A New Reagent for the Syntheses of *N*-Monoalkylated Hydroxylamines; *N*-Tosyl-*O*-2,4,6-trimethylbenzylhydroxylamine

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The reactions of *N*-tosyl-*O*-2,4,6-trimethylbenzylhydroxylamine with primary alkyl halides yielded the protected hydroxylamines. The simultaneous cleavage of *N*-tosyl- and *O*-2,4,6-trimethylbenzyl groups with hydrogen bromide in acetic acid gave the corresponding *N*-monoalkylated hydroxylamines such as *N*-benzylhydroxylamine, 1-amino-3-hydroxyaminopropane and DL-3-hydroxyamino-2-aminopropionic acid.

Syntheses of naturally-occurring hydroxylamines,[1] which exist as hydroxamates or *N*-nitroso derivatives, have been accomplished using various methods including method A to E;

Method A: Zinc dust reduction of nitro group[2] in aqueous solution containing ammonium chloride.

Method B: Acid hydrolysis or hydrazinolysis of nitrone,[3] which is obtainable by the reaction of alkyl halides or acrylic acid derivatives with the appropriate aldoxime in the presence of base.

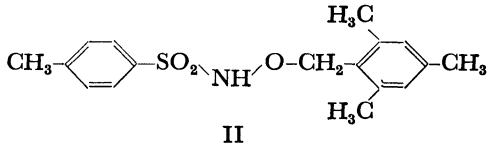
Method C: Direct conversion of alkyl halides[4] by hydroxylamine itself in the absence or presence of solvents.

Method D: Reduction of oxime.[5]

Method E: Hydrolysis of oxazirane,[6] which is obtained by the oxidation of Schiff's base.

In our previous papers, *N*-tosyl-*O*-benzylhydroxylamine (I) has been used for the syntheses of alanosine,[7] 5-*N*-hydroxy-L-ornithine,[8] rhodotorulic acid,[9] and ferrichrome.[10] The *N*-protecting tosyl group of I is always deprotected by the action of 36% hydrogen bromide in acetic acid, while the *O*-protecting benzyl group, after the *N*-acylation, is deblocked by the hydrogenation. In some cases,[8] *N*-tosyl and *O*-benzyl groups may be removed simultaneously by the treatment with 36% hydrogen bromide–acetic acid after long days, but in almost all cases, benzyl group remained intact with the action of this reagent.

In this paper, we describe a new reagent for the syntheses of *N*-monosubstituted hydroxylamines; *N*-tosyl-*O*-2,4,6-trimethylbenzylhydroxylamine (II). 2,4,6-Trimethylbenzyl group has been used for the first time by Stewart[11] for the masking of carboxyl groups in the peptide chemistry and is known to be acid-sensitive.



II

The reagent (II) was prepared according to the procedure[8] for the analogue (I); the tosylation of *O*-2,4,6-trimethylbenzylhydroxylamine, which was prepared by the 2,4,6-trimethylbenzylation of *N*-carboethoxyhydroxylamine and the subsequent alkaline hydrolysis, afforded II. Using this reagent, *N*-benzylhydroxylamine (III), 1-amino-3-hydroxyaminopropane (IV), and DL-3-hydroxyamino-2-aminopropionic acid (DL-V) were synthesized.

Synthesis of N-*Benzylhydroxylamine (III) and the Conditions of the Removal of the Protecting Groups.* Reaction of benzyl chloride and II in the presence of sodium methoxide gave *N*-benzyl-*N*-tosyl-*O*-2,4,6-trimethylbenzylhydroxylamine (VI).

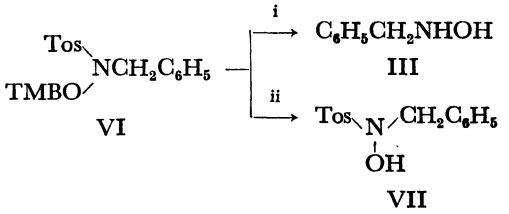


Fig. 1. Tos: tosyl, TMB: 2,4,6-trimethylbenzyl.
i: hydrogen bromide–acetic acid
ii: trifluoroacetic acid

The treatment of VI with 36% hydrogen bromide-acetic acid in the presence of phenol gave III. 18% Hydrogen bromide–acetic acid was also effective for the simultaneous removal of the two protecting groups. The use of trifluoroacetic acid as a deprotecting agent gave another result; only the 2,4,6-trimethylbenzyl group was removed and the *N*-tosyl group remained intact. The product was *N*-benzyl-*N*-tosylhydroxylamine, whose structure was determined by the elemental analysis, IR, and NMR spectra. Absorption of *N*-hydroxy group of VII appeared at 3360 cm^{-1} in IR and δ 10.19 in NMR.

Synthesis of 1-Amino-3-hydroxyaminopropane (IV). 1-Amino-3-hydroxyaminopropane (IV) is a component of schizokinen, an iron-transport compound from *Bacillus megaterium* and was synthesized by Neilands *et al.*[2a] by method A. The higher analogues of IV, 1-amino-4-hydroxyaminobutane[2c] and 1-amino-5-hydroxyaminopentane,[2d,e] were also synthesized previously by the same method. Condensation of 3-bromopropylphthalimide and II in the presence of sodium methoxide gave 1-phthalimido-3-(*N*-tosyl-*N*-2,4,6-trimethylbenzyloxy)aminopropane (VIII). VIII was converted by the action of hydrazine hydrate to 1-amino-3-(*N*-tosyl-*N*-2,4,6-trimethylbenzyloxy)aminopropane (IX), which was identified as the hydrochloride. The action of 36% hydrogen bromide-acetic acid on IX gave IV as the di-hydrobromide.

Synthesis of DL-*3-Hydroxyamino-2-aminopropionic Acid (DL-V).* First synthesis[4c,d] of DL-V was achieved by method C; condensation of methyl L- or DL-3-chloro-2-acetaminopropionate (X) with hydroxylamine in the absence of solvents and the subsequent acid

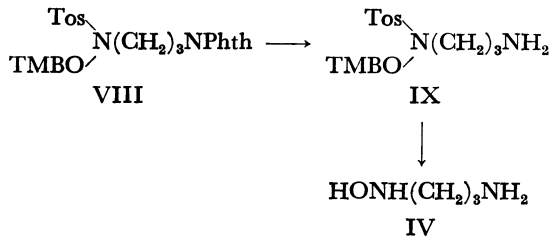


Fig. 2. Phth: phthalyl

hydrolysis gave DL-V. In recent years, improved synthesis[3g] of DL-V using method B was reported; the reaction of X with *anti*-benzaldoxime and the subsequent acid hydrolysis gave DL-V in excellent yield.

The higher homologues of DL-V, 5-*N*-hydroxy-DL-ornithine[2b,3e,f,4d] and 6-*N*-hydroxy-DL-lysine,[2b,3e,4d] were obtained by method A, B, or C.

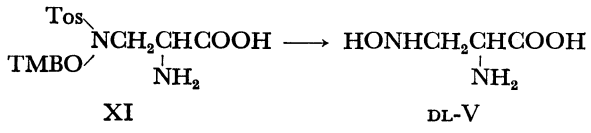


Fig. 3.

DL-2-Amino-3-(*N*-tosyl-*N*-2,4,6-trimethylbenzyloxy)-aminopropionic acid (XI) was synthesized, according to the procedure[7] for DL-2-amino-3-(*N*-tosyl-*N*-benzyloxy)aminopropionic acid, from ethyl 2,3-dibromopropionate and II as the starting materials. The protected amino-hydroxyamino acid (XI) was converted to DL-V by the treatment with 36% hydrogen bromide-acetic acid in the presence of phenol at room temperature.

Experimental

Melting points were determined with a Yanagimoto electric micromelting point apparatus, unless otherwise indicated and are uncorrected. Infrared spectra were recorded on a Hitachi EPI G-3 spectrophotometer as KBr disk. Nuclear magnetic resonance spectra were run on a Hitachi Perkin-Elmer R-20 High Resolution spectrometer, using tetramethylsilane as an internal standard.

N-*Carboethoxy*-O-*2,4,6-trimethylbenzylhydroxylamine.* To an ice-cooled solution of *N*-carboethoxyhydroxylamine (23.1 g, 0.22 mol) in methanol (50 ml) was added a solution of potassium hydroxide (12.3 g, 0.22 mol) in methanol (50 ml). After stirring for 30 min, 2,4,6-trimethylbenzyl chloride (33.7 g, 0.2 mol) in methanol (50 ml) was added at room temperature and the mixture was refluxed for 1 hr. The precipitated potassium chloride was removed and the filtrate was evaporated *in vacuo*. Ether (150 ml) and water (50 ml) were added. The organic layer was separated and dried. After evaporation of the solvent, the residue was distilled to give a pure product. Yield, 25.5 g (53.8%); bp 148—153 °C/0.9 mmHg.

Found: C, 65.40; H, 7.78%. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07%.

O-*2,4,6-Trimethylbenzylhydroxylamine.* A mixture of *N*-carboethoxy-*O*-2,4,6-trimethylbenzylhydroxylamine (47.5 g, 0.2 mol) and potassium hydroxide (45 g, 0.8 mol) in water (200 ml) was refluxed for 5 hr. After 12 hr, the crystallized substance was collected and washed with water. Yield, 23.6 g (70.6%). Recrystallization from ether–petroleum ether gave an analytical sample, mp 54—55 °C.

Found: C, 72.51; H, 8.95; N, 8.23%. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48%.

N-*Tosyl*-O-*2,4,6-trimethylbenzylhydroxylamine (II).* To an ice-cooled solution of *O*-2,4,6-trimethylbenzylhydroxylamine (16.5 g, 0.1 mol) in pyridine (80 ml) was added a solution of tosyl chloride (19.2 g, 0.101 mol) in pyridine (60 ml). Stirring was continued for another 5 hr at room temperature and then the solvent was evaporated *in vacuo*. Ethyl acetate (150 ml) was added to the residue and washed successively with 1M hydrochloric acid and water. The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give crystals. Yield, 26.8 g (84%); mp 132—134 °C. Recrystallization from ether–petroleum ether gave an analytical sample, mp 135—136 °C.

Found: C, 63.85; H, 6.67; N, 4.32%. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39%.

N-*Benzyl*-N-*tosyl*-O-*2,4,6-trimethylbenzylhydroxylamine (VI).* To a stirred solution of sodium (1.2 g) in methanol (150 ml) were added II (14.8 g, 40 mmol) and benzyl chloride (6.3 g, 50 mmol) and then the mixture was refluxed for 3 hr. The deposited crystals were collected and washed successively with water and ether. Yield, 12.8 g (78.1%); mp 128—131 °C. Recrystallization from ethanol gave an analytical sample, mp 129—131 °C.

Found: C, 70.22; H, 6.64; N, 3.38%. Calcd for $C_{24}H_{27}NO_3S$: C, 70.38; H, 6.65; N, 3.42%.

N-*Benzylhydroxylamine (III).* *a*): A solution of VI (1.64 g, 4 mmol) in 36% hydrogen bromide–acetic acid (10 ml) containing phenol (1.5 g) was stirred for 20 hr and then concentrated *in vacuo*. To the residual oil was added ether (30 ml) and water (10 ml). The aqueous layer was separated, concentrated to a small volume, and adjusted to pH 8 with solid sodium carbonate. The crystals were collected, after the solution was stored in an ice box for 12 hr. Yield, 0.24 g (49%); mp 56—56.5 °C (lit,[1a] mp 57 or 58 °C). Recrystallization from petroleum ether unchanged the mp. Triphenyltetrazolium test was positive. IR: 3255 and 3150 cm^{-1}.

b): III was also obtained from VI by the treatment with 18% hydrogen bromide- acetic acid. Yield, 32.7%.

N-*Benzyl*-N-*tosylhydroxylamine (VII).* A solution of VI (0.82 g, 2 mmol) in trifluoroacetic acid (5 ml) containing phenol (0.4 g) was stirred at room temperature for 20 hr. The deposits were collected. Yield, 0.43 g (79.5%); mp 171—173 °C. Recrystallization from ethanol gave an analytical sample, mp 175—177 °C. This compound gave negative ferric chloride and triphenyltetrazolium tests. IR: 3375, 1595, 1380 and 1170 cm^{-1}. NMR (d_6-DMSO): δ 2.45 (s, 3H), 4.02 (s, 2H), 7.33, 7.50 and 7.84 (9H), and 10.18 (s, 1H).

Found: C, 60.58; H, 5.45; N, 5.00%. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05%.

*1-Phthalimido-3-(*N-*tosyl*-N-*2,4,6-trimethylbenzyloxy)aminopropane (VIII).* To a stirred solution of sodium (1.38 g, 60 mmol) in methanol (150 ml) were added 3-bromopropylphthalimide (13.4 g, 50 mmol) and II (15.95 g, 50 mmol). The mixture was refluxed for 3 hr and concentrated *in vacuo*. To the residue, water (50 ml) and ether (50 ml) were added and the mixture was stirred for 5 hr. Then crystals were collected, dried and recrystallized from *n*-propyl alcohol. Yield, 17.2 g (68.0%); mp 139—140 °C.

Found: C, 66.32; H, 6.17; N, 5.27%. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53%.

*1-Amino-3-(*N-*tosyl*-N-*2,4,6-trimethylbenzyloxy)aminopropane (IX).* A suspension of VIII (2.53 g, 5 mmol) in ethanol (130 ml) was warmed at 60—65 °C. To the resultant solution, hydrazine hydrate (2.5 g, 50 mmol) was added.

After stirring for 6 hr at 60—65 °C, the mixture was adjusted to pH 5 with acetic acid and the precipitates were filtered off. The filtrate was concentrated *in vacuo* and water (50 ml) was added. Insoluble substance was removed and the filtrate was extracted with ethyl acetate (50 ml). The aqueous layer was evaporated. To the residual oil, ethanol (20 ml) was added and evaporated. This operation was repeated three times and finally water (30 ml) was added. The solution was adjusted to pH 8 with 7% aq. ammonia and extracted with ethyl acetate (50 ml×2). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to give IX quantitatively as a colorless oil. IX was characterized as the monohydrochloride monohydrate. Recrystallization from methanol–ether gave an analytical sample. mp 99—102 °C.

Found: C, 55.87; H, 7.27; N, 6.50%. Calcd for $C_{20}H_{28}N_2O_3S \cdot HCl \cdot H_2O$: C, 55.73; H, 7.25; N, 6.50%.

1-Amino-3-hydroxyaminopropane Dihydrobromide (IV·2HBr). To the crude oil (IX), which was obtained from VIII (5 mmol) as described above, phenol (2 g) and 36% hydrogen bromide-acetic acid (10 ml) were added. After stirring for 24 hr at room temperature, dry ether (150 ml) was added. The deposited crystals were collected and washed with dry ether. Yield, 1.13 g (90%). Recrystallization from methanol–ether gave an analytical sample, mp 157—159 °C. Triphenyltetrazolium test was positive.

Found: C, 14.77; H, 5.02; N, 10.97%. Calcd for $C_3H_{12}N_2OBr_2$: C, 14.30; H, 4.80; N, 11.12%.

Ethyl 2-Bromo-3-(N-tosyl-N-2,4,6-trimethylbenzyloxy)aminopropionate. To a solution of sodium (2.8 g) in ethanol (500 ml) was added II (31.9 g, 0.1 mol). Then ethyl 2,3-dibromopropionate (29 g, 0.11 mol) was added dropwise at room temperature. After stirring for 12 hr, the deposited crystals were collected and washed with water. Yield, 18 g. The filtrate was concentrated *in vacuo* to a small volume to give 12 g of a second crop. Total yield, 30 g (60%). Recrystallization from ethanol gave an analytical sample, mp 98—99 °C. IR: 1740 cm^{-1}.

Found: Br, 15.65%. Calcd for $C_{22}H_{28}NO_5SBr$: Br, 16.03%.

2-Bromo-3-(N-tosyl-N-2,4,6-trimethylbenzyloxy)aminopropionic Acid. To a solution of the ester (12.5 g, 25 mmol), obtained as described above, in acetone (300 ml) was added M sodium hydroxide (40 ml) and the mixture was stirred at room temperature. After 72 hr, the solution was adjusted to pH 4 with M citric acid and then concentrated *in vacuo*. Ethyl acetate (300 ml) and water (100 ml) were added to the residue and the organic layer was dried over sodium sulfate. The solvent was removed to give a crystalline product. Yield, 8.1 g (69%). Recrystallization from carbon tetrachloride gave an analytical sample, mp 168—170 °C. IR: 1700 cm^{-1}.

Found: Br, 16.93%. Calcd for $C_{20}H_{24}NO_5SBr$: Br, 16.99%.

DL-*2-Amino-3-(N-tosyl-N-2,4,6-trimethylbenzyloxy)aminopropionic Acid (XI).* A solution of the bromide (9.4 g, 20 mmol), obtained as described above, in concd. aq. ammonia (500 ml) was stored at room temperature for 10 days and then concentrated *in vacuo* to a small volume. After acidified with acetic acid to pH 4, the crystals were collected and washed successively with water, hot methanol and water. Yield, 5.3 g (65%); mp 189—191 °C (decomp.).

Found: C, 58.97; H, 6.47; N, 6.84%. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89%.

DL-*2-Amino-3-hydroxyaminopropionic Acid* (DL-*V*). A solution of XI (1.02 g, 2.5 mmol) in 36% hydrogen bromide–acetic acid (5 ml) containing phenol (1 g) was stirred at room temperature. After 45 hr, dry ether (70 ml) was added. The deposits were collected and dissolved in water. The aqueous solution was extracted with ether and concentrated *in vacuo*. The residue redissolved in a small quantity of water was adjusted to pH 8 with 7% aq. ammonia and ethanol was added until the solution was cloudy. The precipitated crystals were collected, after the solution was stirred in an ice box for 12 hr. Yield, 0.17 g (56.7%). Recrystallization from water–ethanol gave an analytical sample, mp 167—168 °C (decomp.) in an open capillary in a liquid bath (lit. mp 163—165 °C (decomp.)[4c,d] 180—181 °C (decomp.)[4g]). Triphenyltetrazolium test was positive. IR: 3275, 3250, 1635, 1585, and 1525 cm^{-1}.

Found: C, 29.97; H, 6.57; N, 22.91%. Calcd for $C_3H_8N_2O_3$: C, 30.00; H, 6.71; N, 23.33%.

Bibliography and Footnotes

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