Synthesis of Hydroxamic Acids by Using the Acid Labile *O*-2-Methylprenyl Protecting Group

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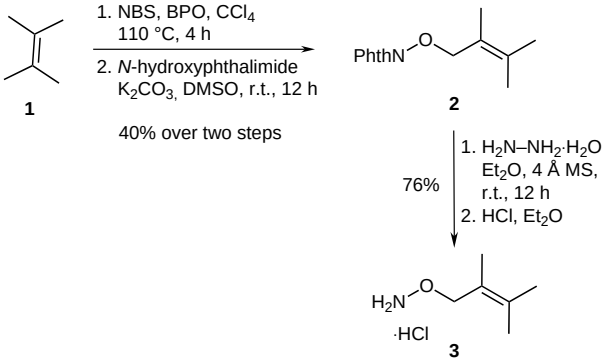
Abstract: Coupling of carboxylic acids with *O*-2-methylprenyl hydroxylamine provided O-protected hydroxamic acids, which could be deprotected by treatment with trifluoroacetic acid (TFA) in dichloromethane giving volatile by-products. Protected hydroxamic acids could be N-arylated or alkylated followed by deprotection to give N-substituted hydroxamic acids.

Key words: protecting groups, cleavage, carboxylic acids, hydroxamic acids, hydroxylamine

Hydroxamic acids have received particular attention as metalloproteinase inhibitors due to their ability to coordinate with metal ions in the active site of an enzyme.[1] One of the commonly used methods to install the hydroxamic acid functionality involves coupling of a carboxylic acid with an O-protected hydroxylamine followed by deprotection of the resulting intermediate. Such an approach avoids diacylation and, in addition, the less polar protected intermediates can be purified prior to deprotection. Nevertheless, currently used protecting groups for hydroxamic acids are often unsuitable due to chemoselectivity problems and formation of by-products in the deprotection step that are difficult to remove. For example, benzyl protection can be used if no other functional group sensitive to hydrogenolysis is present in the molecule[2] and this method may lead to competitive N–O bond cleavage.[3] By-product removal after deprotection requires chromatography or crystallization of the product if DMB,[4] PMB,[5] Tr[6] or TBS[2b,7] protecting groups are used. THP is a very convenient protection group that gives a water-soluble by-product during acidic deprotection.[8] However, work-up typically involves aqueous extraction, which is not suitable for water-soluble products. Recently, a similar *O*-(1-isobutoxyethyl) protection has been introduced that gives volatile by-products under acidic cleavage conditions.[9] A minor disadvantage of *O*-THP and *O*-(1-isobutoxyethyl) protection is that these groups posses a stereogenic center, which can complicate the NMR spectra.

Our research efforts have focused on developing an alternative O-protecting group for hydroxamic acids that could be cleaved to generate volatile by-products. Initially the prenyl group was investigated as a potential acid-labile O-protection for hydroxamic acids. However, this group appeared to be stable under relatively mild acid conditions compatible with the hydroxamic acid functionality. Next, we turned our attention to the 2-methylprenyl group, which could be more labile under acidic conditions due to the additional carbenium ion stabilizing effect of the 2-methyl group.[10]

O-Methylprenyl hydroxylamine was prepared according to Scheme 1. Radical bromination of 2,3-dimethyl-2-butene (**1**) gave the allylic bromide,[11] which, without purification, was transformed into *N*-hydroxyphthalimide derivative **2**. Intermediate **2** was treated with hydrazine hydrate to give the volatile hydroxylamine, which was isolated by precipitation as the hydrochloride salt **3**.



Scheme 1 Synthesis of *O*-2-methylprenyl hydroxylamine hydrochloride (**3**)

Carboxylic acids **4a**–**j** (Figure 1) were coupled with hydroxylamine derivative **3** using EDCI (method A) or HATU (method B) to give O-2-methylprenyl-protected hydroxamic acids **5a**–**j** in good yields (Table 1). Screening of cleavage conditions at several TFA concentrations in CH_2Cl_2 revealed that 10 vol% TFA (method C) gave clean conversion of the protected intermediate **5a** into hydroxamic acid **6a** in a reasonable reaction time (Table 1, entry 1). These conditions were applied to other protected hydroxamic acids **5b**–**j** to give pure products **6b**–**h**, without additional purification, according to HPLC and NMR analysis (Table 1, entries 2–8). The only exceptions were protected hydroxamic acids **5i** and **5j**, which gave products **6i** and **6j**, respectively, with lower purity (Table 1, entries 9 and 11). In these cases, addition of TESH (method D) as a cation scavenger improved the purity of the products (Table 1, entries 10 and 12).[12]

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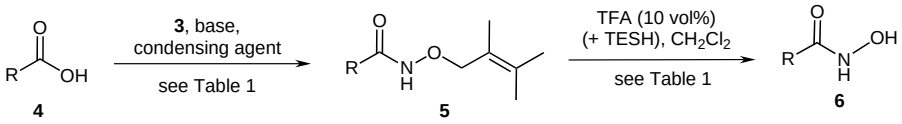
Table 1 Synthesis of Hydroxamic Acids **6a–j** from Coupling of Carboxylic Acids **4a–j** with Hydroxylamine Derivative **3** and Deprotection



Entry	Substrate	Protection method[a]	Yield of **5** (%)	Deprotection method[b]	Time (h)	Purity of **6** (%)[c]
1	**4a**	A	99	C	1.5	99
2	**4b**	A	95	C	3	97
3	**4c**	B	90	C	2	92
4	**4d**	B	98	C	2.5	96
5	**4e**	A	93	C	1.5	88[d]
6	**4f**	B	92	C	2	97[d]
7	**4g**	A	83	C	2	94
8	**4h**	A	96	C	2	99
9	**4i**	A	88	C	1.5	38
10				D	1.5	91
11	**4j**	A	83	C	1.5	88
12				D	3	91

[a] Method A: EDCI, HOBT, DIPEA, DMFA, r.t., 12 h; Method B: HATU, DIPEA, CH_2Cl_2, r.t., 0.5 h;
[b] Method C: TFA (10 vol%)/CH_2Cl_2; Method D: TFA (10 vol%)/TESH (10 vol%)/CH_2Cl_2.
[c] HPLC purity at 254 and 210 nm (the least pure given) if not stated otherwise; quantitative yield by NMR with methylsulfone as internal standard.

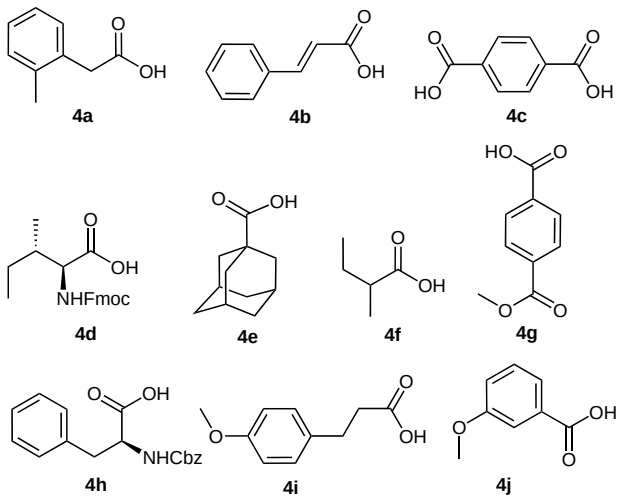


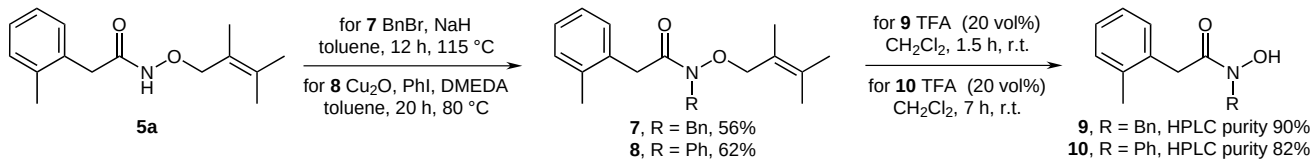
Figure 1 Structure of carboxylic acids **4**

The stability of the *O*-2-methylprenyl-protected hydroxamic acids was also investigated with **5a** under various reaction conditions (Table 2). Conditions given in entries 1–5 were selected as potential alternative deprotection conditions. However, none of them provided hydroxamic acid **6a** in appreciable yields. The 2-methylprenyl group appeared to be stable to Pd(0) deprotection, fluoride ions and strongly basic aqueous media.

Finally, we demonstrated that N-substituted hydroxamic acids can be obtained from their *O*-2-methylprenyl-protected precursors (Scheme 2). Substrate **5a** was alkylated with benzylbromide[13] to give intermediate **7** or arylated with iodobenzene[14] to give intermediate **8**.

Deprotection of compounds **7** and **8** gave hydroxamic acids **9** and **10**. For O-protected N-phenyl substituted hydroxamic acid **8**, a higher concentration of TFA in CH_2Cl_2 (20 vol%) was necessary to achieve the cleavage in a reasonable reaction time. This was attributed to lower electron density on the oxygen, which prevented protonation of the hydroxamic acid.

In summary, we have demonstrated that coupling of carboxylic acids with *O*-2-methylprenyl hydroxylamine fol-



Scheme 2 Synthesis and deprotection of N-substituted hydroxamic acids

Table 2 Deprotection Conditions Investigated for **5a**

Entry	Reaction conditions	LC/MS result
1	DDQ (1.2 equiv), CH_2Cl_2/H_2O, r.t., 12 h	mixture
2	AcCl, MeOH, r.t., 12 h	mixture
3	I_2, Zn, MeOH, r.t., 12 h	mixture (14% **6a**)
4	TMSOTf (5 vol%) CH_2Cl_2, r.t., 12 h	mixture (20% **6a**)
5	$FeCl_3$ (100 mol%), CH_2Cl_2, r.t., 12 h	mixture
6	$[Pd(PPh_3)_4]$ (5 mol%), MeOH, r.t., 48 h or reflux 4 h	stable
7	TBAF (2 equiv), THF, r.t., 24 h	stable
8	NaOH (1 M), THF, r.t., 12 h	stable

lowed by deprotection under acidic conditions is an efficient method for the synthesis of hydroxamic acids. *O*-2-Methylprenyl protection may also be useful for the synthesis of other *N*-hydroxy compounds such as *N*-hydroxyamidines and *N*-hydroxyguanidines. This is a topic of further investigation in our group.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are synthetic procedures for compounds **2**–**10**, their spectroscopic characterization as well as NMR spectra of compounds **2**, **3**, **5a–j**, **6a–j** and **7**–**10**.

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(12) Typical procedure for deprotection: To a solution of O-protected hydroxamic acid **5i** (33 mg, 0.13 mmol) in CH_2Cl_2 (2.6 mL) and triethylsilane (0.26 mL), was added TFA (0.26 mL) in one portion at r.t. The resulting mixture was stirred at r.t. for 90 min. Solvents were evaporated and the reaction mixture was treated several times with Et_2O and evaporated. The residue was dried in vacuo overnight to give hydroxamic acid **6i** in quantitative yield as colorless crystals. For characterization of compound **6i**, see: Usachova, N.; Leitis, G.; Jirgensons, A.; Kalvins, I. *Synth. Commun.* **2010**, *40*, 927.

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