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Microwave-Assisted Conversion of 4-Nitrophenyl Esters into *O*-Protected Hydroxamic Acids

Thomas Kurz,*[a] Miriam K. Pein,[a] Linda Marek,[a] Christoph T. Behrendt,[a] Lukas Spanier,[a] Krystina Kuna,[a] and Karin Brücher[a]

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The microwave-assisted synthesis of *O*-protected hydroxamic acids starting from 4-nitrophenyl esters and *O*-protected hydroxylamines is described.

Introduction

Due to the ability of hydroxamic acids to act as bidentate chelating agents for a variety of different metal cations the hydroxamate functionality represents a key pharmacophore in the development of novel metalloenzyme inhibitors. Hydroxamic acids have been described as ACE-, PDF-, HDAC-, MMP- and TACE-inhibitors.[1] Recently, the introduction of the first HDAC-inhibitor Vorinostat (Zolinza®) for the treatment of cutaneous T-cell lymphoma has demonstrated the potential of hydroxamic acids in drug design.[2] Besides Vorinostat, several hydroxamate-based analogs are already in advanced clinical trials.[3] Naturally occurring hydroxamic acids like the antibiotic Fosmidomycin and various siderophores have as well attracted the interest of organic and medicinal chemists.[4,5] Fosmidomycin is a promising drug candidate for the treatment of malaria tropica currently in phase 2 clinical trials (Figure 1).[6] In heterocyclic chemistry α-functionalized hydroxamic acids have found wide applications as building blocks for the preparation of different heterocycles.[7]

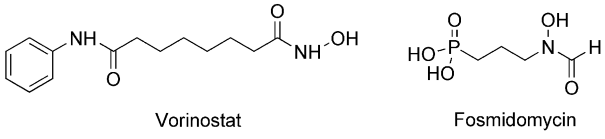

Figure 1. Vorinostat and Fosmidomycin.

Since their discovery by Lossen conventional, combinatorial and microwave-assisted concepts have been developed for the preparation of hydroxamic acids.[1] A common and efficient strategy for the synthesis of free hydroxamic acids represents the introduction of the hydroxamate group at the end of a synthetic sequence by hydroxylaminolysis of unactivated carboxylic esters.[1,7,8] In 2007 Massaro and co-workers described the microwave-assisted transformation of methyl esters into hydroxamic acids using hydroxylamine as a nucleophile.[9] Recently, Woodward reported the microwave-assisted, DABAL-Me_3-catalyzed preparation of Weinreb amides starting from *N*,*O*-dimethyl hydroxylamine hydrochloride, sodium hydride and aliphatic esters.[10] Due to their diprotic nature, the hydroxamate functionality is often introduced into a molecule in an *O*-protected form during a synthetic sequence.[1,8] Commonly *O*-protected hydroxamic acids are prepared by reacting *O*-protected hydroxylamines with reactive carboxylic acid derivatives (e.g. acid halides, anhydrides) and by carbodiimide or 1,1′-carbonyldiimidazole mediated coupling reactions.[1] Furthermore, Giacomelli and co-workers reported the synthesis of *O*-protected hydroxamic acids using 2-chloro-4,6-dimethoxy-1,3,5-triazine as activating reagent.[11] However, in some cases the activation step is only incomplete and the yields are poor. The direct transformation of unactivated aliphatic esters into *O*-Bn-protected hydroxamic acids using *O*-benzylhydroxylamine as a nucleophile has only been accomplished in the presence of $AlMe_3$ and LiHMDS, respectively.[12,13] Several protecting groups with different characteristics are currently used in hydroxamic acid chemistry. Among them, the *O*-benzyl-group is one of the most important protecting groups.[14] *O*-Benzylhydroxamates are readily deprotected under mild reaction conditions in high yields by catalytic hydrogenation on Pd-C. A structurally related group represents the *O*-1-naphthylmethyl group. Other common *O*-protecting groups are for instance the *O*-THP and the *O*-DMB group.[15,16]

As not all synthetic problems can be solved using the existing methods, novel protocols for the synthesis of hydroxamic acids are needed. In contrast to the microwave-assisted preparation of free hydroxamic acids, the micro-

[a] Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine Universität Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany
E-mail: Thomas.Kurz@uni-duesseldorf.de

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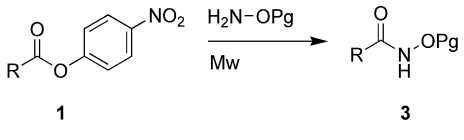
wave-assisted synthesis of *O*-protected hydroxamates has not been described before. We have now studied the microwave-assisted preparation of *O*-protected hydroxamic acids by reacting 4-nitrophenyl esters with differently *O*-protected hydroxylamines. 4-Nitrophenyl esters are easily accessible, less moisture sensitive than acid chlorides and storable at room temperature over a long period of time. To the best of our knowledge, 4-nitrophenyl esters have not been used for the preparation of *O*-protected hydroxamic acids so far.

Results and Discussion

4-Nitrophenyl esters **1a**–**g** as well as four *O*-protected hydroxylamines **2a**–**d** [*O*-benzyl(Bn)-hydroxylamine, *O*-1-naphthylmethyl-hydroxylamine, *O*-3,4-dimethyloxybenzyl-(DMB)-hydroxylamine and *O*-tetrahydropyranyl(THP)-hydroxylamine] have been prepared according to literature procedures.[16–18] First we investigated the microwave-assisted acylation of *O*-benzylhydroxylamine by 4-nitrophenyl benzoate (**1a**) in microwave pressure tubes at 300 W (Scheme 1). After several unsatisfactory attempts to synthesise the expected *N*-(benzyloxy)amide **3a** in presence of different bases (e.g. triethylamine and DMAP), we turned our attention to glacial acetic acid as a catalyst. Interestingly, the acid-catalysed reaction of **1a** and *O*-benzylhydroxylamine in dry toluene afforded the *O*-Bn-protected hydroxamic acid **3a** in 86% yield after a reaction time of only 12 minutes. In contrast, the corresponding reaction of **1a** with *O*-benzylhydroxylamine in refluxing toluene provided compound **3a** in only 24% yield after 4 hours. The reaction of both substrates in a sealed tube at 115 °C furnished **3a** in 29% yield after 2 hours. When pentafluorophenyl benzoate was used as an acylating agent instead of 4-nitrophenyl benzoate, the *O*-Bn-protected hydroxamic acid **3a** was obtained in 44% yield after 28 min under microwave irradiation. The aromatic and heteroaromatic 4-nitrophenyl ester analogs **1b** and **1c** provided the corresponding *O*-Bn-protected hydroxamic acids **3b** and **3c** in yields of 72% and 87% after only 10 min at 300 W (Table 1). Finally, Cbz-protected 4-nitrophenyl ester **1d** was also successfully converted into the corresponding Cbz-protected *N*-(benzyloxy)amide **3d**.



Scheme 1. Microwave-assisted synthesis of *O*-protected hydroxamic acids.

When *O*-benzylhydroxylamine was replaced by *O*-(1-naphthylmethyl)hydroxylamine and *O*-3,4-DMB-hydroxylamine, respectively, the corresponding *O*-substituted hydroxamic acids **3e**–**m** were obtained in 49–94% yield after 10–20 min under microwave irradiation (Table 1). Finally, we investigated the microwave-assisted acylation of *O*-THP-hydroxylamine under similar reaction conditions. In contrast to the smooth formation of *O*-arylmethyl-substituted hydroxamic acids **3a**–**m**, the *O*-THP-substituted analogs **3n** and **3o** were obtained in only 39% and 41% yield respectively. The relatively low yields in case of compounds **3n** and **3o** are most likely due to the partial deprotection of *O*-THP-protected hydroxamic acids **3n**,**o** in the presence of glacial acetic acid. The formation of the corresponding free hydroxamic acids as by-products during the microwave reactions was confirmed by TLC analysis as well as by their purple coloured reactions with ethanolic $Fe(Cl)_3$ solution. Treatment of compound **1g** with *O*-THP-hydroxylamine without glacial acetic acid as a catalyst provided the corresponding *O*-THP protected hydroxamic acid **3o** in 66% yield.

The progress of all microwave reactions was monitored by IR spectroscopy and TLC. The IR spectra showed the disappearance of the ester C=O band of **1a**–**g** at 1737–1760 cm^{-1} as well as the formation of a new, sharp carbonyl band of the hydroxamic acids (**3a**–**o**) at 1636–1676 cm^{-1}. A simple work up procedure followed by recrystallisation from appropriate solvents or chromatographic purification furnished compounds **3a**–**o** as analytically pure products. The structures of all novel compounds were elucidated by ^1H NMR, ^{13}C NMR, IR spectroscopy and elemental analysis (see Exp. Section).

Conclusions

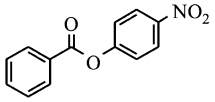
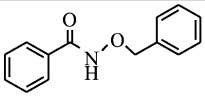
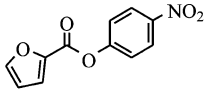
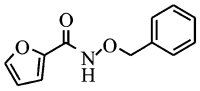
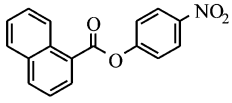
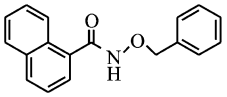
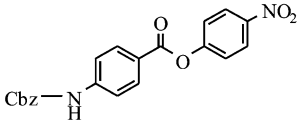
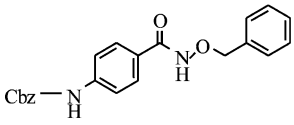
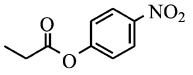
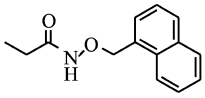
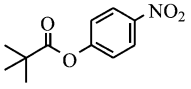
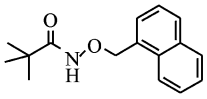
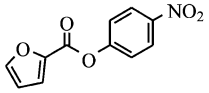
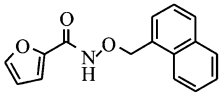
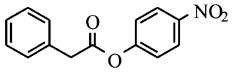
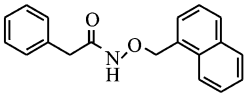
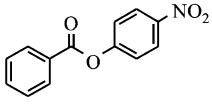
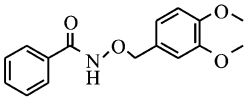
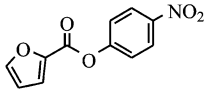
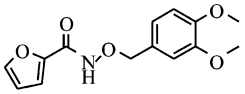
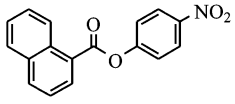
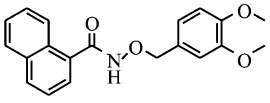
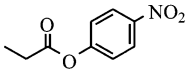
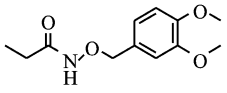
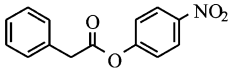
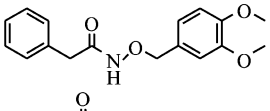
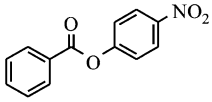
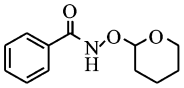
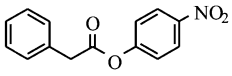
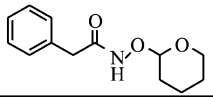
In conclusion, we have developed an efficient, fast and convenient method for the microwave-assisted synthesis of various *O*-protected hydroxamic acids starting from reactive 4-nitrophenyl esters and differently *O*-protected hydroxylamines.

Experimental Section

General: Melting points: Mettler FP 5, uncorrected values. IR: Varian 800 FT-IR Scimitar series; KBr pellets unless otherwise stated. NMR: Bruker Avance 500 (500 MHz for ^1H; 125 MHz for ^{13}C). Recorded in [D_6]DMSO or $CDCl_3$ using tetramethylsilane as an internal standard. Elemental analysis: Perkin–Elmer PE 2400 CHN elemental analyser instrument. Microwave-assisted synthesis: CEM microwave model Discover.

Microwave-Assisted Synthesis of Compounds 3a–o. General Procedure: 4-Nitrophenyl esters **1a**–**g** (1 mmol) and the appropriate *O*-protected hydroxylamine **2a**–**d** (1.4 mmol) were dissolved in dry toluene (2 mL) and added into a 10 mL glass pressure tube for microwave-assisted reactions equipped with a magnetic stirrer bar. Two drops of glacial acetic acid were added, before the tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for the indicated time (Table 1). The reaction mixture was cooled to room temperature and transferred to a round bottomed flask. The solvent was evaporated, ethyl acetate (25 mL) was added and the mixture was washed subsequently with citric acid solution (10%, 15 mL), a saturated, aqueous sodium carbonate solution (5 × 10 mL) and water (10 mL). The organic layer was dried with Na_2SO_4, filtered, and the solvent was evaporated. The remaining residues were purified by crystallisation from appropriate solvents or by filtration through a short silica gel column

Table 1. *O*-Protected hydroxamic acids **3a**–**o**.

Substrate		Product		Time [min]	Yield [%]
	**1a**		**3a**	12	86
	**1b**		**3b**	10	87
	**1c**		**3c**	10	72
	**1d**		**3d**	15	75
	**1e**		**3e**	10	70
	**1f**		**3f**	15	49
	**1b**		**3g**	10	81
	**1g**		**3h**	10	73
	**1a**		**3i**	20	56
	**1b**		**3j**	15	94
	**1c**		**3k**	15	69
	**1e**		**3l**	15	71
	**1g**		**3m**	13	73
	**1a**		**3n**	12	41
	**1g**		**3o**	10	39

(3 cm) with ethyl acetate/*n*-hexane (3:7) as an eluent. Crystallisation from ethyl acetate/*n*-hexane provided compounds **3a**–**o** as analytically pure solids.

Parameters for the Microwave-Assisted Synthesis of Compounds 3a–o: Discover mode; power: 300 W; ramp time: 1 min; hold time: 10–20 min (Table 1); temperature: 115 °C; pressure: 6 bar; PowerMax cooling mode.

***N*-(Benzyloxy)naphthalene-1-carboxamide (3c):** Colourless solid, yield 72% (200 mg), m.p. 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.12 (s, 2 H, CH_2), 7.35–7.55 (m, 9 H), 7.82–7.86 (m, 1 H), 7.88–

7.92 (m, 1 H), 8.19–8.25 (m, 1 H), 8.44 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 78.5, 124.5, 125.1, 125.3, 125.6, 126.6, 127.4, 128.3, 128.7, 128.9, 129.4, 130.3, 130.6, 131.3, 133.6, 135.2, 139.8, 158.6 ppm. IR: $\tilde{\nu}$ = 1644 (C=O) cm^{-1}. $C_{18}H_{15}NO_2$ (277.33): calcd. C 77.96, H 5.45, N 5.05; found C 77.90, H 5.58, N 5.12.

***N*-[(Naphthalen-2-yl)methoxy]furan-2-carboxamide (3g):** Colourless solid, yield 81% (216 mg), m.p. 122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.50 (s, 2 H, CH_2), 6.49 (dd, J = 1.72, 3.49 Hz, 1 H), 7.20 (d, J = 3.43 Hz, 1 H), 7.36–7.37 (m, 1 H), 7.42–7.45 (m, 1 H), 7.50–7.55 (m, 2 H), 7.60–7.63 (m, 1 H), 7.89 (d, J = 8.18 Hz, 2 H), 8.43 (d, J = 8.42 Hz, 1 H), 8.78 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.2, 112.1, 115.7, 124.4, 125.1, 126.2, 126.9, 128.5, 129.0, 130.0, 130.7, 132.2, 133.8, 144.4, 145.7, 157.2 ppm. IR: $\tilde{\nu}$ = 1649 (C=O) cm^{-1}. $C_{16}H_{13}NO_3$ (267.28): calcd. C 71.90, H 4.90, N 5.24; found C 71.93, H 4.99, N 5.30.

***N*-(3,4-Dimethoxybenzyloxy)furan-2-carboxamide (3j):** Colourless solid, yield 94% (261 mg), m.p. 94 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 6 H, CH_3), 4.96 (s, 2 H, CH_2), 6.49–6.52 (m, 1 H), 6.86 (d, J = 8.08 Hz, 1 H), 6.97 (d, J = 8.04 Hz, 1 H), 7.01 (s, 1 H), 7.19 (d, J = 3.28 Hz, 1 H), 7.41 (s, 1 H), 8.75 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.9, 78.8, 110.9, 112.1, 112.3, 115.7, 122.2, 127.5, 144.4, 145.8, 149.1, 156.9 ppm. IR: $\tilde{\nu}$ = 1676 (C=O) cm^{-1}. $C_{14}H_{15}NO_5$ (277.28): calcd. C 60.65, H 5.45, N 5.05; found C 60.78, H 5.56, N 5.06.

***N*-[(Tetrahydropyran-2-yl)oxy]-2-phenylacetamide (3o):** Colourless solid, yield 39% (92 mg) (microwave-assisted), 66% (155 mg) (conventional synthesis), m.p. 119 °C. ^{1}H NMR (500 MHz, [D_6]-DMSO): δ = 1.47–1.72 (m, 6 H), 3.35 (s, 2 H), 3.50–3.55 (m, 1 H), 3.91–3.97 (m, 1 H), 4.83 (s, 1 H), 7.22–7.34 (m, 5 H), 11.25 (s, 1 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 18.6, 25.0, 28.1, 41.5, 61.7, 101.3, 126.8, 126.9, 128.6, 128.6, 129.3, 136.0, 167.3 ppm. IR: $\tilde{\nu}$ = 1652 (C=O) cm^{-1}. $C_{13}H_{17}NO_3$ (235.29): calcd. C 66.36, H 7.28, N 5.95; found C 66.22, H 7.34, N 6.09.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, spectroscopic data, elemental analysis and melting points for compounds **3d**–**f**,**h**,**k**,**m**.

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