A New Method for the Preparation of Aliphatic Hydroxamic Acids; Reaction of Primary Nitroalkanes with Selenium Dioxide in the Presence of Triethylamine

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In 1978, Olah and coworkers reported the conversion of aldoximes to nitriles using sulfur dioxide/triethylamine and sulfur dioxide/trimethylamine complexes. Concurrently, we achieved the same transformation using selenium dioxide in the absence of amines. Subsequently, Olah et al. showed that sulfur dioxide/trialkylamine complexes can also be used to effect the conversion of primary nitroalkanes to nitriles in 74–78% yield.

Now we have found that the reaction of primary nitroalkanes 1 with selenium dioxide in the presence of triethylamine results, under certain conditions, in the formation of hydroxamic acids 2 in 63–76% yield (Table).

\[ R\text{-CH}_2\text{-NO}_2 + 2\text{H}_3\text{SeO}_2 / \text{CH}_2\text{Cl}_2 \rightarrow R\text{-CH}_2\text{-NHOH} \]

Only one other method has been reported for the direct conversion of primary nitroalkanes to hydroxamic acids, namely, the reaction of nitroalkanes 1, or their sodio derivatives, with concentrated sulfuric acid. However, this method suffers from low yields (28–45%) and a lack of selectivity and, therefore, has been primarily used for the preparation of the corresponding carboxylic acids.

In general, hydroxamic acids are prepared by the acylation of hydroxylamine with various acylating agents, such as carboxylic acid chlorides or ethyl esters. The latter method is more selective and, therefore, more frequently used. Though yields of 80–90% have been usually obtained in the case of aromatic hydroxamic acids, the yields of aliphatic hydroxamic acids vary widely, and range in the case of the lower members of the series, between 30 and 60% (Table).

The direct conversion of primary nitroalkanes to hydroxamic acids with selenium dioxide in the presence of triethylamine is dependent on the molar ratio of the reactants. Thus, it is important that a 1:1:2 ratio of nitroalkane : selenium dioxide : triethylamine is used. If the above ratio of reactants is changed to 1:2:2, a mixture of the hydroxamic acid and the corresponding nitrile 3 is obtained. A decrease of the quantity of triethylamine to a 1:1:1 ratio of the reactants also results in such a mixture. In the absence of triethylamine, no reaction occurs, and the nitroalkane is recovered unchanged.

By the present method, lower molecular weight primary nitroalkanes, which are commercially available, can be readily converted to the corresponding hydroxamic acids. In the case of nitromethane and nitroethane, it is essential to convert the corresponding hydroxamic acids into their copper complexes for purification and isolation. The free hydroxamic acids can then be recovered from the copper complex by reaction with hydrogen sulfide.
The mechanism of the reaction is currently not fully understood. However, on the basis of the results with variable molar ratios of reactants, it can be assumed that, for reaction to give hydroxamic acids, both a selenium dioxide/triethylamine complex and free triethylamine must be present. Although selenium dioxide/diethylamine complexes are unknown, selenium dioxide/triethylamine complexes were reported, and it is conceivable that the selenium dioxide/triethylamine complexes are simply too unstable for isolation. We propose the following mechanism for the formation of 2, involving a selenium dioxide/triethylamine complex and the free amine.

\[ R-\text{CH}_2\text{NO}_2 + \text{SeO}_2 \rightarrow R-\text{C}=\text{N}^\ominus + 2 \text{SeO}_2\text{Se}^\ominus \]

Scheme A

In the case of a comitant, but undesirable, nitrite formation, the following pathway might be invoked, in adaptation of the mechanism proposed by Olah and coworkers for the conversion of nitroalkanes to nitriles using sulfur dioxide/triethylamine complexes.

\[ R-\text{C}=\text{N}^\ominus + \text{Se}^\ominus \text{SeN} \text{Se}^\ominus \rightarrow R-\text{C}=\text{N} + \text{Se}^\ominus \text{SeN} \text{Se}^\ominus \]

Scheme B

In conclusion, we feel that the present method, because of its selectivity and good yields, provides a simple and efficient new route for the preparation of aliphatic hydroxamic acids which are difficult to obtain by conventional methods.

**Materials:** All reagents were of the best quality commercially available. Triethylamine, dichloromethane, nitromethane of 99% purity, and nitroethane of 98% purity were obtained from Aldrich Chemical Co. of Milwaukee, Wisconsin. 1-Nitropropane of 97% purity was obtained from Trudom Chemical Inc. of Hauptsuppe, New York. All of these reagents were used without purification. All other 1-nitroalkanes were prepared by a standard method with purity of at least 98% as determined by G.L.C. The selenium dioxide, of 99.4% purity, was obtained from the Vencron Corporation of Danvers, Maryland.

**Analytical Procedures:** All melting points and boiling points were measured using calibrated thermometers. All I.R. analyses were performed on a Perkin-Elmer Infracord Spectrophotometer, Model 137. 1-H-N.M.R. analyses were performed on a Varian T-60 NMR Spectrometer using TMS as internal standard (Table). The purity of 1-nitroalkanes was determined using an Aerograph A90-P3 gas chromatograph with a thermal conductivity detector. The following overall conditions were maintained: injector temperature, 225 °C; detector temperature, 255 °C; bridge current, 150 ma; sample size, 1.8 μl with the appropriate attenuations. The column used was 20% Carboxaw 20M on 60/80 mesh acid washed Chromosorb W, 6 ft by 0.25 in. Analyses were performed isothermally at 165 °C, with a flow rate of 40 ml of He/min. Identification of products were made by the comparison of retention time and peak enhancement ("spiking") with authentic samples. In all cases, the reactions were monitored by thin layer chromatography on pre-coated 0.2 mm Aluminum oxide "Polygram", Alox N/uv254 sheets (Brinkmann Instruments, Inc., Des Plaines, Illinois) using short-wave U.V. radiation for spot visualization. Benzene was used as an eluent in all cases. The 1-nitroalkanes typically had Rf values of 0.95 to 1.00, and the corresponding hydroxamic acids 0.75 to 0.95. Purification by column chromatography was performed on neutral aluminum oxide, activity I, according to Brockmann, eluent: benzene.

**Aliphatic Hydroxamic Acids 2a, b, General Procedure:** Method A: 1:1:2 mol ratio of 1-SeO₂ · (C₂H₅)₂NI.
A solution of the 1-nitroalkane 1 (0.02 mol) in dichloromethane (40 ml) is added dropwise with vigorous stirring at 0–5 °C under anhydrous conditions, to a suspension of selenium dioxide (2.22 g, 0.02

**Table. Preparation of Hydroxamic Acids 2 Using Selenium Dioxide and Triethylamine**

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<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>A</td>
<td>63</td>
<td>30⁰, 35⁰</td>
<td>81–82</td>
<td>CH₂NO₂</td>
<td>1620, 1650</td>
<td>8.05 (s, 1H); 9.20–10.30 (s, 2H)</td>
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<td></td>
<td></td>
<td>B</td>
<td>70</td>
<td>50⁰, 44⁰</td>
<td>91–92</td>
<td>CH₂NO₂</td>
<td>1625, 1660</td>
<td>1.72 (s, 3H); 9.22–9.92 (s, 2H)</td>
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<tr>
<td>2b</td>
<td>CH₃</td>
<td>A</td>
<td>66</td>
<td>60⁰, 45⁰</td>
<td>88–89</td>
<td>CH₂NO₂</td>
<td>1625, 1660</td>
<td>7.51 (s, 3H)</td>
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<tr>
<td></td>
<td></td>
<td>B</td>
<td>70</td>
<td>50⁰, 44⁰</td>
<td>91–92</td>
<td>CH₂NO₂</td>
<td>1625, 1660</td>
<td>1.0–1.22 (s, 3H); 9.52–2.5 (s, 2H); 8.5–9.5 (s, 1H); 10.6–10.85 (s, 1H)</td>
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<tr>
<td>2c</td>
<td>C₂H₅</td>
<td>A</td>
<td>66</td>
<td>60⁰, 44⁰</td>
<td>88–89</td>
<td>CH₂NO₂</td>
<td>1625, 1660</td>
<td>7.51 (s, 3H)</td>
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<td>B</td>
<td>70</td>
<td>50⁰, 44⁰</td>
<td>91–92</td>
<td>CH₂NO₂</td>
<td>1625, 1660</td>
<td>1.0–1.22 (s, 3H); 9.52–2.5 (s, 2H); 8.5–9.5 (s, 1H); 10.6–10.85 (s, 1H)</td>
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<tr>
<td>2d</td>
<td>n-C₃H₇</td>
<td>A</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1655</td>
<td>0.90–1.15 (s, 3H); 1.15–1.75 (s, 3H)</td>
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<td></td>
<td></td>
<td>B</td>
<td>72</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1660</td>
<td>2.0–2.25 (s, 2H); 6.0–6.0 (s, 2H)</td>
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<tr>
<td>2e</td>
<td>n-C₃H₇</td>
<td>A</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1655</td>
<td>0.90–1.15 (s, 3H); 1.15–1.75 (s, 3H)</td>
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<td></td>
<td></td>
<td>B</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1660</td>
<td>2.0–2.25 (s, 2H); 6.0–6.0 (s, 2H)</td>
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<tr>
<td>2f</td>
<td>n-C₃H₇</td>
<td>A</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1655</td>
<td>0.71–1.1 (s, 3H); 1.10–1.95 (m, 8H); 2.05–2.30 (s, 2H); 7.80–9.95 (s, 2H)</td>
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<td></td>
<td></td>
<td>B</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1655</td>
<td>0.71–1.1 (s, 3H); 1.10–1.95 (m, 8H); 2.05–2.30 (s, 2H); 7.80–9.95 (s, 2H)</td>
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<tr>
<td>2g</td>
<td>n-C₃H₇</td>
<td>A</td>
<td>73</td>
<td>10⁰, 28⁰</td>
<td>124–126</td>
<td>CH₃NO₂</td>
<td>1625, 1655</td>
<td>0.71–1.1 (s, 3H); 1.10–1.95 (m, 8H); 2.05–2.30 (s, 2H); 7.80–9.95 (s, 2H)</td>
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* Yield of pure, isolated product.

<sup>a</sup> Prepared by acylation of hydroxylamine with corresponding ester; values in brackets refer to preparation by reaction of nitroalkane 1 with sulfuric acid; no yields reported in Lit.⁰⁰.

<sup>b</sup> The microanalyses are in satisfactory agreement with the calculated values (C ± 0.29, H ± 0.26, N ± 0.22).
mol) in dichloromethane (40 ml). Triethylamine (4.08 g, 0.04 mol) is then added dropwise while the temperature is maintained at 0–10 °C. The mixture turns amber, then red in color within 10 min following the addition. The mixture is stirred at 20–22 °C for 30 min, then heated under reflux for 1 h, cooled to ambient temperature, and filtered through a packing of diatomaceous earth. The filtrate is concentrated on a rotating evaporator at 20–23 °C/12–15 torr. The product contains impurities even after two purifications by column chromatography. Final purification is achieved by dissolving the crude material in water (25 ml), then carefully adding a solution of copper(II) acetate monohydrate (3% w/w in water) until no more green precipitate is formed (~75 ml). The mixture is filtered, and the filter cake is washed with water (2 × 10 ml), methanol (1 × 10 ml), then dried in a vacuum desiccator for 4 d. The dried copper complex is suspended in methanol (25 ml), and anhydrous hydrogen sulfide is slowly introduced with external cooling of the reaction mixture in an ice/water bath. The green suspension turns black within 5 min. The introduction of hydrogen sulfide is maintained for an additional 5 min, following the appearance of the copper(II) sulfide. The suspension is filtered to remove the black precipitate of copper(II) sulfide, and the colorless filtrate is concentrated on a rotating evaporator at 20–22 °C/12–15 torr to give the pure hydroxamic acids 2a or 2b which solidify after cooling at 0 °C for 1–2 d (Table).

### Aliphatic Hydroxamic Acids 2e–g: General Procedure

**Method B**: 1:1, 2:1 mol ratio of 1-SeO₂/C₃H₄N₂H₄.

A solution of the 1-nitrosoane (1) (0.02 mol) in dichloromethane (40 ml) is added dropwise with vigorous stirring at 0–5 °C, under anhydrous conditions, to a suspension of selenium dioxide (2.22 g, 0.02 mol) in dichloromethane (40 ml). Triethylamine (4.08 g, 0.04 mol) is then added dropwise while the temperature is maintained at 0–10 °C. The mixture turns amber, then red in color within 10 min following the addition. The mixture is stirred at 20 °C for 30 min, heated under reflux for 1 h, then cooled to room temperature prior to addition of water (20 ml). The organic layer is separated and the aqueous layer is extracted with dichloromethane (2 × 20 ml). The combined organic layers are washed with water (1 × 20 ml), saturated sodium chloride solution (1 × 20 ml), then dried over anhydrous sodium sulfate. The mixture is filtered and the filtrate concentrated on a rotating evaporator at 20–23 °C/12–15 torr. Benzene (15 ml) is added, followed by zinc dust (1.0 g) in order to facilitate the remolecule of residual selenium dioxide. The mixture is heated under reflux for 10 min, then filtered through a packing of diatomaceous earth. The filtrate is purified by column chromatography on neutral aluminum oxide, activity I, according to Brockmann, to give the hydroxamic acids 2e-g, which solidify on cooling for 1–6 d (Table).

### Reaction of 1-Nitrosoate (1g) with Selenium Dioxide and Triethylamine using a 1:2:2 Mol Ratio

As described in Method B a solution of 1-nitrosoate (1g) (0.80 g, 0.005 mol) in dichloromethane (10 ml) is added dropwise with vigorous stirring at 0–5 °C under anhydrous conditions to a suspension of selenium dioxide (0.56 g, 0.005 mol) in dichloromethane. Triethylamine (0.51 g, 0.005 mol) is then added dropwise, while the temperature is maintained at 0–10 °C. The mixture turns amber, then red in color within 10 min following the addition. The mixture is stirred at 21–22 °C for 30 min, heated under reflux for 1 h, cooled to room temperature, and worked up as described previously. The crude material is chromatographed to give n-octanohydroxamic acid (2g); yield: 0.12 g (15%); m.p. 73–75 °C; lit.52; m.p. 74–75 °C, and a liquid which is distilled to give octanoic acid (3g); yield: 0.32 g (50%); b.p. 34–35 °C/0.02 torr; nD₂0: 1.4214; Lit.55; b.p. 206 °C/106 torr; nD₂0: 1.4203; and unreacted 1-nitrosoate (1g); yield: 0.17 g (21%); b.p. 54–56 °C/0.35 torr; nD₂0: 1.4223; Lit.54, b.p. 66 °C/10 torr; nD₂0: 1.4321.

### Reaction of 1-Nitrosoate (1g) with Selenium Dioxide and Triethylamine using a 1:1:1 Mol Ratio

As described in Method B, a solution of 1-nitrosoate (1g) (0.80 g, 0.005 mol) in dichloromethane (10 ml) is added dropwise with vigorous stirring at 0–5 °C under anhydrous conditions to a suspension of selenium dioxide (0.56 g, 0.005 mol) in dichloromethane. The mixture is stirred at 21–22 °C for 30 min, heated under reflux for 1 h, cooled to room temperature, and worked up as described previously. The crude material is chromatographed to give n-octanohydroxamic acid (2g); yield: 0.05 g (7%); m.p. 73–75 °C, and a liquid which is distilled to give octanoic acid (3g); yield: 0.13 g (20%); b.p. 34–35 °C/0.02 torr; nD₂0: 1.4213, and unreacted 1-nitrosoate (1g); yield: 0.40 g (49%); b.p. 54–56 °C/0.10 torr; nD₂0: 1.4322.

### Attempted Reaction of 1-Nitrosoate (1g) with Selenium Dioxide in the Absence of Triethylamine

As described in Method B, a solution of 1-nitrosoate (1g) (0.80 g, 0.005 mol) in dichloromethane (10 ml) is added dropwise with vigorous stirring, under anhydrous conditions, at 0–5 °C to a suspension of selenium dioxide (0.56 g, 0.005 mol) in dichloromethane (10 ml). The mixture is stirred at 20 °C for 30 min, then heated under reflux for 1 h. No color changes are observed. The mixture is cooled to room temperature and water (5 ml) is added. The organic layer is drawn off, and the aqueous layer is extracted with dichloromethane (2 × 5 ml). The combined organic layers are dried with anhydrous sodium sulfate, filtered, and concentrated on a rotating evaporator at 20–22 °C/12 torr. The resulting liquid is distilled to give 1-nitrosoate (1g); yield: 0.75 g (94% recovery); b.p. 53–55 °C/0.35 torr; nD₂0: 1.4324.

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16. B. Beilstein Handbuch der Organischen Chemie, Vol. II (1920); II. 1st supplement (1929); II. 2nd supplement (1942), Springer-Verlag Berlin.
J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe, A. Zugaza-Bilbao, Synthesis 1980 (7), 547–551. The substituent R in Table 1 entries 2 and 20 and Table 2, entry 1 should be: \( \text{N} - \text{N} - \text{CH}_3 \)

A more correct name for reagent 4 (as used in index) is 3,3'-[(Chlorophosphoryliden)-bis[2-oxo-1,3-oxazolidine].

J. Becher, Synthesis 1980 (8), 589–612; The structure of compound 36 (p. 593) should be:

C\(_2\)H\(_5\)O\(\text{O}^-\) \(\text{CH}_2^-\) \(\text{COOC}_2\)H\(_5\)

C\(_2\)H\(_2\)O\(\text{O}^+\)


G. Sosnovsky, J. A. Krogh, Synthesis 1980 (8), 654–656; The first line of the text should read: In 1978, Olah and Vankar reported the conversion of

D. A. Walsh, Synthesis 1980 (9), 677–688; The correct name for compound 39 (p. 680) is N-(2-Carboxyphenyl)-N,N-dimethylformamidine.

M. A. Smoczkiwicz, J. Jasiaczak, Synthesis 1980 (9), 739–740; Compounds 2 should be named as 20,21-dioxo derivatives; the name for compound 1a (p. 740, Table 1) should be 21-hydroxy-3,20-dioxopregna-4-ene.

Abstract 5878, Synthesis 1980 (9), 759; The title should be: Hydrofluorination, Halofluorination, and Nitrofluorination of Alkenes and Alkynes by Pyridinium Poly(Hydrogen Fluoride).

T. Wagner-Jauregg, Synthesis 1980 (10), 769–798; The name of compounds 52a and b (p. 772) should be cis- and trans-1-methyl-3-phenylindan.

The heading for Table 2 (p. 784) should be:

| Tabelle 2 | Herstellung von 1-Arylacenaphthen-Derivaten durch Photocyclisierung von 1-(1-Arylethenyl)-naphtalin-Derivaten in Abwesenheit von Oxidationsmitteln |

The structures of the products in this Table should be of the type:

The first paragraph on p. 785 (right-hand side) should read:

Ausz den konjugierten 1,2-Diiminen 667 und Phenyl-isocyanaten oder Benzoyl-isocyanat entstehen criss-cross-Addukte (668, Schema 2.2.1.-E)^441,444.

The last line on p. 794 should read:

und der Hydroxamsäuretetrais deutlich gesteigert563.

Reference 441 (p. 796) should be:


H. Alper, D. E. Laycock, Synthesis 1980 (10), 799; The last structure for R1 – R2 in the Table should be:

T. Takajo, S. Kambe, Synthesis 1980 (10), 833–836; Products designated as 4a,b,c,d in Table 1 (p. 834) and Table 2 (p. 835) should be designated as 4a,b,f,g, respectively.

P. Di Cesare, P. Dusausoy, B. Gross, Synthesis 1980 (11), 953–954; The first formula scheme (p. 954) should be:

R−OH \(\xrightarrow{\text{Ac}_2\text{O}, \text{pyridine}}\) R−O−C−CH\(_3\)

\(\text{FeCl}_3\), H\(_2\)O, 80°C

R−OH \(\xrightarrow{\text{Ac}_2\text{O}}\) R−O−C−CH\(_3\)

Z. H. Kudzin, W. J. Stec, Synthesis 1980 (12), 1032–1034; The heading for the first procedure (p. 1033) should be: 3-(Tris[t-butoxy]silylthio)-propanal [3, R = (t-C\(_3\)H\(_7\))\(_3\)Si].

R. E. Zipkin, N. R. Natale, I. M. Tafier, R. O. Hutchins, Synthesis 1980 (12), 1035–1036; The substituents R1 – R2 in the Table for product 4e should be:

\(-\text{(CH}_3\text{)}_2\text{C}−\text{C}−\text{(CH}_3\text{)}_2\text{CH}_3\)

Abstract 5948, Synthesis 1980 (12), 1040; Compounds 2 should be named carboximidium dichlorides.

Abstract 5963, Synthesis 1980 (12), 1045; The title should be: Acyl Fluorides, Chlorides, Bromides, and Iodides from Carboxylic Acids.

Abstract 5973, Synthesis 1980 (12), 1047; The title should be: Acetoxylation-Arylthlenylation of Alkenes.