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O-Arenesulfonyl-*N*-alkylhydroxylamines as Aminating Reagents

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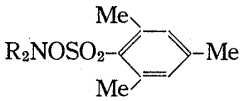
O-(*p*-Toluenesulfonyl)-*N*-methyl-, -*N*-ethyl-, and -*N*-isopropyl-hydroxylamines and *O*-mesitylenesulfonyl-*N*-methylhydroxylamine were prepared. The *N*-methyl and *N*-ethyl derivatives were found to react with tertiary amines and triphenylphosphine to give the corresponding *N*-(alkylamino)ammonium salts and *P*-(alkylamino)phosphonium salts, but the *N*-isopropyl derivative was less reactive, probably due to steric effects. These reagents also reacted with tri-*n*-butylborane to give the corresponding alkyl-*n*-butylamines.

Keywords——electrophilic aminating reagent; *tert*-butoxycarbonylation; di-*tert*-butyl dicarbonate; *N*-(methylamino)ammonium salts; *P*-(methylamino)triphenylphosphonium salt; *N*-(methylamino)pyridinium salt; secondary amines

O-Mesitylenesulfonylhydroxylamine (MSH) (**1**)[1] and *O*-mesitylenesulfonyl-*N*,*N*-dialkylhydroxylamines (**2**)[2] are well known aminating reagents. It therefore seemed of interest to prepare *O*-arenesulfonyl-*N*-alkylhydroxylamines (**12**—**14**) and examine their chemical properties.



1: R=H
2: R=Me, Et

Chart 1

The synthetic route used for the preparation of **12**—**14** is essentially the same as that reported for *O*-2,4-dinitrophenyl-*N*-methylhydroxylamine,[3] and is illustrated in Chart 2. *tert*-Butoxycarbonylation of *N*-methylhydroxylamine hydrochloride (**3**) with di-*tert*-butyl dicarbonate[4] in the presence of potassium carbonate gave *N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine (**6**) in 86% yield. Treatment of **6** with *p*-toluenesulfonyl chloride in methylene chloride in the presence of triethylamine afforded **9a** in 75% yield. Hydrolysis of **9a** with trifluoroacetic acid gave **12a** in 97% yield. In a similar manner, *O*-(*p*-toluenesulfonyl)-*N*-ethyl- (**13**) and -*N*-isopropyl-hydroxylamines (**14**) were prepared. These compounds could be recrystallized from hot *n*-hexane but decomposed gradually at room temperature [stable at −10°C for several weeks]. The *O*-mesitylenesulfonyl derivative **12b** was also prepared and

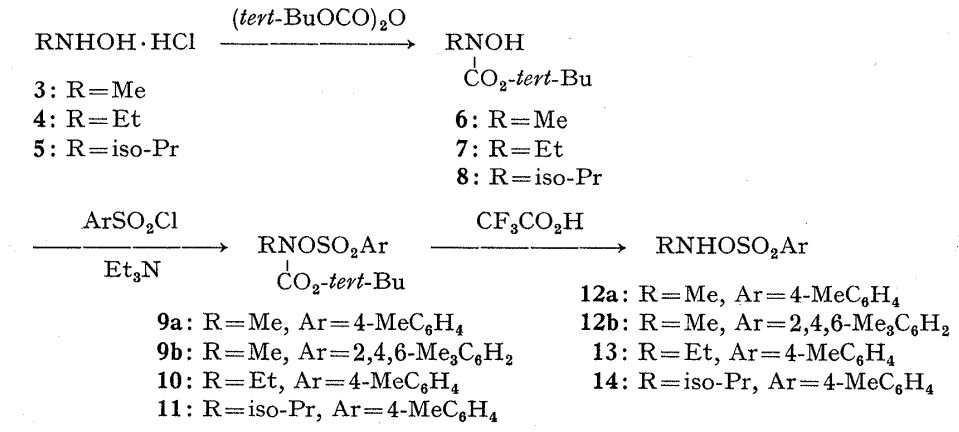
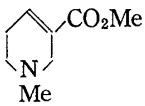
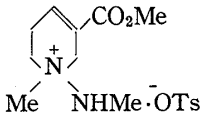
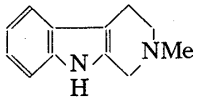
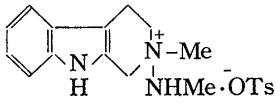
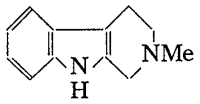
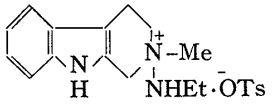
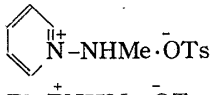


Chart 2

was found to be stable at room temperature, but its chemical properties were not further examined due to the low overall yield in the preparation of **12b.**

Compound **12a** was found to react with tertiary amines and triphenylphosphine in methylene chloride at room temperature to give the corresponding *N*-(methylamino)ammonium salts and *P*-(methylamino)phosphonium salt. The *N*-ethyl derivative **13** showed reactivity similar to that of **12a** but the *N*-isopropyl derivative **14** was much less reactive. The results are summarized in Table I. These reactions are extremely sensitive to electronic and steric effects of the attacking nucleophiles. Thus, an aromatic amine, *N*,*N*-dimethylaniline gave a low yield of the *N*-aminated product and tertiary amines possessing an α-branch, such as nicotine, tropine, and securinine, which are known to undergo ready amination with **1**,[1] failed to react with **12a**. The reaction of pyridine with **12a** gave the *N*-(methylamino)pyridinium

Table I. Reactions of **12**—**14** with Tertiary Amines, Triphenylphosphine, and Tri-*n*-butylborane

Substrate	Reagent	Product	Yield (%)	mp, °C (recrystd from)	Formula	Analysis (%) Calcd (Found) C	H	N
n-Bu_3N	**12a**	n-$Bu_3\overset{+}{N}NHMe\cdot\overset{-}{O}Ts$	84	109—110 (EtOH–Et_2O)	$C_{20}H_{38}N_2O_3S$	62.14 (61.80	9.91 9.90	7.25 7.07)
$Me(CH_2)_{11}NMe_2$	**12a**	$Me(CH_2)_{11}\overset{+}{N}(NHMe)Me_2\cdot\overset{-}{O}Ts$	84	110.5—112 (CH_2Cl_2–Et_2O)	$C_{22}H_{42}N_2O_3S$	63.73 (63.50	10.21 10.22	6.76 6.79)
$C_6H_{11}NMe_2$	**12a**	$C_6H_{11}\overset{+}{N}(NHMe)Me_2\cdot\overset{-}{O}Ts$	70	143.5—144.5 ($CHCl_2$–Et_2O)	$C_{16}H_{28}N_2O_3S$	58.51 (58.08	8.59 8.67	8.53 8.46)
$PhNMe_2$	**12a**	$Ph\overset{+}{N}(NHMe)Me_2\cdot\overset{-}{O}Ts$	40	[a]				
	**12a**		94	121—122 (CH_2Cl_2–Et_2O)	$C_{16}H_{24}N_2O_5S$	53.92 (53.77	6.79 6.79	7.86 7.97)
	**12a**		92	156—158 (EtOH–Et_2O)	$C_{20}H_{25}N_3O_3S$	61.99 (61.86	6.50 6.60	10.84 10.72)
	**13**		92	191.5—192.5 (EtOH)	$C_{21}H_{27}N_3O_3S$	62.81 (62.94	6.79 6.88	10.47 10.42)
	**12a**		14	[b]				
Ph_3P	**12a**	$Ph_3\overset{+}{P}NHMe\cdot\overset{-}{O}Ts$	72	177.5—178.5 (CH_2Cl_2–Et_2O)	$C_{26}H_{26}NO_3PS$	67.36 (67.26	5.65 5.63	3.02 3.08)
Ph_3P	**13**	$Ph_3\overset{+}{P}NHEt\cdot\overset{-}{O}Ts$	80	118—119.5 (CH_2Cl_2–Et_2O)	$C_{27}H_{28}NO_3PS$	67.91 (68.01	5.91 6.04	2.93 3.08)
Ph_3P	**14**	$Ph_3\overset{+}{P}NH\text{-}i\text{-}Pr\cdot\overset{-}{O}Ts$	39	151.5—152.5 ($CHCl_3$–Et_2O)	$C_{28}H_{30}NO_3PS$	68.40 (68.26	6.16 6.10	2.85 3.09)
n-Bu_3B	**12a**	n-BuNHMe	52	[c]				
n-Bu_3B	**13**	n-BuNHEt	77	[d]				
n-Bu_3B	**14**	n-BuNH-i-Pr	47	[e]				

[a] Isolated and characterized as its picrate, mp 163—164°C (dec.) (from EtOH) (*Anal.* Calcd for $C_{15}H_{17}N_5O_7$: C, 47.50; H, 4.52; N, 18.46. Found: C, 47.55; H, 4.47; N, 18.23).
[b] Isolated as its picrate, mp 148—150°C [lit. mp 148—149°C: T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *J. Pharm. Soc. Japan*, **83**, 308 (1963)].
[c] Characterized as its picrate, mp 111—113°C (lit. mp 111—112°C: J. Graymore, *J. Chem. Soc.*, **1932**, 1355).
[d] Characterized as its hydrochloride, mp 196—198°C [lit. mp 197°C: K.N. Campbell, A.H. Sommers, and B.K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944)].
[e] Characterized as its hydrochloride, mp 194—196°C [lit. mp 195—196°C: K.N. Campbell, A.H. Sommers, and B.K. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

salt in only 14% yield,[5] and some typical heteroaromatic amines such as 2-methylpyridine, isoquinoline, and 1-methylimidazole did not react with **12a**. An attempt to aminate diethyl sulfide, diphenyl sulfide, and allyl phenyl sulfide was also unsuccessful.

In comparison with **1**, the reactivity of **12**—**14** towards nucleophiles is considerably lowered. This can be attributed to the electron-donating effect and steric interference of the *N*-alkyl substituents of **12**—**14**.

We have also examined the reactions of **12**—**14** with some electrophiles. Thus, **12a** did not react with benzaldehyde or *N*-propylidenecyclohexylamine but underwent a ready reaction with tri-*n*-butylborane to give *n*-butylmethylamine.[6] The reaction of **13** and **14** with tri-*n*-butylborane gave the corresponding secondary amines (see Table I).

Experimental[7]

General Procedure for the Preparation of *N*-*tert*-Butoxycarbonyl-*N*-alkylhydroxylamines (6—8)——To an ice-cooled solution of an *N*-alkylhydroxylamine hydrochloride (3—5) (0.1 mol) in 50% aqueous tetrahydrofuran (40 ml) was added powdered K_2CO_3 (7.25 g, 0.055 mol), followed by a solution of di-*tert*-butyl dicarbonate (24.0 g, 0.11 mol) in tetrahydrofuran (30 ml). The mixture was stirred at 0°C for 2 h and room temperature for 3 h, then tetrahydrofuran was removed under reduced pressure and the residue was dissolved in methylene chloride. The solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by distillation.

N-*tert*-Butoxycarbonyl-*N*-methylhydroxylamine (**6**) (86%) has bp 60—65°C/3 mmHg (lit. bp 50—50.5 °C/0.3 mmHg[8a] and 91°C/17 mmHg[8b]). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3250, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9, *tert*-Bu), 1.90 (br s, 1, OH), 3.15 (s, 3, NMe).

N-*tert*-Butoxycarbonyl-*N*-ethylhydroxylamine (**7**) (83%) has bp 60—61°C/0.7 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1680. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (t, 3, J=7 Hz, $CH_2C\underline{H}_3$), 1.48 (s, 9, *tert*-Bu), 3.48 (q, 2, J=7 Hz, $C\underline{H}_2CH_3$), 5.1 (br s, 1, OH).

N-*tert*-Butoxycarbonyl-*N*-isopropylhydroxylamine (**8**) (58%) has bp 68—69°C/1.5 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3240, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.18 [d, 6, J=7 Hz, $CH(C\underline{H}_3)_2$], 1.47 (s, 9, *tert*-Bu), 4.14 [septet, 1, J=7 Hz, $C\underline{H}(CH_3)_2$], 6.7 (br s, 1, OH).

General Procedure for the Preparation of *O*-Arenesulfonyl-*N*-*tert*-butoxycarbonyl-*N*-alkylhydroxylamines (9—11)——An *N*-*tert*-butoxycarbonyl-*N*-alkylhydroxylamine (3 mmol) and triethylamine (3 mmol) were dissolved in $CHCl_3$ (15 ml). The solution was cooled to −10——5°C and a solution of *p*-toluenesulfonyl chloride (572 mg, 3 mmol) or mesitylenesulfonyl chloride (656 mg, 3 mmol) in $CHCl_3$ (5 ml) was added dropwise. The resulting mixture was allowed to come to room temperature and stirred for 3 h. The mixture was washed with water, aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated. The residue was crystallized from *n*-hexane.

O-(*p*-Toluenesulfonyl)-*N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine (**9a**) (86%) has mp 51—52°C (from *n*-hexane). IR ν_{max}^{KCl} cm^{-1}: 1710, 1370, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (s, 9, *tert*-Bu), 2.46 (s, 3, toluene ring Me), 3.24 (s, 3, NMe), 7.30, 7.83 (both d, 2 each, J=8.5 Hz, toluene ring protons). *Anal.* Calcd for $C_{13}H_{19}NO_5S$: C, 51.81; H, 6.35; N, 4.65. Found: C, 51.69; H, 6.42; N, 4.78.

O-Mesitylenesulfonyl-*N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine (**9b**) (44%) has mp 67—69°C (from *n*-hexane). IR ν_{max}^{KCl} cm^{-1}: 1730, 1365, 1145. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (s, 9, *tert*-Bu), 2.32 (s, 3, mesitylene ring Me), 2.66 (s, 6, mesitylene ring Me), 3.24 (s, 3, NMe), 6.99 (s, 2, mesitylene ring protons). *Anal.* Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.36; H, 7.11; N, 4.24.

O-(*p*-Toluenesulfonyl)-*N*-*tert*-butoxycarbonyl-*N*-ethylhydroxylamine (**10**) (81%) has mp 78—79°C (from petroleum ether). IR ν_{max}^{KCl} cm^{-1}: 1705, 1370, 1140. ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, 3, J=7 Hz, $CH_2C\underline{H}_3$), 1.22 (s, 9, *tert*-Bu), 2.45 (s, 3, toluene ring Me), 3.64 (q, 2, J=7 Hz, $C\underline{H}_2CH_3$), 7.29, 7.81 (both d, 2 each, J=J=8 Hz, toluene ring protons). *Anal.* Calcd for $C_{14}H_{21}NO_5S$: C, 53.31; H, 6.72; N, 4.44. Found: C, 53.44; H, 6.87; N, 4.65.

O-(*p*-Toluenesulfonyl)-*N*-*tert*-butoxycarbonyl-*N*-isopropylhydroxylamine (**11**) (39%) has mp 47.5—48.5°C (from petroleum ether). IR ν_{max}^{KCl} cm^{-1}: 1750, 1360, 1150. ^{1}H-NMR ($CDCl_3$) δ 1.20 [d, 6, J=7 Hz, $CH(C\underline{H}_3)_2$], 1.29 (s, 9, *tert*-Bu), 2.46 (s, 3, toluene ring Me), 4.11 (septet, 1, J=7 Hz, $C\underline{H}(CH_3)_2$], 7.30, 7.84 (both d, 2 each, J=8 Hz, toluene ring protons). *Anal.* Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25. Found: C, 54.57; H, 7.15; N, 4.23.

General Procedure for the Preparation of *O*-Arenesulfonyl-*N*-alkylhydroxylamines (12—14)——Trifluoroacetic acid (1.5 ml) was added dropwise to an ice-cooled solution of **9**—**11** (1 mmol) in methylene chloride (1 ml), and the mixture was stirred at 0°C for 3 h. The reaction mixture was poured into ice-water and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and concentrated.

O-(*p*-Toluenesulfonyl)-*N*-methylhydroxylamine (**12a**) (97%) has mp 54—55°C (from *n*-hexane). IR ν_{max}^{KCl} cm^{-1}: 3270, 1350, 1170. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (s, 3, toluene ring Me), 2.73 (s, 3, NMe), 5.72 (s, 1,

NH), 7.30, 7.81 (both d, 2 each, $J=8.5$ Hz, toluene ring protons). MS *m/e*: 201 (M^+). *Anal.* Calcd for $C_8H_{11}NO_3S$: C, 47.75; H, 5.51; N, 6.96. Found: C, 47.57; H, 5.53; N, 7.05.

O-Mesitylenesulfonyl-*N*-methylhydroxylamine (**12b**) (99%) has mp 82—83°C (from *n*-hexane). IR ν_{max}^{KCl} cm^{-1}: 3260, 1350, 1170. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, 3, mesitylene ring Me), 2.5—3.0 (br, 1, NH), 2.64 (s, 6, mesitylene ring Me), 2.76 (s, 3, NMe), 6.99 (s, 2, mesitylene ring protons). *Anal.* Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.61; N, 6.11. Found: C, 52.17; H, 6.72; N, 6.13.

O-(*p*-Toluenesulfonyl)-*N*-ethylhydroxylamine (**13**) (76%) has mp 28—30°C (from *n*-hexane). IR $\nu_{max}^{liq.\ film}$ cm^{-1}: 3260, 1360, 1170. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.42 (s, 3, toluene ring Me), 2.95 (q, 2, $J=7$ Hz, $C\underline{H}_2CH_3$), 5.21 (br s, 1, NH), 7.24, 7.74 (both d, 2 each, $J=8$ Hz, toluene ring protons). Analysis was carried out by high-resolution mass spectrometry: Calcd for $C_9H_{13}NO_3S$, *m/e* 215.0613; found, *m/e* 215.0597.

O-(*p*-Toluenesulfonyl)-*N*-isopropylhydroxylamine (**14**) (81%) has mp 68—70°C (from *n*-hexane). IR ν_{max}^{KCl} cm^{-1}: 3250, 1350, 1170. ^{1}H-NMR ($CDCl_3$) δ: 0.93 [d, 6, $J=7$ Hz, $CH(C\underline{H}_3)_2$], 2.42 (s, 3, toluene ring Me), 3.18 [septet, 1, $J=7$ Hz, $C\underline{H}(CH_3)_2$], 3.72 (s, 1, NH), 7.23, 7.76 (both d, 2 each, $J=8$ Hz, toluene rign protons). *Anal.* Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 51.99; H, 6.56; N, 6.17.

General Procedure for the Reaction of 12—14 with Some Nucleophiles——A mixture of a tertiary amine or phosphine (0.5 mmol) and **12**—**14** (0.5 mmol) in methylene chloride was allowed to stand at room temperature overnight. The reaction mixture was concentrated and triturated with ether. The solid was collected and recrystallized. The results are summarized in Table I.

General Procedure for the Reaction of 12—14 with Tri-*n*-butylborane——To an ice-cooled solution (1 ml) of 1 M tri-*n*-butylborane in tetrahydrofuran was added a solution of **12**—**14** (1.1 mmol) in tetrahydrofuran (2 ml) with stirring under an argon atmosphere. After being stirred at room temperature for 2 h, the reaction mixture was acidified with dilute HCl and washed with ether. The aqueous layer was made alkaline with aqueous potassium hydroxide and extracted with ether. The extract was dried ($MgSO_4$) and treated with picric acid or hydrogen chloride to give the picrate or hydrochloride. The results are summarized in Table I.

References and Notes

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6) For the amination of organoboranes; see C.F. Lane, "Synthetic Reagents," Vol. 3, J.S. Pizey, Ed. Ellis Horwood, Chichester, 1977, p. 1.
7) Melting points are uncorrected. NMR spectra were determined with a Hitachi R-20A spectrometer (60 MHz), using tetramethylsilane as an internal standard. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. High resolution mass spectra were obtained with a JMS-D-300 instrument with a direct inlet system at 70 eV.
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