Synthesis B. C. Hamper et al. PSP

A Practical Gram-Scale Synthesis of Acrylohydroxamic Acid

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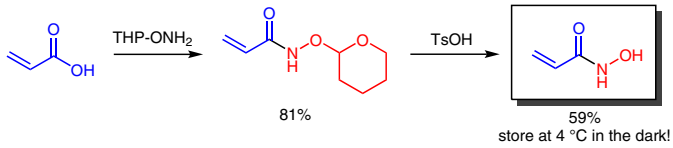

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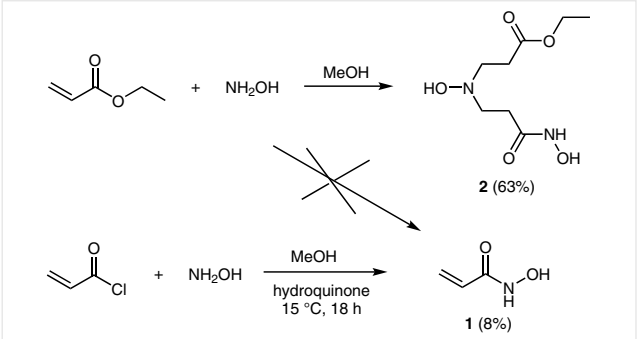
Abstract Acrylohydroxamic acid, which is a useful monomer for the preparation of polymeric materials, has been prepared in a straightforward, two-step synthesis from readily available starting materials. The key steps are coupling of acrylic acid with *O*-tetrahydropyranylhydroxyl amine to provide protection of the hydroxylamine functionality, followed by acid cleavage of the protecting group.

Key words hydroxamic acids, acrylohydroxamic acid, chelating agents, monomers, functionalized polymers, metal chelation

In the course of synthesis of small organic molecules we occasionally come across chemical structures that are deceptively simple yet synthetically challenging.[1–3] Often these compounds can serve as valuable synthons or building blocks for the preparation of more complex structures, combinatorial libraries or polymeric materials.[4] Our studies on the properties of metal-chelating resins required the synthesis of acrylohydroxamic acid (**1**) as a potential intermediate for the synthesis of polymeric materials and as an analytical standard.[5]

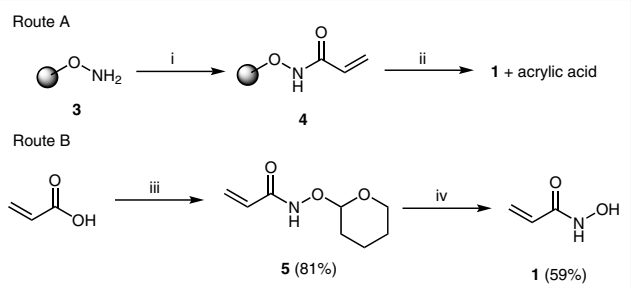
Hydroxamic acids and their derivatives are of interest because of their ability to form bidentate ligand complexes with a variety of metal ions.[6] Acrylohydroxamic acid (**1**; Scheme 1) has been reported as a potential precursor for the preparation of copolymers for chelation of metals such as Cu, Pb, and As and as antistatic surface protection films.[7,8] Although **1** has been reported numerous times, to our knowledge, only four published methods for its preparation have appeared.[9–12] In 1917, Jones and Neuffer reported a crystalline solid (mp 115–116 °C) obtained from reaction of ethyl acrylate and hydroxylamine, which they attributed to structure **1**.[9] However, in 1965, Becke and Mutz were able to demonstrate that reaction of equimolar amounts of ethyl acrylate and hydroxylamine result in the formation of dimer monohydroxamic acid **2** as a crystalline product (mp 115–116 °C).[10] By evaluation of different molar ratios in the reaction, they were able to establish that hydroxylamine undergoes β-addition to two acylate esters to give β,β′-hydroxyiminodipropionate diester followed by reaction with a second equivalent of hydroxylamine to give monohydroxamic acid **2**. Becke and Mutz were able to obtain the desired hydroxamic acid **1** in low yield by reaction of acryloyl chloride with hydroxylamine. Polymerization during workup was noted as the major cause of low yield. More recently, preparation of **1** has been suggested by direct reaction of acrylamide with NH_2OH-HCl or by treatment of acrylic acid with NH_2OH-HCl in the presence of 2,4,6-trichloro-1,3,5-triazine coupling reagent.[11,12] However, we were unable to reproduce these results in our laboratories and the authors' limited reported spectral data did not support assignment to monomeric hydroxamic acid **1**.



Scheme 1 Reaction of ethyl acrylate and acyloyl chloride with hydroxylamine[10]

Prior studies and our own attempts at a single-step synthesis of **1** have shown that the target compound is prone to both addition reactions with free hydroxylamine and

polymerization. This suggested that a protection scheme for the reactive hydroxylamine functionality was required. Two potential routes were investigated for the preparation of **1**, each consisting of two steps using a protection group strategy for formation and release of the hydroxamic acid functional group (Scheme 2). Route A used protected hydroxylamine **3** derived from Wang's resin, which has been previously reported for the synthesis of MMP-13 selective hydroxamates.[13] Treatment of **3** with acryloyl chloride resulted in resin-bound hydroxamic acid **4**. Cleavage of the resin with trifluoroacetic acid (TFA) gave the desired product **1**. However, the material obtained by direct cleavage was contaminated with acrylic acid, probably the result of a mixture of free benzyl alcohol and O-alkylated hydroxylamine sites in the original resin. The product was purified by silica chromatography and resulted in a clear oil that, based on ^{1}H NMR spectroscopic analysis, contained minor amounts of contaminants. Attempts at crystallization of the Route A product were unsuccessful.



Scheme 2 Synthesis of acrylohydroxamic acid **1**. *Reagents and conditions*: (i) acryloyl chloride, Et_3N, CH_2Cl_2; (ii) TFA, $CDCl_3$; (iii) THP-ONH_2, DCC, CH_2Cl_2; (iv) TsOH·H_2O, MeOH.

Coupling of acrylic acid and tetrahydropyranyl hydroxylamine (THP-ONH_2) with N,N-dicyclohexylcarbodiimide (DCC) afforded protected acrylamide **5** in 81% yield (Scheme 2, route B).[14] This initial solid obtained by crystallization (mp 101 °C) can be used directly for the preparation of **1**. For synthesis of our high-purity analytical standard, we chose to further purify **5** by silica chromatography, which led to a slight increase in mp (103 °C), but did not noticeably impact the NMR or IR spectral data. Hydrolysis of the THP group with tosylic acid gave, after workup, a clear oil, which was purified by chromatography to afford **1** as a white, crystalline solid. Even in the solid form, acrylohydroxamic acid (**1**) is prone to polymerization. However, we found that the crystalline solid can be stored at 4 °C in the dark for up to two years without noticeable decomposition. Due to the propensity of **1** to undergo polymerization at room temperature, we have limited our synthesis to one gram or less of the final product. While multigram scale synthesis might be achievable with larger scale chromatographic equipment, one would need to validate the stability of **1** (for example with differential scanning calorimetry) prior to carrying out larger scale runs.

Previous reports on **1** gave a range of physical properties including various recorded melting points,[9–12] which all differed from our results and were probably due to varying degrees of purity of the final product. The product generated by Route B was obtained directly from silica chromatography as a white solid (mp 83–84 °C). Repeated chromatographic purification or recrystallization did not lead to changes in either melting point or quality of the spectral data. The ^{1}H NMR of **1** in DMSO-d_6 showed the expected vinyl signals with an upfield doublet of doublets at 5.66 ppm and two vinyl signals appearing as a multiplet at 6.14 ppm. ^{13}C NMR and IR spectra were particularly useful for evaluating the purity of our target compound. ^{13}C NMR analysis showed three distinct signals including the carbonyl at 163.2 ppm and the two olefinic carbon signals at 129.7 and 125.9 ppm. IR spectra obtained by ATR showed a strong absorbance at 1596 (C=C) and 1650 cm^{-1} (C=O) and a relatively sharp aliphatic region showing absorbance at 2811, 3032, and 3200 cm^{-1}. Upon polymerization, the aliphatic region becomes very broad from 2300 to 3300 cm^{-1}. The double bond region shows a complete loss of the C=C signal at 1596 cm^{-1} and a shift of the carbonyl absorption from 1650 to 1626 cm^{-1} due to loss of the α,β-unsaturated double bond. Elemental composition was determined by elemental analysis and HRMS of the cesium salt adduct using positive ion FAB-MS. A crystal structure of **1** prepared by recrystallization from hexanes–ethyl acetate provided the final structural proof (Figure 1).

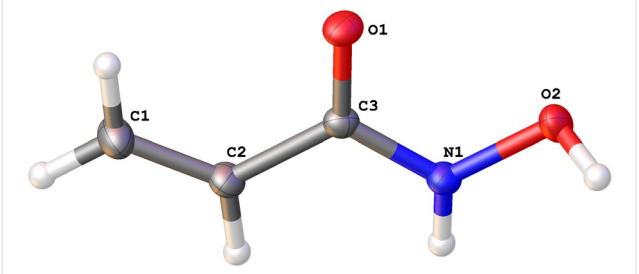


Figure 1 Crystal structure of **1**. Projection view with 50% probability ellipsoids.

In summary, we have developed an efficient and reliable two-step procedure for the preparation of single-gram quantities of acrylohydroxamic acid (**1**). The key transformation is the preparation of a crystalline O-THP intermediate, which can be easily purified and stored as a room-temperature, shelf-stable crystalline solid. Release of **1** from the O-THP intermediate **5** can be carried out as needed to provide the more reactive final product. The individual steps are high yielding, highly reproducible and will have wide application for the preparation of polymeric materials and chelating agents based on monomer **1**.

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless otherwise noted. Dichloromethane (CH_2Cl_2) was dried over calcium hydride (CaH_2). Commercial reagents of high purity were purchased and used without further purification. Hydroxylamine, polymer bound on Wang resin, was obtained from NovaBiochem (Millipore Sigma, PN 8.55117; 1.9 mmol/g). Reactions were monitored by thin-layer chromatography (TLC) using TLC silica gel 60 Å 254 nm plates and visualizing with UV light or $KMnO_4$ stain. Silica gel (230–400 mesh) was used for flash column chromatography. IR spectra were obtained with a Thermo Nicolet Avatar 360 FTIR spectrophotometer. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300 or 500 (^{1}H) and 75 or 125 (^{13}C) MHz, respectively. ^{1}H NMR spectra were referenced to residual $CHCl_3$ (7.27 ppm) or DMSO-d_6 (2.54 ppm), ^{13}C NMR spectra were referenced to the center line of $CDCl_3$ (77.2 ppm) or DMSO (40.4 ppm). Coupling constants, *J*, are reported in Hz. Reverse-phase HPLC analysis was conducted with an Agilent 1100 system equipped with UV diode array and ELS detectors. A Zorbax XBD-C_{18} column was employed using gradient of 95% H_2O/5% CH_3CN to 95% CH_3CN over 6 min followed by a hold of 95% CH_3CN for 3 min. Mobile phase solvents were prepared from HPLC grade CH_3CN and H_2O containing 0.1% TFA.

O-Resin-Bound Acrylohydroxamic Acid (4)

A mixture of hydroxylamine Wang resin (NovaBiochem PN 8.55117; 0.53 g, 1.9 mmol/g, 1.0 mmol) in CH_2Cl_2 (10 mL) was prepared in a peptide reactor and agitated for 10 min. The resulting suspension was treated sequentially with triethylamine (0.35 mL, 0.253 g; 2.5 mmol) and acryloyl chloride (0.16 mL, 0.181 g, 2.0 mmol). The reaction was agitated for 2 h, filtered, and retreated with CH_2Cl_2 (10 mL), triethylamine (0.35 mL) and acryloyl chloride (0.16 mL). After agitation for 2 h, the mixture was filtered and washed sequentially three times each with CH_2Cl_2, MeOH, DMF, MeOH, and CH_2Cl_2. The resin was dried overnight in a vacuum oven at r.t. to afford **4** as an amber resin.

IR (ATR): 3026, 2920, 1751, 1698, 1612.

Treatment of resin **4** (94 mg) with a 1:1 mixture of $CDCl_3$ and TFA (1 mL) afforded direct cleavage of the products in an NMR compatible solvent. Analysis of the filtrate by ^{1}H NMR showed a mixture of products corresponding to acrylic acid and the desired acrylohydroxamic acid (**1**). Further attempts at chromatographic purification or crystallization led to a loss of product **1**.

N-(Tetrahydro-2*H*-pyran-2-yloxy)acrylamide (5)

To a solution of acrylic acid (0.72 g, 10 mmol) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (THP-ONH_2; 1.29 g (11.0 mmol) in CH_2Cl_2 (15 mL) cooled in an ice-water bath was added dropwise a solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC; 2.27 g, 11.0 mmol) in CH_2Cl_2 (20 mL). The addition rate was controlled to keep the reaction temperature below 5 °C. After stirring for 1 h, the reaction mixture was filtered through Celite and concentrated to give an oily, white solid. Recrystallization from CCl_4 (25 mL) afforded **5** (1.38 g, 80.6%) as a white, crystalline solid (mp 100–101 °C). Further purification by silica chromatography (50%, EtOAc/hexanes) gave the product.

Yield: 1.06 g (61.9%); white solid; mp 102.5–103 °C; HPLC (C_{18} reverse phase): t_R = 1.037 min (>98% by UV210 and 254); TLC: R_f = 0.71 (100% EtOAc).

IR (ATR): 3181 (NH), 2989, 2946, 1656 (C=O), 1626 cm^{-1}.

NMR data was obtained at 50 °C to overcome broad resonance peaks due to hindered rotation.

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C): δ = 9.25 (br s, 1 H), 6.36 (d, *J* = 16.8 Hz, 1 H), 6.20 (br s, 1 H), 5.66 (d, *J* = 10.9 Hz, 1 H), 4.95 (s, 1 H), 3.94 (t, *J* = 10.0 Hz, 1 H), 3.59 (m, 1 H), 1.78 (m, 3 H), 1.60 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$, 50 °C): δ = 164.6 (C=O, very br s), 127.6 (br s), 103.1, 63.0, 34.2, 28.4, 25.3, 19.0.

MS (FAB+): *m*/*z* (%) = 194 (40) [M + Na], 176 (40), 73 (100).

HRMS (FAB+): *m*/*z* calcd for $C_8H_{13}NO_3Na$: 194.0793; found: 194.0790.

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.39; H, 7.73; N, 8.16.

Acrylohydroxamic Acid (1)

To a solution of **4** (1.71 g) in MeOH (40 mL) was added *p*-toluenesulfonic acid monohydrate (TsOH·H_2O; 200 mg). After 90 min, the reaction was complete as determined by TLC [R_f = 0.40 (EtOAc)]. The mixture was concentrated at r.t. to give an oil, which was purified by chromatography (silica; EtOAc) to give **1**.

Yield: 0.51 g (58.6%); white solid; mp 83–84 °C.

IR (ATR): 3202 (NH), 3032, 2811, 1650 (C=O), 1596 (C=C), 1547, 1054, 969 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.82 (br s, 1 H), 9.08 (br s, 1 H), 6.14 (m, 2 H), 5.66 (dd, *J*=8.1, 3.6 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.2 (C=O), 129.7, 125.9.

MS (FAB+): *m*/*z* (%) = 219 (100) [M+Cs], 176 (40), 110 (30) [M + Na].

HRMS (FAB+): *m*/*z* calcd for $C_3H_5NO_2Cs$: 219.9375; found: 219.9375.

Anal. Calcd for $C_3H_5NO_2$: C, 41.38; H, 5.79; N, 16.09. Found: C, 41.58; H, 5.85; N, 16.03.

A sample for X-ray crystallography was prepared by room-temperature recrystallization. A solution of **1** in EtOAc was treated slowly with hexanes and allowed to crystallize over a period of 7 days to afford long needles of a white, crystalline solid (mp 83–84 °C). Spectral properties were identical to those of the previously obtained material. Crystal data: Monoclinic space group C2/c; *a* = 11.6765(9) Å, *b* = 8.7896(6) Å, *c* = 8.0357(5) Å, *β* = 100.178(5)°; *V* = 811.74(10) Å^3; *R*1 = 0.0471, *wR*2 = 0.136.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589103.

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