Synthesis of hydroxamic acids by using acid labile $O$-2-methylprenyl protecting group

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General
Reagents and starting materials were purchased from various commercial sources and used as received. Purification was performed by flash silica gel chromatography using Merck Kieselgel (230 – 400 mesh), eluting with ethyl acetate and benzine in different ratio. Thin layer chromatography was performed on silica gel and was visualized by staining with KMnO4 or in UV at 210 nm or 254 nm. NMR spectra were recorded on Varian Mercury spectrometer (400 MHz) with chemical shifts values ($\delta$) in ppm relative to solvents (CDCl₃ $\delta$=7.26 and DMSO $\delta$=2.50 ppm for $^1$H NMR) signal as internal standard. Spin-spin coupling constant ($J$ value recorded in Hz) were measured directly from the spectra integral, multiplicity ($s$=singlet, $brs$=broad singlet, $d$=doublet, $t$=triplet, $q$=quartet, $p$=pentet, sextet).
Synthesis of compound 3
1-Bromo-2,3-dimethyl-2-butene was prepared using the literature procedure\(^1\) by the reaction of 1 (3.4 g, 40.5 mmol) and \(N\)-bromosuccinimide (7.1 g, 40.5 mmol) in \(CCl_4\) (25 mL). The reaction mixture was refluxed for 4 h and the solvent was evaporated. The reaction mixture was submitted to the next step with no additional purification.

\(\ce{O} \ 2 \ce{H2N-NH2*H2O} \ 3 \ce{H2N-O} \ 1. \ce{NH2} \ 1. \ NBS, BPO, CCl4, 110°C \ 2. \ce{N-hydroxyphthalimide} \ K_2CO_3, DMSO, r.t \ 40\% \text{ in two steps} \)

To a solution of \(N\)-hydroxyphthalimide (7.09 g, 43.5 mmol) in DMSO (70 mL), \(K_2CO_3\) (6 g, 43.5 mmol) was added and the resulting mixture was intensively stirred at room temperature for 20 min. To this, a solution of 1-bromo-2,3-dimethyl-2-butene (7.09 g, 43.5 mmol) in DMSO (17 mL) was added and the reaction mixture was stirred at room temperature overnight. The mixture was poured in ice-water (300 mL), the precipitate formed was filtered off, washed with water, dried in vacuo at 50 °C under \(P_2O_5\) and purified by flash chromatography, eluent EtOAc: Petroleum ether (1 : 4). Pure fractions were evaporated to dryness to afford 2 (3.97 g, 40%) as crystalline material.

To a stirred solution of hydrazine hydrate (3.4 mmol, 335 µL) and 4Å molecular sieves in Et\(_2\)O (10 mL), solution of 2 (2 mmol, 490 mg) in Et\(_2\)O (10 mL) was added. The mixture was stirred overnight at room temperature, filtered through silica gel and silica gel was washed with several portions of Et\(_2\)O. Organic phase was treated with concentrated HCl in Et\(_2\)O (till pH~2), and stirred for 30 min. The precipitate was filtered off and washed with Et\(_2\)O, dried in vacuo at 40 °C, to give 3 as a colourless solid (230 mg, 76%).

2-(2,3-Dimethylbut-2-enyloxy)isoindoline-1,3-dione (2)

\(1^H\)-NMR \(\delta_H \ (400 \text{ MHz, CDCl}_3\): 7.82 (2H, q, J=3.1, 5.48, 4.7-CH-Phth), 7.73 (2H, q, J=3.1, 5.48 Hz, 5.6-CH-Phth), 4.70 (2H, s, -O-CH\(_2\)-CCH\(_3\)=C(CH\(_3\))\(_2\)), 1.90 (3H, s, CH\(_3\)), 1.75 (3H, s, CH\(_3\)), 1.70 (3H, s, CH\(_3\)). \(13^C\)-NMR \(\delta_C \ (400 \text{ MHz, CDCl}_3\): 163.68, 135.15, 134.29, 129.00, 123.33, 122.09, 78.79, 21.04, 20.33, 17.57.

O-(2,3-Dimethylbut-2-enyl)hydroxylamine (3)

\[ \text{H}_2\text{N}^\text{O} \text{O} \text{O} \text{NH}_2 \]

\[^1\text{H-NMR} \; \delta_\text{H} (400 \text{ MHz, DMSO}): 10.78 (2\text{H, brs, NH}_2), 4.49 (2\text{H, s, } -\text{O-CH}_2\text{C=}), 1.74 (3\text{H, s, CH}_3), 1.68 (6\text{H, s, } 2\times\text{CH}_3) ; \]^1\text{C-NMR} \; \delta_\text{C} (400 \text{ MHz, CDCl}_3): 135.00, 120.88, 74.78, 20.71, 20.21, 16.97;

Element analysis (experimental): N=8.68; C=44.69; H= 9.54; (calculated*0.5H_2O): N=8.72; C=44.86; H=9.41.

2. Typical procedure for synthesis of protected hydroxamic acids 5

**Method A:** To a stirred solution of carboxylic acid 4 (1 equiv.) in DMFA, EDCI (1.2 equiv.), HOBr (1.2 equiv.) and DIEA (3 equiv.) was added. The resulting solution was stirred for 10 min at room temperature and O-methylprenylhydroxylamine hydrochloride (3) (1.4 equiv.) was added. The mixture was stirred at room temperature overnight. The reaction mixture was treated with water and extracted with EtOAc (in the case of formation of precipitate, the product was filtered off and dried in vacuo over P_2O_5). The organic phase was washed with water several times, dried over Na_2SO_4, filtered and evaporated. The product was purified by flash chromatography if necessary.

*N-(2,3-Dimethylbut-2-enyloxy)-2-o-tolylacetamide (5a)*

\[ \text{H}_2\text{N}^\text{O} \text{O} \text{O} \text{NH} \]

\[^1\text{H-NMR} \; \delta_\text{H} (400 \text{ MHz, DMSO}): 10.99 (1\text{H, brs, NH}), 7.17 - 7.10 (4\text{H, m, Ph}), 4.25 (2\text{H, s, } -\text{CH}_2\text{-O-}), 3.29 (2\text{H, s, } -\text{CH}_2\text{-Ph}), 2.25 (3\text{H, s, } o\text{-CH}_2\text{-Ph}), 1.69 (3\text{H, s, } -\text{CH}_3), 1.64 (3\text{H, s, CH}_3\text{, partially overlapped with } -\text{CH}_3\text{ signal}), 1.63 (3\text{H, s, CH}_3\text{, partially overlapped with } -\text{CH}_3\text{ signal})

*N-(2,3-Dimethylbut-2-enyloxy) cinnamamide (5b)*

\[ \text{H}_2\text{N}^\text{O} \text{O} \text{O} \text{NH} \]

\[^1\text{H-NMR} \; \delta_\text{H} (400 \text{ MHz, DMSO}): 11.10 (1\text{H, brs, NH}), 7.52-7.38 (6\text{H, m, Ph-CH=}), 6.42 (1\text{H, d, J}=16.0 \text{ Hz, Ph-CH=CH-}), 4.34 (2\text{H, s, } -\text{CH}_2\text{-O-}), 1.74 (3\text{H, s, } -\text{CH}_3\text{, partially overlapped with } -\text{CH}_3\text{ signal}), 1.72 (3\text{H, s, } -\text{CH}_3\text{, partially overlapped with } -\text{CH}_3\text{ signal}), 1.67 (3\text{H, s, } -\text{CH}_3\text{)}

3,7-Dimethyl-bicycle[3.3.1]nonane-1-carboxylic acid (2,3-dimethylbutyl-2-enyloxy)-amide (5e)
Methyl 4-(2,3-dimethylbut-2-enyloxycarbamoyl)benzoate (5g)

\[ \text{\textit{H}-NMR } \delta_{\text{H}} (400 \text{ MHz, DMSO}): 10.52 (1\text{H, brs, NH}), 4.20 (2\text{H, brs, } -\text{CH}_2\text{-O-}), 1.94 (3\text{H, brs, } -\text{CH} - \text{ adamantane}), 1.73 (3\text{H, brs, } -\text{CH}_3), 1.73 (3\text{H, brs, } -\text{CH}_3 \text{, overlapped}), 1.71 (3\text{H, brs, } -\text{CH}_3 \text{, overlapped}), 1.71-1.63 (12\text{H, m, adamantane}) \]

\[ \text{(S)-Benzyl 1-(2,3-dimethylbut-2-enyloxyamino)-1-oxo-3-phenylpropan-2-ylcarbamate (5h)} \]

\[ \text{\textit{H}-NMR } \delta_{\text{H}} (400 \text{ MHz, DMSO}): 11.74 (1\text{H, s, NH}), 8.02 (2\text{H, dd, } J=1.9, 8.6 \text{ Hz, arom}), 7.85 (2\text{H, d, } J= 8.3 \text{ Hz, arom}), 4.40 (1\text{H, brs, } -\text{CH}_2\text{-O-}), 3.86 (3\text{H, s, } -\text{OCH}_3), 1.77 (3\text{H, brs, } -\text{CH}_3), 1.73 (3\text{H, brs, } -\text{CH}_3), 1.64 (3\text{H, brs, } -\text{CH}_3) \]

\[ \text{N-(2,3-Dimethylbut-2-enyloxy)-3-(4-methoxyphenyl)propanamide (5i)} \]

\[ \text{\textit{H}-NMR } \delta_{\text{H}} (400 \text{ MHz, DMSO}): 10.75 (1\text{H, brs, NH}), 7.90 (2\text{H, dd, } J = 8.6, 1.9 \text{ Hz, 3,5-Ph}), 6.82 (2\text{H, dd, } J = 8.6, 1.9 \text{ Hz, 2,6-Ph}), 4.19 (2\text{H, s, } -\text{CH}_2\text{-O-}), 3.70 (3\text{H, s, } -\text{OCH}_3), 2.73 (2\text{H, t, } J=7.8 \text{ Hz, } \text{Ph-CH}_2\text{-CH}_2^-), 2.19 (2\text{H, t, } J=7.8 \text{ Hz, } \text{Ph-CH}_2\text{-CH}_2^-), 1.67 (6\text{H, brs, 2*CH}_3), 1.64 (3\text{H, s, CH}_3) \]

\[ \text{N-(2,3-Dimethylbut-2-enyloxy)-3-methoxybenzamide (5j)} \]

\[ \text{\textit{H}-NMR } \delta_{\text{H}} (400 \text{ MHz, DMSO}): 11.53 (1\text{H, s, NH}), 7.39-7.27 (3\text{H, m, arom}), 7.10 (1\text{H, dq, } J=0.8, 2.3, 4.7 \text{ Hz, arom}), 4.38 (2\text{H, brs, } -\text{CH}_2\text{-O-}), 3.79 (3\text{H, s, } -\text{OCH}_3), 1.77 (3\text{H, brs, } -\text{CH}_3), 1.74 (3\text{H, brs, } -\text{CH}_3), 1.67 (3\text{H, s, } -\text{CH}_3) \]
**Method B:** To a stirred solution of acid (1 equiv.) in dry DCM, HATU (4 equiv.), HOBt (4 equiv.) and DIEA (6 equiv.) was added sequentially. The resulting solution was stirred at room temperature for 10 min followed by addition of O-methylprenylhydroxylamine hydrochloride (3) (2 equiv.). After stirring at room temperature for 30 min, the solvent was removed in vacuo and the residue was purified by flash chromatography to give an O-protected hydroxamic acid in quantitative yield.

**N,N’-Bis-(2,3-dimethyl-but-2-enyloxy)-terephthalamide**

\[ \text{N,N’-Bis-(2,3-dimethyl-but-2-enyloxy)-terephthalamide} \]

\[ \text{1H-NMR } \delta_{\text{H}} (400 MHz, DMSO): 11.66 (2H, s, 2*NH), 7.78 (4H, s, phenyl), 4.39 (4H, brs, -CH}_2\text{-O-), 1.77 (6H, s, methylprenyl group 2*CH}_3\text{ partially overlapped) 1.73 (6H, s, methylprenyl group 2*CH}_3\text{ partially overlapped), 1.67 (6H, s, methylprenyl group 2*CH}_3\text{ partially overlapped).} \]

**N-(9H-Fluoren-9-yl)Methyl (2R,3S)-4-(2,3-dimethylbut-2-enyloxyamino)-2,3-dimethyl-4-oxobutylcarbamate (5d)**

\[ \text{N-(9H-Fluoren-9-yl)Methyl (2R,3S)-4-(2,3-dimethylbut-2-enyloxyamino)-2,3-dimethyl-4-oxobutylcarbamate} \]

\[ \text{1H-NMR } \delta_{\text{H}} (400 MHz, DMSO): 11.03 (1H, brs, NH hydroxamic), 7.88 (2H, d, J=7.4 Hz, fluorene), 7.75 (2H, d, J=7.4 Hz, fluoren), 7.55 (1H, d, J=9.0 Hz, NH-fluoren), 7.41 (2H, t, J=7.4 Hz, fluoren), 7.31 (2H, m, fluoren), 4.31-4.19 (3H, m, -CH}_2\text{-CH-fluoren), 4.21 (2H, s, -CH}_2\text{-O-), 3.62 (1H, t, J=9.0 Hz, -CH-NHFmoc), 1.76 (1H, d, NHFmoc, J=8.3 Hz), 1.73 (1H, m, overlapped), 1.69 (3H, s, methylprenyl group CH}_3\text{ partially overlapped), 1.66 (3H, s, methylprenyl group CH}_3\text{ partially overlapped), 1.62 (3H, s, methylprenyl group CH}_3\text{ partially overlapped), 1.48-1.41 (1H, m, CH}_3\text{-CH}_2\text{-CH), 1.14-1.04 (1H, m, CH}_3\text{-CH}_2\text{-CH), 0.81 (3H, t, J=7.0 Hz, CH}_3\text{-Ile), 0.80 (3H, d, J=6.7 Hz, CH}_3\text{-Ile)} \]

**N-(2,3-Dimethylbut-2-enyloxy)-2-methylbutanamide (5f)**

\[ \text{N-(2,3-Dimethylbut-2-enyloxy)-2-methylbutanamide} \]

\[ \text{1H-NMR } \delta_{\text{H}} (400 MHz, DMSO): 10.75 (1H, brs, NH, J=10.7, 11.7 Hz, -CH}_2\text{-O-), 1.95 (1H, dsextet, J=1.6, 6.7, 7.4 Hz, -CH}_2\text{-CH), 1.70 (6H, s, 2*-CH}_3\text{), 1.65 (3H, s, -CH}_3\text{), 1.50-1.40 (1H, m, CH}_3\text{-CH}_2\text{-CH), 1.33-1.23 (1H, m, CH}_3\text{-CH}_2\text{-CH), 0.95 (3H, d, J=6.7 Hz, CH}_3\text{-CH}_2\text{-CH), 0.78 (3H, t, J=7.4 Hz, CH}_2\text{- CH-)} \]
3. Typical procedure for deprotection of hydroxamic acids
To a solution of O-protected hydroxamic acid (5a-5j) in DCM (0.1 mmol/1 mL) TFA (10 vol%) was added in one portion at room temperature. After the completion of reaction (TLC control), solvents were evaporated and the reaction mixture was treated several times with Et₂O and evaporated to give the desired compound in quantitative yield.

(TESH - triethylsilane was added if necessary to the solution of hydroxamic acid in DCM followed by the addition of TFA).

Compounds 6(a, b, e, i)², 6c³, 6d⁴, 6g⁵, 6h⁶, 6j⁷ have been previously described in the literature.

N-Hydroxy-2-methylbutanamide (6f)

\[ \text{O} \quad \text{NH} \quad \text{OH} \]

\[ ^1H\text{-NMR } \delta_H \text{(400 MHz, DMSO):} \]

1.35 (1H, brs, NH), 8.66 (1H, brs, OH), 1.97 (1H, dsextet, J=1.9, 6.7, 7.8 Hz, -CH₂-CH⁻), 1.52-1.41 (1H, m, CH₃-CH₂-CH), 1.33-1.23 (1H, m, CH₃-CH₂-CH⁻), 0.96 (3H, d, J=7.0 Hz, CH₃-CH₂-CH), 0.79 (3H, t, J=7.4 Hz, CH₃-CH⁻).

4. Synthesis of compound 7
To a solution of O-protected hydroxamic acid 5a (0.3 mmol) in toluene (3 mL), NaH (1.2 equiv.) was added followed by the addition of the solution of benzylbromide (2 equiv.) in toluene (3 mL). The reaction mixture was stirred in an inert atmosphere for 12 h at 110°C (TLC control). The reaction mixture was cooled to room temperature then diluted with EtOAc and extracted with KHSO₄ (5%). The organic phase was dried over Na₂SO₄, filtrated and evaporated. Purified by flash chromatography EtOAc: Petroleum ether (1:10) to give the desired product 7. Yield 56%.

N-benzyl-N-(2,3-dimethylbut-2-enyloxy)-2-o-tolylacetamide (7)

\[ \text{O} \quad \text{N} \quad \text{O} \]

\[ ^1H\text{-NMR } \delta_H \text{(400 MHz, DMSO):} \]

7.35-7.25 (5H, m, arom), 7.15-7.10 (4H, m, arom), 4.82 (2H, brs, -N-CH₂-Ph), 4.42 (2H, brs, -CH₂-O⁻), 3.82 (2H, s, -CH₂-Ph), 2.15 (3H, s, o-CH₂-Ph), 1.68 (3H, brs, overlapped with methylgroup signal, -CH₃), 1.67 (3H, s, CH₃, with methyl group signal -CH₃ signal), 1.64 (3H, s, CH₃, partially overlapped with CH₃ signal)

² For the compounds 6a, b, e, i see: Usachova N., Leitis G., Jirgensons A., Kalvins I.; Synth. Commun. 2010, 40, 927.
⁶ For 6h see: Jorga B., Compagne J.-M., Synlett 2004, 1826
⁷ For 6j see: Ghosh H., Baneerjee A., rout S.K., Patel B. K., ARIKVOC 2011, 209.
5. Synthesis of compound 8:

Compound 8 was prepared following the general procedure as described in the literature. Purified by flash chromatography EtOAc:Petroleum ether (1:4) to give the desired product. Yield 62%.

\[ N-(2,3\text{-dimethylbut-2-enyloxy})-N\text{-phenyl-2-o-tolylacetamide (8)} \]

\[ \text{\textsuperscript{1}H-NMR} \delta_{\text{H}} (400 \text{ MHz, DMSO}) : 7.46-7.41 (4\text{H, m, arom}), \]
\[ 7.26 (1\text{H, brs, } p\text{-arom}), 7.16-7.11 (4\text{H, m, arom}), 4.38 (2\text{H, s, } -\text{CH}_2\text{-O-}), 3.92 (2\text{H, brs, } -\text{CH}_2\text{-Ph}), 2.19 (3\text{H, s, o-CH}_3\text{-Ph}), 1.68 (3\text{H, brs, overlapped with methylgroup signal, } -\text{CH}_3\text{), 1.66 (3H, s, CH}_3\text{, with methylgroup signal -CH}_3\text{ signal}), 1.63 (3\text{H, s, CH}_3\text{, partially overlapped with CH}_3\text{ signal).} \]

6. Deprotection of compounds 7 and 8

Deprotection was performed following the general procedure (see paragraph 3). Concentration of TFA – 20 vol%, stirred at room temperature till complete consumption of starting material (TLC control). The mixture was evaporated too the dry residue.

\[ N\text{-benzyl- N-hydroxy-2-o-tolylacetamide (9)} \]

\[ \text{\textsuperscript{1}H-NMR} \delta_{\text{H}} (400 \text{ MHz, DMSO}) : 10.01 (1\text{H, brs, } \text{NH}), 7.35-7.25 \]
\[ (5\text{H, m, phenyl}), 7.14-7.09 (4\text{H, m, tolyl}), 4.72 (2\text{H, s, } -\text{N-CH}_2\text{-Ph}), \]
\[ 3.77 (2\text{H, s, } -\text{CH}_2\text{-Ph}), 2.20 (3\text{H, s, o-CH}_3\text{-Ph}). \]

\[ N\text{-hydroxy- N-phenyl-2-o-tolylacetamide (10)} \]

\[ \text{\textsuperscript{1}H-NMR} \delta_{\text{H}} (400 \text{ MHz, DMSO}) : 10.72 (1\text{H, brs, } \text{OH}), 7.63 (2\text{H, d,} \]
\[ J=8.2 \text{ Hz, 3,6-tolyl}) 7.36 (2\text{H, t, } J=7.4 \text{ Hz, 4,5-tolyl}), 7.19-7.10 (5\text{H,} \]
\[ \text{m, phenyl}), 3.93 (2\text{H, s, } -\text{N-CH}_2\text{-Ph}), 2.23 (3\text{H, s, o-CH}_3\text{-Ph}). \]

\[ \text{8 Kukosha T.; Trufilkina N.; Belyakov S.; Katkevics M.} \text{Synthesis 2012, 44, 2413.} \]
7. NMR spectra of compounds 2, 3, 5a-j, 6a-j, 7-10

2-(2,3-Dimethylbut-2-enyloxy)isoindoline-1,3-dione (2)
2-(2,3-Dimethylbut-2-enyloxy)isoindoline-1,3-dione (2)
$O$-(2,3-Dimethylbut-2-enyl)hydroxylamine (3)
$O$-(2,3-Dimethylbut-2-enyl)hydroxylamine (3)
N-(2,3-Dimethylbut-2-enyloxy)-2-o-tolylacetamide (5a)
N-Hydroxy-2-o-tolyl-acetamide (6a)
$N$-(2,3-Dimethylbut-2-enyloxy) cinnamamide (5b)
(E)-N-Hydroxy-3-phenyl-acrylamide (6b)
3,7-Dimethyl-bicyclo[3.3.1]nonane-1-carboxylic acid (2,3-dimethylbutyl-2-enyloxy)-amide (5e)
Adamantane-1-carboxylic acid hydroxyamide (6e)
Methyl 4-(2,3-dimethylbut-2-enyloxycarbamoyl)benzoate (5g)
N-Hydroxy-terephthalamic acid methyl ester (6g)
(S)-Benzyl 1-(2,3-dimethylbut-2-enyloxyamino)-1-oxo-3-phenylpropan-2-ylcarbamate (5h)
(S)-N-Hydroxy-2-methyl-3-phenyl-propionamide (6h)
$N$-(2,3-Dimethylbut-2-enyloxy)-3-(4-methoxyphenyl)propanamide (5i)
N-Hydroxy-3-(4-methoxy-phenyl)-propionamide (6i)
N-(2,3-Dimethylbut-2-enyloxy)-3-methoxybenzamide (5i)
N-Hydroxy-3-methoxy-benzamide (6j)
$N,N'$-Bis-(2,3-dimethyl-but-2-enyloxy)-terephthalamide (5c)
$N,N'$-Dihydroxy-terephthalamide (6c)
(9H-Fluoren-9-yl)methyl (2R,3S)-4-(2,3-dimethylbut-2-enyloxyamino)-2,3-dimethyl-4-oxobutylcarbamate (5d)
((1S,2S)-1-Hydroxycarbamoyl-2-methyl-butyl)-carbamic acid 9H-fluoren-9-ylmethyl ester (6d)
N-(2,3-Dimethylbut-2-enyloxy)-2-methylbutanamide (5f)
N-Hydroxy-2-methylbutanamide (6f)
$N$-(2,3-Dimethylbut-2-enyloxy)-$N$-phenyl-2-o-tolylacetamide (8)
N-Benzyl-N-(2,3-dimethylbut-2-enyloxy)-2-o-tolylacetamide (7)
$N$-Benzyl-$N$-hydroxy-2-o-tolylacetamide (9)
N-Hydroxy-N-phenyl-2-o-tolylacetamide (10)