Reaction of *N*-Aroyl-*N*-*t*-butylhydroxylamines with Thionyl Chloride. Synthesis of Substituted Benzohydroximoyl Chlorides

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Synopsis. The reaction of *N*-benzoyl-*N*-*t*-butylhydroxylamine with thionyl chloride in carbon tetrachloride gave *O*-chlorosulfinylbenzohydroximoyl chloride as the main product. On treating with ethanol, the compound gave benzohydroximoyl chloride in good yield. The reaction was applied to the synthesis of substituted benzohydroximoyl chlorides.

We have previously shown that *N*-[2-(methylthio)-benzoyl]-*N*-alkylhydroxylamines gave 2-substituted 1,2-benzisothiazol-3(2*H*)-ones in good yields on treating with thionyl chloride and pyridine.[1] In the course of our study on the reaction of the hydroxylamine derivatives, the reaction of *N*-benzoyl-*N*-*t*-butylhydroxylamine with thionyl chloride was found to give benzohydroximoyl chloride in good yield. Benzohydroximoyl chloride and its derivatives have been exensively used for the synthesis of heterocyclic compounds as precursors of benzonitrile oxides.[2] We wish to report here an efficient method for the synthesis of substituted benzohydroximoyl chlorides.

Results and Discussion

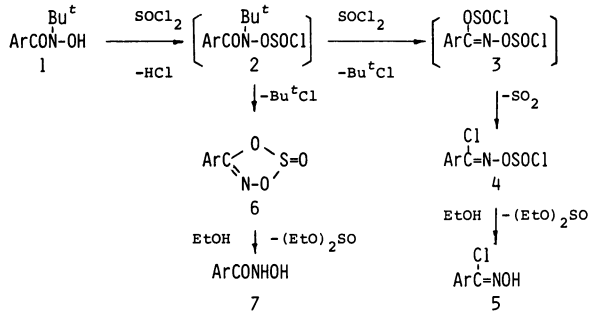
N-Aroyl-*N*-*t*-butylhydroxylamines (**1**) were prepared by hydrolysis of *N*-aroyl-*O*-benzoyl-*N*-*t*-butylhydroxylamines with sodium hydroxide in methanol, as reported previously.[3] The reaction of **1** with thionyl chloride was carried out at −30 °C. A detailed product analysis was performed for the reaction of **1a** with thionyl chloride in carbon tetrachloride. After removal of the solvent and the excess thionyl chloride, the IR spectrum of the reaction product showed the characteristic bands of *O*-chlorosulfinylbenzohydroximoyl chloride (**4a**) together with weak bands at 1770 cm^{-1} and 1330 cm^{-1}. On treating with ethanol, the product gave benzohydroximoyl chloride (**5a**) (78%), benzohydroxamic acid (**7a**) (8%) ethyl benzoate (**8a**) (4%), and diethyl sulfite. The results suggest that the reaction product is a mixture of **4a**, 5-phenyl-1,3,2,4-dioxathiazole 2-oxide (**6a**), and benzoyl chloride. *t*-Butyl chloride was detected by ^{1}H-NMR spectrum of the reaction mixture. Chloride **4a** was difficult to isolate from the reaction mixture, because **4a** was sensitive to heat and moisture. The compound **4a** and **6a**[4] were prepared by the reactions of **5a** and **7a** with thionyl chloride, respectively, and the reactions of **4a** were examined. On heating of **4a** in boiling toluene, benzonitrile was formed in 82% yield. When **4a** was treated with aqueous acetone, benzohydroximoyl chloride was obtained in 90% yield. On treating **4a** with ethanol, **5a** and diethyl sulfite were formed in 90 and 70% yields, respectively.

The reaction of **1a** with thionyl chloride was carried out in various solvents, and the reaction mixture was treated with ethanol. Benzohyxroximoyl chloride (**5a**) was obtained as the main product, together with small amounts of **7a**, **8a**, and diethyl sulfite. No significant difference was observed in the yields of **5a**, except for the reaction in acetonitrile. When the reaction of **1a** with thionyl chloride was carried out in acetonitrile, **5a** and **7a** were formed in 20 and 45% yields, respectively after treatment of the reaction mixture with ethanol. Ethyl phenylcarbamate (**9a**) and 3-phenyl-5-methyl-1,2,4-oxadiazole (**10a**) were also obtained in 9 and 27% yields, respectively, by the reaction in acetonitrile.

Similarly, the reaction of *N*-aroyl-*N*-*t*-butylhydroxylamines (**1b—h**) with thionyl chloride in carbon tetrachloride gave *m*- and *p*-substituted benzohydroximoyl chlorides (**5b—h**) after treatment with ethanol. The results are summarized in Table 1. On the other hand, *N*-(*o*-methoxybenzoyl)-*N*-*t*-butylhydroxylamine (**1i**) and *N*-(*o*-chlorobenzoyl)-*N*-*t*-butylhydroxylamine (**1j**) did not give the corresponding benzohydroximoyl chlorides under the same reaction conditions.

Although benzohydroximoyl chlorides are usually prepared by chlorination of benzaldehyde oximes,[5-8] *p*-methoxybenzohydroximoyl chloride is difficult to obtain by chlorination of *p*-methoxybenzaldehyde oxime. In the chlorination, the strong electron-donating substituent facilitates chlorination on the aromatic ring, giving a mixture of chlorinated products.[9,10] As given in Table 1, the present reaction is successfully applied to the synthesis of *m*- and *p*-substituted benzohydroximoyl chlorides bearing both electron-donating and electron-withdrawing substituents. In addition, the present method is useful for the synthesis of **5e**, which has a sulfide group which is usually oxidized during the chlorination.

The most probable mechanism for the present reaction is shown in Scheme 1. The reaction proceeds through intermediates, *N*-aroyl-*O*-chlorosulfinyl-*N*-*t*-



Scheme 1.

Table 1. Yields of substituted benzohydroximoyl chlorides

Substrate		Solvent	Product	Yield[a]	Mp θ_m/°C
1	Ar			%	
1a	C_6H_5	CCl_4	**5a**	78	51—52 (lit,[5] 48—52)
1a		CH_2Cl_2	**5a**	66	
1a		CS_2	**5a**	78	
1a		C_6H_6[b]	**5a**	77	
1a		Hexane	**5a**	66	
1a		CH_3CN	**5a**	20[c]	
1b	*p*-$CH_3C_6H_4$	CCl_4	**5b**	66	71—72 (lit,[6] 68—69)
1c	*p*-$CH_3OC_6H_4$	CCl_4	**5c**	62	88—89 (lit,[9] 88—89)
1d	*m*-$CH_3OC_6H_4$	CCl_4	**5d**	88	66—67
1e	*p*-$CH_3SC_6H_4$	CCl_4	**5e**	73	91.5—92.5
1f	*p*-ClC_6H_4	CCl_4	**5f**	88	91.5—92.5 (lit,[7] 88.5—89.5)
1g	*m*-ClC_6H_4	CCl_4	**5g**	74	68—69 (lit,[7] 69—70)
1h	*p*-$NO_2C_6H_4$	CCl_4[d]	**5h**	87	125.5—126.5 (lit,[7] 124—125)

a) Isolated yields. b) The reaction was carried out at 5 °C for 5 h and allowed to stand overnight. c) Compounds **7a**, **8a**, and **10a** were obtained in 45, 9, and 27% yields, respectively. d) The reaction was carried out at 25 °C for 15 h.

butylhydroxylamines (**2**), and bis(chlorosulfinyl) compound (**3**). The intermediates **2** and **3** are transformed to **6** and **4** by the subsequent eliminations of *t*-butyl chloride and sulfur dioxide, respectively. In the reaction of **1** with thionyl chloride in acetonitrile, oxadiazole **10** would be formed by cycloaddition of acetonitrile and benzonitrile oxides.

Experimental

Preparation of N-*Aroyl*-N-*t*-*butylhydroxylamines (1).* *N*-Aroyl-*N*-*t*-butylhydroxylamines (**1**) were prepared by hydrolysis of the corresponding *N*-aroyl-*O*-benzoyl-*N*-*t*-butylhydroxylamines with sodium hydroxide in methanol, as reported previously.[3]

Reaction of N-*Aroyl*-N-*t*-*butylhydroxylamines (1) with Thionyl Chloride.* A typical run was as follows: Thionyl chloride (10 g, 84 mmol) was added to a stirred mixture of *N*-benzoyl-*N*-*t*-butylhydroxylamine (**1a**) (1.932 g, 10 mmol) and carbon tetrachloride (30 cm³) at −30 °C. The mixture was stirred at −30 °C for 5 h, and allowed to stand overnight at room temperature. The solvent and excess thionyl chloride were evaporated under reduced pressure. Ethanol (10 cm³) was added to the residue, and the mixture was stirred at room temperature for 2 h. After removal of the ethanol, the residue was separated by column chromatography on silica gel, using dichloromethane and ethyl acetate as the eluents. The fractions obtained by dichloromethane as the eluent gave **5a** (1.218 g, 78%) and **8a** (0.062 g, 4%). Benzohydroxamic acid (**7a**) (0.110 g, 8%) was obtained with the chromatography with ethyl acetate as the eluent. Similarly, the reaction of **1b—h** with thionyl chloride gave **5b—h**. **5d**; Found: C, 51.78; H, 4.24; N, 7.54%. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55%. **5e**; Found: C, 47.64; H, 3.84; N, 6.87%. Calcd for C_8H_8ClNOS: C, 47.64; H, 4.00; N, 6.95%.

Preparation of O-Chlorosulfinylbenzohydroximoyl Chloride (4a). Thionyl chloride (5.0 g, 42 mmol) was added to a solution of benzohydroximoyl chloride (1.555 g, 10 mmol) in dichloromethane (30 cm³) and the mixture was allowed to stand overnight. Removal of the solvent and excess thionyl chloride *in vacuo* gave *O*-chlorosulfinylbenzohydroximoyl chloride (**4a**) (2.303 g, 97%) as a colorless oil. IR (neat) 1590, 1580, 1240, 880, 760, 690, and 600 cm⁻¹.

Preparation of 5-Phenyl-1,3,2,4-dioxathiazole 2-oxide (6a). A mixture of benzohydroxamic acid (**7a**) (2.742 g, 20 mmol) and thionyl chloride (10 g, 84 mmol) in dichloromethane (30 cm³) was allowed to stand for 6 h at 30 °C. The excess thionyl chloride and the solvent were evaporated under reduced pressure to give (**6a**) (3.554 g, 97%). IR (neat) 1605, 1325, 1240, 1060, 850, and 720 cm⁻¹.

Thermal Decomposition of 4a A solution of **4a** (0.246 g, 1.03 mmol) in toluene (10 cm³) was refluxed for 4 h. The products were analyzed by GLC.

Hydrolysis of 4a. A solution of **4a** (0.463 g, 1.95 mmol) in acetone (8 cm³) and water (2 cm³) was allowed to stand overnight. After evaporation of acetone, the residue was extracted with diethyl ether. The extract was washed with water and dried over anhydrous calcium chloride. Removal of the ether gave **5a** (0.272 g, 90%).

Alcoholysis of 4a. A solution of **4a** (0.463 g, 1.95 mmol) in ethanol (10 cm³) was allowed to stand for 2 h. The reaction mixture was subjected to GLC analysis, and the remainder was chromatographed on silica gel to isolate the products. Diethyl sulfite (70%, GLC) and **5a** (0.272 g, 90%) were obtained.

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