giacomelli, G.; Porcheddu, A.; Salaris, M. Simple one-flask method for the preparation of hydroxamic acids. *Org. Lett.* **2003**, *5*, 2715–2717, and references cited therein.
5. Armstrong, A. *N,N′*-Carbonyldiimidazole. In *Encyclopedia of Reagents for Organic Synthesis*; L. A. Paquette (Ed.); John Wiley & Sons Ltd.: West Sussex, UK, 1995; vol. 2, pp. 1006–1010.
6. Staab, H. A.; Luking, M.; Durr, F. H. Darstellung von Imidazolen: Synthese von Amiden, Hydraziden und Hydroxamsäuren nach der Imudazolidmethode. *Chem. Ber.* **1962**, *95*, 1275–1283.

7. (a) Welch, J. T.; Lin, J. Fluoroolefin containing dipeptide isosteres as inhibitors of dipeptidyl peptidase IV(CD26). *Tetrahedron* **1996**, *52*, 291–304; (b) Desos, P.; Lepagnol, J. M.; Morain, P.; Lestage, P.; Cordi, A. A. Structure–activity relationships in a series of 2(1*H*)-quinolones bearing different acidic function in the 3-position: 6,7-Dichloro-2(1*H*)-oxoquinoline-3-phosphonic acid, a new potent and selective AMPA/kainate antagonist with neuroprotective properties. *J. Med. Chem.* **1996**, *39*, 197–206.
8. Some of the results summarized in this article have been presented as a student poster by one of the authors: Usachova, N. Operationally simple synthesis of hydroxamic acids from carboxylic acids. Presented at the Paul Walden Fifth Symposium on Organic Chemistry, Riga, September 17–18, 2007. Abstract in *Latvian. J. Chem.* **2007**, *4*, 397.
9. Corrie, J. E. T.; Kirby, G. W.; Sharma, R. P. Formation of isocyanates by deoxygenation of *C*-nitrosocarbonyl compounds. *J. Chem. Soc., Perkin Trans. 1* **1982**, *7*, 1571–1574.
10. Porcheddu, A.; Giacomelli, G. Angeli-Rimini's reaction on solid support: A new approach to hydroxamic acids. *J. Org. Chem.* **2006**, *71*, 7057–7059.
11. Stepanov, F. N.; Stolyarov, Z. E. Synthesis and antiherpetic activity of N-(3-amino-1-adamantyl)calix[4]arenes. *Zh. Org. Khim.* **1970**, *6*, 1186.
12. Brown, D. A.; Geraty, R. A.; Glennon, J. D.; Choileain, N. N. A facile synthesis of aliphatic dihydroxamic acids of general formula RONR′-CO-$(CH_2)_n$-CO-NR′OR. *Synth. Commun.* **1985**, *15*(13), 1159–1164.