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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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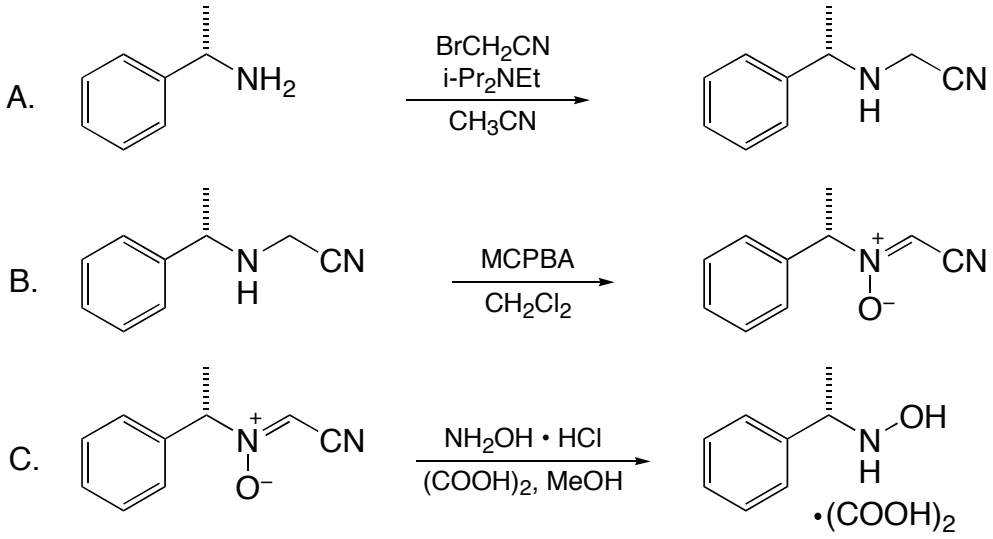
TRANSFORMATION OF PRIMARY AMINES TO *N*-MONOALKYLHYDROXYLAMINES: *N*-HYDROXY-(*S*)-1-PHENYLETHYLAMINE OXALATE

[(Benzenemethanamine, *N*-hydroxy-α-methyl-, (*S*)-, ethanedioate)]



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1. Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. ***1962****, 42, 50 (Org. Synth.* ***1973****, Coll. Vol. 5, 414). [Note added January 2011].*

A. (S)-[(1-Phenylethyl)amino]acetonitrile. A 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirrer bar, rubber septum and argon gas inlet is charged with (*S*)-1-phenylethylamine (10.17 g, 83.92 mmol) (Note 1), acetonitrile (MeCN) (170 mL) (Note 2), and diisopropylethylamine (*i*-Pr_2NEt) (29.2 mL, 168 mmol) (Note 3). After stirring the solution for 5 min, bromoacetonitrile (6.43 mL, 92.3 mmol) (Note 3) is added via syringe over 10 min. The reaction mixture is stirred at ambient temperature until completion of the reaction (Note 4). The mixture is then concentrated on a rotary evaporator to give a white solid, to which is added saturated aqueous sodium bicarbonate ($NaHCO_3$) solution (100 mL); the suspension is extracted with dichloromethane (CH_2Cl_2) (100 mL). The organic phase is washed with brine (100 mL), and the combined aqueous phases are back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a slightly yellow oil (21.6 g). To the crude oil

is added CH_2Cl_2 (10 mL) and the resulting solution is passed through a short column of silica gel (5 cm i. d. × 10 cm, 100 g of SiO_2) (Note 5). A forerun was obtained by elution with 400 mL of 9:1 hexanes:ethyl acetate, followed by collection of the desired fractions with 100 mL of 9:1 hexanes:ethyl acetate, then 700 mL of 7:3 hexanes:ethyl acetate (Note 6). Concentration of the appropriate fractions on a rotary evaporator and then under high vacuum gives (*S*)-[(1-phenylethyl)amino]acetonitrile as a colorless oil (13.62 g, 101%) (Note 7)

B. [(1S)-1-Phenylethyl]imino]acetonitrile N-oxide. A 1-L, three-necked flask equipped with a mechanical stirrer, argon gas inlet, and thermometer is charged with (*S*)-[(1-phenylethyl)amino]acetonitrile (10.34 g, 64.54 mmol) and CH_2Cl_2 (200 mL) (Note 8), and the resulting solution is cooled in an ice bath. *m*-Chloroperbenzoic acid (MCPBA) (ca. 77%, 34.3 g, 153 mmol) (Note 9) is added in portions over 30 min (Notes 10-12). After completion of the addition, the ice bath is removed and the mixture is stirred at ambient temperature. When the reaction is complete (Note 13), the mixture is cooled in an ice bath again, and aqueous sodium thiosulfate ($Na_2S_2O_3$) (16.0 g, 129 mmol, in 60 mL of H_2O) and saturated $NaHCO_3$ (200 mL) are added. The resulting slurry is stirred vigorously for 15 min until the white solid completely dissolves. The two-phase solution is separated using a separatory funnel. The aqueous phase is extracted with CH_2Cl_2 (100 mL). The organic layer is washed with brine (100 mL), and the combined aqueous phases are back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to afford crude nitrone (11.5 g) as slightly yellow crystals (Note 14).

C. N-Hydroxy-(S)-1-phenylethylamine oxalate. A 1-L, round-bottomed flask equipped with a reflux condenser, Teflon-coated magnetic stirrer bar, and argon gas inlet is charged with crude nitrone (11.5 g) and methanol (MeOH) (130 mL) (Note 15). After addition of hydroxylamine hydrochloride (20.8 g, 323 mmol) (Note 16) in one portion at ambient temperature, the mixture is warmed to 60 °C (55 °C internal) and is stirred at that temperature for 2 h (Note 17). The reaction mixture is cooled to room temperature and diluted with CH_2Cl_2 (260 mL). After stirring for 5 min, the resulting precipitate is collected by filtration and the filter cake is washed with CH_2Cl_2 (40 mL). The filtrate is neutralized with saturated $NaHCO_3$

(150 mL) and partitioned. The aqueous phase is extracted with CH_2Cl_2 (100 mL). The organic phase is washed with brine (100 mL), and the combined aqueous phases are back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts are dried over anhydrous sodium sulfate, filtered and concentrated to a minimum volume at a temperature below 25 °C (Note 18) under reduced pressure. To the residue is added a MeOH (25 mL) solution of oxalic acid (11.6 g, 129 mmol) (Note 19) and ether (Et_2O) (100 mL), precipitating white crystals, which are collected by filtration and washed with Et_2O (3 × 20 mL). After drying under reduced pressure, (*S*)-*N*-1- phenylethylhydroxylamine oxalate (12.6 g, 86% for two steps) is obtained as white crystals. The oxalate salt was recrystallized from hot ethanol (110 mL) and washed with Et_2O (50 mL) to provide analytically pure material (10.45, 71% for two steps) (Notes 20, 21). Concentration and recrystallization of the mother liquor provides additional (*S*)-*N*-1-phenylethylhydroxylamine oxalate (0.85 g, 6%).

2. Notes

1. (*S*)-1-Phenylethylamine was purchased from Aldrich Chemical Co., Inc. and used as received. The enantiomeric purity of (*S*)-1-phenylethylamine was determined as the dinitrobenzoyl derivative to be 95% ee using a chiral stationary phase HPLC column and a chiral stationary phase SFC column (see (Note 21)). The submitters used reverse phase CSP HPLC analysis for this purpose (Daicel CROWNPAK CR, aq. $HClO_4$ (pH 1.5), 0.8 mL/min, 25 °C, 210 nm).

2. Reagent grade acetonitrile was purchased from Fisher Scientific Co. and used as received.

3. Diisopropylethylamine and bromoacetonitrile were purchased from Aldrich Chemical Co., Inc. and used as received.

4. There is a slight exotherm (≈10 °C) over the first 30 min. The reaction typically takes 10-12 h to complete and was monitored by TLC analysis on Merck silica gel 60 F-254 plates eluting with isopropylamine:hexane:EtOAc (5:45:50), R_f = 0.68 (visualized with 254-nm UV lamp and ninhydrin spray).

5. Silica gel was purchased from Merck (40-100 mesh, spherical, neutral).

6. The submitters found that the crude product can be purified by distillation (110-120 °C, 1.5 mm). Starting from 24.3 g of amine, 21.8 g (68%) of the desired product was isolated. The reduced yield was due to dialkylation of the product with unreacted bromoacetonitrile during distillation.

7. While the product was sufficiently pure for the subsequent step, ^{1}H NMR analysis indicated the presence of 4 wt.% of bromoacetonitrile, which was absent after the Step B work-up. To secure analytically pure material, the checkers distilled chromatographically purified product to obtain 9.93 g (74%) of (*S*)-[(1-phenylethyl)-amino]acetonitrile. The pure product exhibits the following physical properties: bp 91-93 °C (1 mm); $[\alpha]_D^{27}$ −217 (c 1.23, $CHCl_3$), $[\alpha]_D^{23}$ −199.3 (c 1.08, EtOH), lit.[2] $[\alpha]_D^{25}$ −248.8 (c 4.7, benzene); IR (film) cm^{-1}: 3335, 2968, 2235, 1957, 1887, 1818, 1494, 1452, 1207, 1132, 870, 763; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (d, *J* = 6.4, 3 H), 1.67 (s (br), 1H), 3.28 (d, *J* = 17.6, 1 H), 3.58 (d, *J* = 17.6, 1 H), 4.04 (q, *J* = 6.5, 1 H), 7.26-7.34 (m, 5H); ^{13}C NMR (166 MHz, $CDCl_3$) δ: 23.9, 35.0, 56.7, 117.8, 126.9, 127.7, 128.7, 142.8. Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.94; H, 7.70; N, 17.32.

8. Reagent grade dichloromethane was purchased from Fisher Scientific Co. and used as received.

9. MCPBA (ca. 65%) was purchased from Aldrich Chemical Co., Inc. and used as received.

10. The reaction temperature was maintained below 7 °C.

11. Alternatively, conversion to the nitrone could be carried out with a catalytic amount of sodium tungstate and hydrogen peroxide[3] as described below: A 200-mL, round-bottomed flask equipped with a 30-mL, dropping funnel, Teflon-coated magnetic stirbar and argon gas inlet is charged with (*S*)-[(1-phenylethyl)amino]acetonitrile (6.10 g, 38.1 mmol), MeOH (64 mL), and sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) (504 mg, 1.53 mmol) in one portion. With cooling with an ice-bath, 30% aqueous hydrogen peroxide (14.7 mL, 153 mmol) is added to the solution over 20 min. The reaction mixture is then allowed to warm to ambient temperature. After TLC analysis shows completion of the reaction (usually 10 to 20 h), aqueous $Na_2S_2O_3$ (15 mL) is added slowly with cooling (ice-bath). The resulting suspension is

extracted with CH_2Cl_2 (100 mL). The organic extracts are washed with brine (100 mL), and the combined aqueous phases are back-extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts are dried over anhydrous sodium sulfate, filtered, and concentrated to dryness on a rotary evaporator to give crude nitrone (6.1 g) as a slightly yellow solid. The nitrone is directly converted to hydroxylamine oxalate without further purification (5.40 g, 62% yield for 2 steps). The enantiomeric purity of the hydroxylamine was shown to be >99% ee upon reduction with Zn/AcOH and derivatization (see (Note 21)).

12. Conversion to the nitrone could also be carried out with magnesium monoperoxyphthalate (MMPP)[4] as follows: A 1-L, three-necked, flask equipped with a 30-mL addition funnel, Teflon-coated magnetic stirbar, thermometer and argon gas inlet, is charged with an aqueous solution (153 mL) of magnesium monoperoxyphthalate hexahydrate (26.0 g, 80%, 42 mmol), which is then cooled in an ice-bath. A solution of (*S*)-[(1-phenylethyl)amino]acetonitrile (6.11 g, 38.1 mmol) in MeOH (30 mL) is subsequently added dropwise over a period of 20 min (the addition funnel is washed with 8 mL of MeOH). The resulting mixture is then stirred at ambient temperature for 30 min. After the reaction is complete, the mixture is cooled in an ice-bath and is diluted with CH_2Cl_2 (200 mL). With vigorous stirring, 4.8 g (19 mmol) of $Na_2S_2O_3 \cdot 5H_2O$ and 10 g (96 mmol) of sodium carbonate are added portionwise and the resulting two-phase mixture is partitioned. The aqueous phase is extracted with CH_2Cl_2 (100 mL). The organic phase is washed with brine (100 mL) and the combined aqueous layers are back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated to dryness on a rotary evaporator to give crude nitrone (6.4 g) as a slightly yellow solid. The nitrone is directly converted to hydroxylamine oxalate without further purification (7.51 g, 87% yield for 2 steps). The enantiomeric purity of the hydroxylamine was shown to be >99% ee upon reduction with Zn/AcOH and derivatization (see Note 21).

13. The reaction typically takes 30 min to complete. TLC analysis on Merck silica gel 60 F-254 plates eluting with MeOH:CH_2Cl_2 (2.5:97.5) shows formation of the (Z)-nitrone (R_f = 0.68) (visualized by a 254-nm UV lamp and ethanolic phosphomolybdic acid), with only a trace amount of the (E)-nitrone (R_f = 0.73).

14. Judging by ^{1}H NMR analysis, the crude product is highly pure (Z)-nitrone (92/8, Z/E), which can be used for the next step. Recrystallization from EtOAc-hexane affords pure (Z)-nitrone, which exhibits the following physical properties: mp 89.5-91.0; $[\alpha]_D^{28}$ +83 (c 0.494, $CHCl_3$), $[\alpha]_D^{23}$ +135.8 (c 0.995, EtOH); IR (KBr) cm^{-1}: 3098, 2222, 1541, 1452, 1442, 1377, 1295, 1181, 1074, 1007, 748, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.83 (d, *J* = 7.0, 3 H), 5.18 (quint, *J* = 6.9, 1 H), 6.67 (s, 1 H), 7.43 (br s, 5 H); ^{13}C NMR (166 MHz, $CDCl_3$) δ: 19.0, 79.5, 105.8, 112.2, 128.9, 129.2, 129.8, 136.2. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.83; H, 5.68; N, 15.90.

15. Reagent grade MeOH was purchased from Aldrich Chemical Co., Inc. and used as received.

16. Hydroxylamine hydrochloride was purchased from Aldrich Chemical Co., Inc. and used as received.

17. *Caution! The reaction should be carried out in a well-ventilated hood because of the potential of generating HCN gas.*

18. Care must be exercised not to allow the bath temperature to rise above 25 °C and not to concentrate the solution to complete dryness, both of which would increase the risk of explosion of the hydroxylamine. The checkers found that some of the hydroxylamine would precipitate, resulting in a white slurry that would dissolve upon addition of the next reagent.

19. Oxalic acid was purchased from Aldrich Chemical Co., Inc. and used as received. The checkers found that sonication was helpful in dissolving the oxalic acid in MeOH.

20. The pure product exhibits the following physical properties: mp 177-180 °C (dec.); $[\alpha]_D^{28}$ −2.2 (c 1.06, MeOH); IR (KBr) cm^{-1}: 3220, 2987, 2578, 1761, 1610, 1483, 1458, 1210, 986, 961, 775, 714, 702; ^{1}H NMR (500 MHz, CD_3OD) δ: 1.68 (d, *J* = 6.8, 3 H), 4.52 (q, *J* = 6.9, 1 H), 7.39-7.50 (m, 5 H); ^{13}C NMR (166 MHz, CD_3OD) δ: 16.1, 62.9, 129.9, 130.1, 130.6, 136.0, 166.4. Anal. Calcd for $C_8H_{11}NO\cdot(COOH)_2$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.72; H, 5.68; N, 6.18.

21. The enantiomeric excess of the product was determined by reduction with Zn in AcOH, followed by derivatization with 3,5-dinitrobenzoyl chloride. (*S*)-*N*-1-Phenylethylhydroxylamine oxalate (0.50 g, 2.20 mmol) was placed in a 50-mL, single-necked, round-bottomed flask equipped with an argon inlet, rubber septum, and Teflon-coated stirbar,

followed by acetic acid (AcOH) (glacial, 6 mL), HCl (1M, 12 mL), and Zn dust (5 g). The slurry was heated to 80 °C for 6 h, during which time the Zn began to conglomerate. The reaction mixture was cooled to room temperature and filtered through glass wool. The Zn metal was washed with H_2O (10 mL) and CH_2Cl_2 (20 mL) and the filtrate was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 (40 mL) and 1M NaOH (40 mL). The organic phase was washed with H_2O (20 mL) and brine (20 mL). The combined aqueous phases were back-extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, dried over magnesium sulfate, and concentrated to give crude amine. Bulb-to-bulb distillation of the amine [150 °C (air bath temp), 100 mm] provided (*S*)-1-phenylethylamine (0.21 g, 78%). In a 25-mL, two-necked, round-bottomed flask, with an argon inlet, septum, and Teflon-coated stirbar, was placed (*S*)-1-phenylethylamine (0.18 g, 1.5 mmol) and THF (6 mL). The solution was cooled in an ice bath to 0 °C; triethylamine (0.3 mL, 2.2 mmol) and subsequently 3,5-dinitrobenzoyl chloride (0.38 g, 1.7 mmol) were added. The ice bath was removed and the solution was stirred for 2.5 h at ambient temperature, during which time the solution turned yellow and a white precipitate formed. The slurry was then partitioned between H_2O (15 mL) and Et_2O (15 mL). The organic phase was separated, then washed with brine (10 mL). The combined aqueous phases were back-extracted with Et_2O (10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude amide was purified by column chromatography (30 mm × 150 mm SiO_2, hexane/EtOAc, 4/1→2/1) to provide (*S*)-*N*-(3,5-dinitrobenzoyl)-1-phenylethylamine (0.47 g, 99%). The enantiomeric purity of the derivative was shown to be >99% ee by chiral stationary phase HPLC and SFC. (HPLC: Pirkle S-N1N-Naphthylleucine column, hexane/*i*-PrOH, 3/21 mL/min, t_R 16.54 min (R isomer: t_R = 14.22 min), SFC: Chiralcel OD column, 20% MeOH, 2 mL/min, t_R = 9.136 (R isomer: 8.539 min). The submitters used reverse phase CSP HPLC for this analysis (see Note 1).

Waste Disposal Information

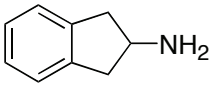
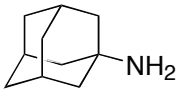
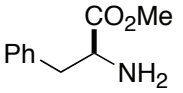
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Although *N*-monoalkylhydroxylamines are important precursors for *N*-hydroxyl-α-amino acid and hydroxamic acids,[5] there are few practical and general methods for the preparation of this class of compounds.[6] Direct oxidation of primary amines with hydrogen peroxide or MCPBA is generally ineffective, often leading to over-oxidation products. A widely used method for the conversion of primary amines to hydroxylamines employs oxidation of the corresponding Schiff bases, although the intermediacy of relatively acid-labile Schiff bases is one of its disadvantages.[7]

The present procedure provides a novel protocol for transformation of primary amines to *N*-monoalkylhydroxylamines in a three-step sequence involving selective mono-cyanomethylation, regioselective nitrone formation using MCPBA, and hydroxylaminolysis.[8] The procedure in Step A is representative of selective mono-cyanomethylation. Depending upon the steric bulk of the alkyl substituents, three conditions can be employed to achieve selective mono-cyanomethylation (Table 1). Since cyanomethylated amines are relatively stable, they can be used as reliable precursors for hydroxylamines. The procedure in Step B illustrates the regioselective formation of nitrone. The significance of the cyano group in directing the formation of nitrones was also demonstrated by the successful application of this method to a wide variety of substrates including α-aminoester derivatives[7b,7d,9] (Table 1). For the conversion of nitrones to hydroxylamines (Step C), we have modified the literature procedure.[7] The use of excess hydroxylamine hydrochloride at higher temperature reduced the reaction time and improved the yields. One of the advantages of the present procedure is that the oxime by-product generated after hydroxylaminolysis, namely NC-CH=NOH, can be easily removed by aqueous extraction.

Table 1

Entry	Amine	Cyanomethylation[a]			Overall Yield (%) of Hydroxylamine from Cyanomethylated Amine
		Conditions	time (h)	Yield (%)	
1	$PhCH_2NH_2$	A	24	95	82
2	$PhCH_2CH_2NH_2$	A	24	96	75
3	$PhCH_2CH_2CH_2NH_2$	A	24	93	74
4		B[b,c]	22	97	79
5	Ph_2CHNH_2	B	15	98	55
6		C	1	89	76
7	$BnO_2CCH_2NH_2$	B[d]	18	91	62
8		B[b,e]	26	92	61

[a]Conditions A. $ClCH_2CN$ (1.5 eq), K_2CO_3 (2.0 eq), CH_3CN, 60°C; Conditions B. $BrCH_2CN$ (1.5) eq), *i*-Pr_2NEt (2.0 eq), CH_3CN, rt; Conditions C. ICH_2CN (2 eq), K_2CO_3 (2.5 eq), DMF, rt.
[b]HCl salt of amine was used.
[c]$BrCH_2CN$ (1.3 eq), *i*-Pr_2NEt (3.0 eq).
[d]$BrCH_2CN$ (1.2 eq), *i*-Pr_2NEt (2.0 eq).
[e]$BrCH_2CN$ (2.0 eq), *i*-Pr_2NEt (3.0 eq).

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*S*)-1-Phenylethylamine: Benzenemethanamine, α-methyl-, (α*S*)- (9); (2627-86-3)

Diisopropylethylamine: 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)- (9); (7087-68-5)

Bromoacetonitrile; Acetonitrile, bromo- (8, 9); (590-17-0)

(*S*)-[(1-Phenylethyl)amino]acetonitrile; Acetonitrile, [[(1*S*)-1-phenylethyl]amino]-, (9); (35341-76-5)

m-Chloroperbenzoic acid: Benzenecarboperoxoic acid, 3-chloro- (9); (937-14-4)

[(1*S*)-1-Phenylethyl]imino]acetonitrile *N*-oxide; Acetonitrile, [oxido[(1*S*)-1-phenylethyl]-imino]-, (9); (300843-73-6)

Hydroxylamine hydrochloride: Hydroxylamine, hydrochloride (8,9); (5470-11-1)

Oxalic acid: Ethanedioic acid (9); (144-62-7)

N-Hydroxy-(*S*)-1-phenylethylamine oxalate; Benzenemethanamine, *N*-hydroxy-α-methyl-, (α*S*)-, ethanedioate (1:1) salt, (9); (78798-33-1)