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Direct Conversion of Sulfinic Acid to Sulfonic Acid Derivatives

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The reaction of sulfinic acid (**1**) with methanol in the presence of NCS-DMS gave methyl sulfinate (**2**) and methyl sulfonate (**3**) in 22% and 45% yields, respectively. Similarly, **1** reacted with morpholine under the same conditions to give the corresponding sulfinamide (**5**) and sulfonamide (**6**) in 23% and 50% yields. In these reactions, the disulfone (**4**) was also obtained as a minor product in some cases. The formation of sulfonic acid derivatives and disulfone was found to proceed through the intermediate formation of the sulfonyl chloride (**7**). The formation mechanism of sulfinic acid derivatives is also discussed.

Keywords——sulfinyl transfer; reaction in the presence of NCS–DMS; reaction mechanism; chloro cation; sulfinic acid; sulfinic acid derivative; sulfonic acid derivative; disulfone; chloramine-T

We recently reported new and convenient one-step syntheses of sulfinic acid derivatives, which involved direct sulfinyl transfer of nucleophiles, such as alcohols and amines, with sulfinic acids by using coupling reagents, such as dicyclohexylcarbodiimide,[1,2)] diethyl azobiscarboxylate and triphenylphosphine,[1,2)] 1-methyl-2-chloropyridinium iodide,[1-3)] and γ-succharine chloride.[3)] In all these methods, there was still room for improvement, particularly as regards the yield of the product. In this connection, we newly examined the utility of N-chlorosuccinimide–dimethyl sulfide (NCS-DMS) as the coupling agent, and unexpectedly found that the main product in the reaction was sulfonic acid derivatives, not the anticipated sulfinic acid derivatives. This paper deals with the reactions of a sulfinic acid in the presence of NCS–DMS and with related reactions.

When *p*-toluenesulfinic acid (**1**) was treated with methanol in the presence of equivalent amounts of NCS, DMS, and triethylamine in dichloromethane at room temperature, methyl

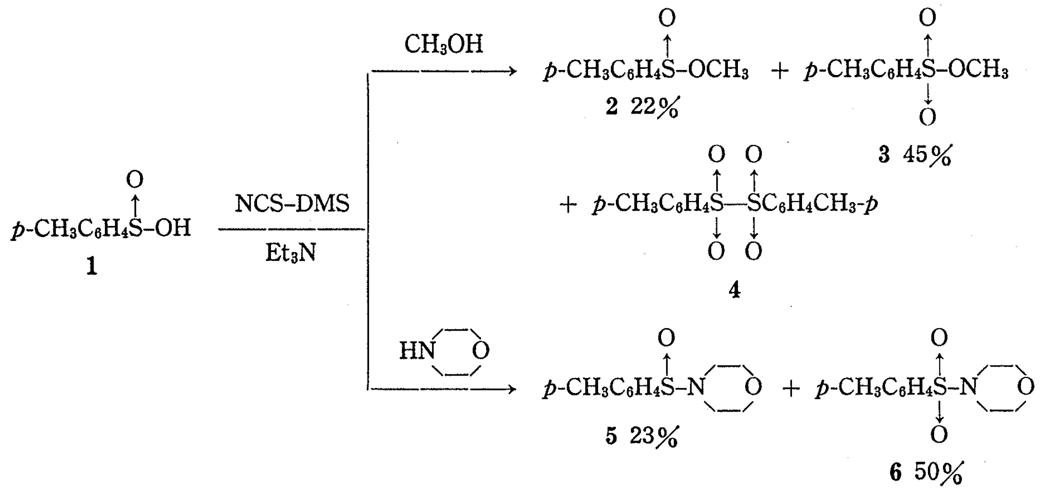

Chart 1

p-toluenesulfinate (**2**) was obtained in 22% yield, as expected. Unexpectedly, methyl *p*-toluenesulfonate (**3**) was also isolated in 45% yield as the main product, together with a small amount of di-*p*-tolyldisulfone (**4**). Similarly, treatment of **1** with morpholine in the presence of NCS–DMS under similar conditions provided the corresponding sulfinamide (**5**) and sulfonamide (**6**) in 23% and 50% yields, respectively.

Thus, we investigated the formation mechanism of the sulfonic acid derivatives (**3** and **6**). NCS–DMS has been shown to be a useful and specific reagent for oxidation and chlorination of certain oxygenated functions. Alcohols are oxidized to ketones[4] and some alcohols are converted to alkyl chlorides without oxidation.[5,6] Recently, sulfenamides were reported to be oxidized by NCS to sulfinamides.[7] In the present study, we examined whether oxidations of **2** and **5** to **3** and **6** occur with NCS or NCS–DMS under similar conditions or not. In fact, such oxidative conversion was not observed at all. When the reactions of **1** with methanol and with morpholine were carried out in the presence of NCS without addition of DMS, **3** and **6** were obtained in 62% and 70% yields, respectively, with no formation of **2** or **5**.

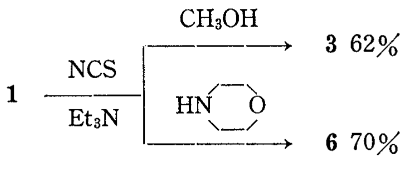

Chart 2

These results show that participation of DMS is not necessary in the formation of sulfonic acid derivatives.

The reaction between **1** and NCS was also examined and found to provide *p*-toluenesulfonyl chloride (**7**) in 60% yield, together with a small amount of di-*p*-tolyldisulfone (**4**) as a by-product. The reaction was achieved by stirring **1** with an equivalent amount of NCS at room temperature for two hours in dichloromethane in the presence of triethylamine. The formation of **4** suggests that this reaction is substantially analogous to the reaction of **1** in the presence of NCS–DMS.

p-Toluenesulfonyl chloride (**7**) was also provided by the reactions of **1** with *t*-butylhypochlorite and with chloramine-T, which are known to behave as chloro cations, like NCS. In both cases, the reaction readily proceeded on stirring the reaction mixture at room temperature in dichloromethane, in 81% and 57% yields, respectively.

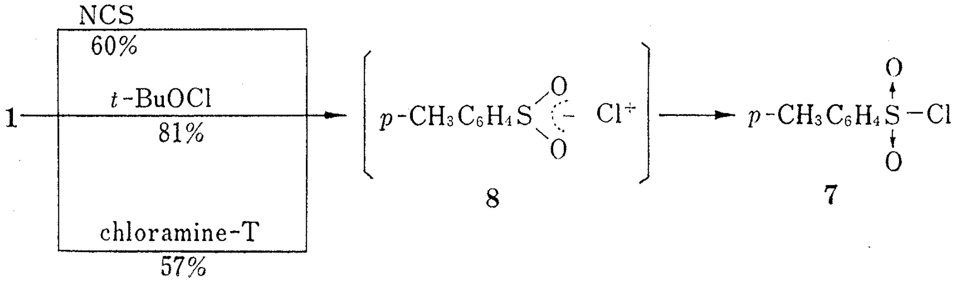

Chart 3

These reactions are presumed to proceed through intermediate formation of the ion pair (**8**) by attack of the sulfinyl oxygen atom on the chloro cation.

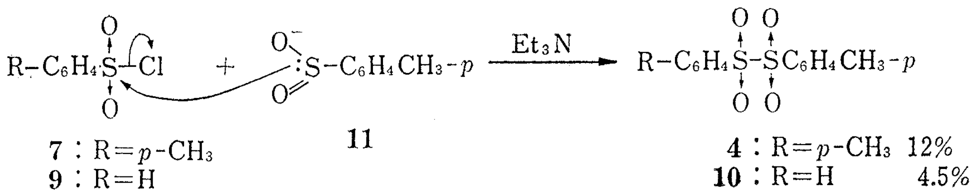

Chart 4

The formation of di-*p*-tolyldisulfone (**4**) as a minor product may be due to the participation of **7** as an intermediate of the reaction. In order to clarify the reaction pathway, the reaction between **1** and **7** was examined under similar conditions. As expected, **4** was formed in a yield of 12%. Analogously, the reaction of **1** with benzenesulfonyl chloride (**9**) gave a 4.5% yield of the corresponding disulfone (**10**).

The intermediate **7** presumably reacts with the sulfinate anion (**11**) formed from sulfinic acid and triethylamine base. The anion (**11**) is an ambident anion and the sulfur atom exhibits nucleophilicity. Nucleophilic attack of sulfonyl chloride on the sulfonyl sulfur atom affords disulfone.

In the reaction of **1** with chloramine-T, a small amount of di-*p*-toluenesulfonylamine (**12**) and *p*-toluenesulfonamide (**13**) arising from chloramine-T were also isolated in addition to **7**. When the same reaction was carried out in the presence of triethylamine, an increased yield (11%) of **12** was obtained. The formation of **12** may be due to the reaction between the intermediate **7** and **13**. In fact, **7** was allowed to react with **13** in the presence of triethylamine to give a 37% yield of **12**. As expected, the reaction of benzenesulfinic acid (**14**) with chloramine-T provided benzenesulfonyl-*p*-toluenesulfonylamine (**15**) in 13% yield.

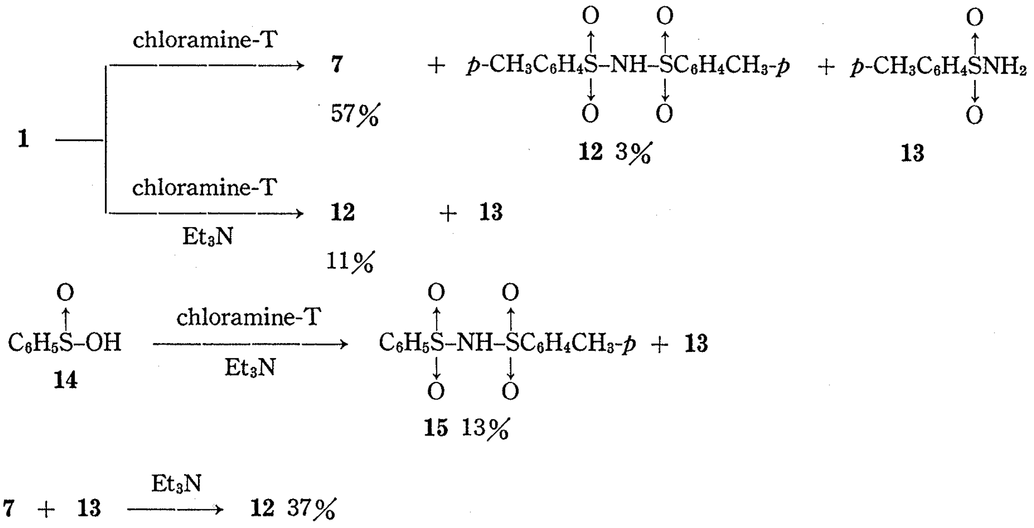

Chart 5

It is evident that the formation of sulfonic acid derivatives (**3** and **6**) in the reactions of the sulfinic acid (**1**) with alcohols and with amines in the presence of NCS–DMS proceeds via the sulfonyl chloride (**7**). The participation of DMS is essential for the formation of sulfinic acid derivatives (**2** and **5**). In the reactions of **1** with methanol and with morpholine in the presence of chloramine-T without DMS, the sulfonate (**3**) and sulfonamide (**6**) were obtained in 56% and 86% yields, respectively, no trace of the sulfinate (**2**) or the sulfinamide (**5**) being formed.

The formation of sulfinic acid derivatives seems to involve the intermediate formation of the sulfinyloxysulfonium salt (**16**), followed by the attack of an alcohol or an amine at the sulfinyl sulfur atom activated by the positive sulfonium group. It is well known that NCS reacts with DMS to form sulfoniumsuccinimide (**17**) immediately.[8]

The formation of sulfonic acid derivatives in this reaction suggests that the reaction between NCS and DMS is in an equilibrium state. If the equilibrium were wholly in favor of the formation of **17**, no formation of sulfonic acid derivatives would occur. Indeed, in the same reaction in the presence of NCS-triphenylphosphine instead of NCS–DMS, no trace of sulfonic acid derivatives was isolated. In this case, the reaction might be completely inclined toward formation of phosphoniumsuccinimide, due to the strong affinity of phosphine for nitrogen.

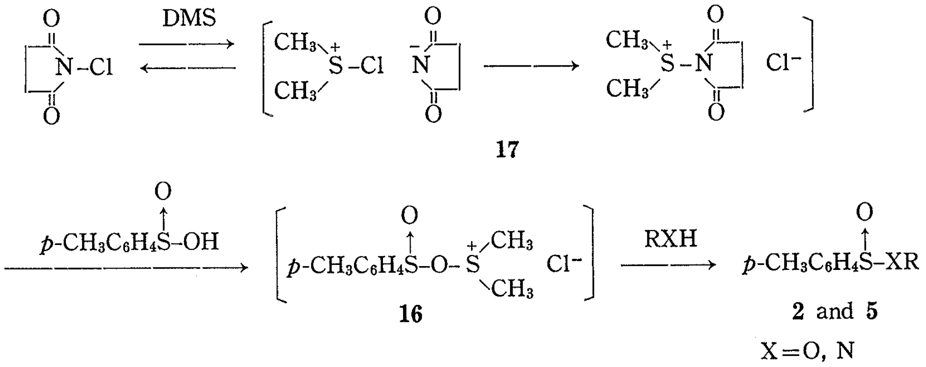

Chart 6

The use of diphenyl sulfide instead of dimethyl sulfide may stabilize the resulting sulfoniumsuccinimide, and as a result, an increased yield of sulfinic acid derivatives can be expected. Contrary to expectation, when **1** was allowed to react with methanol in the presence of NCS-diphenylsulfide, a decreased yield (12%) of **2** was obtained. In the reaction with morpholine, the yield of **5** similarly decreased. On the other hand, the yield of sulfonic acid derivatives increased. These results, different from those anticipated, may be due to the decreased formation of the sulfoniumsuccinimide.

Experimental

All melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IRA-1 grating infrared spectrometer. NMR spectra were taken on a JEOL C-60H high resolution NMR instrument at 60 MHz. Mass spectra (MS) were determined at 75 eV on a JEOL OISG mass spectrometer.

Reaction of 1 with Methanol in the Presence of NCS-DMS——DMS (10 mmol) was added dropwise with stirring into a solution of NCS (10 mmol) in dichloromethane (30 ml) at −5° under a stream of nitrogen gas. Into the stirred solution, **1** (10 mmol), triethylamine (10 mmol) and MeOH (10 mmol) were added slowly in turn. The solution was stirred for 2 hr at room temperature, washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and then dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, the residue was applied to a silica gel (Wakogel C-200) column and eluted with benzene. By this method, compounds **2**, **3**, and **4** were isolated. **2**; Yield, 22%. IR ν_{max}^{film} cm^{-1}: 1130 (SO). **3**; Yield, 45% IR ν_{max}^{film} cm^{-1}: 1377, 1196 (SO_2). These compounds were identified by comparison of their IR spectra with those of corresponding authentic samples. **4**; Yield, 3%. mp 190—195° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1348, 1139 (SO_2). MS *m/e*: 310 (M^+).

Reaction of 1 with Morpholine in the Presence of NCS-DMS——DMS (10 mmol) was added with stirring to a solution of NCS (10 mmol) in dichloromethane (30 ml) at −5° under a nitrogen atmosphere. With continued stirring, **1** (10 mmol), triethylamine (10 mmol) and morpholine (10 mmol) were added slowly in turn, and the whole was stirred for 2 hr at room temperature. The solution was washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and then dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, the residue was applied to a silica gel (Wakogel C-200) column, and eluted with a mixture of benzene and ethyl acetate (5: 1). By this procedure, **5** and **6** were isolated in 23% and 50% yields, respectively. **5**; mp 120°. IR ν_{max}^{KBr} cm^{-1}: 1060 (SO). **6**; mp 148°. IR ν_{max}^{KBr} cm^{-1}: 1341, 1164 (SO_2).

Reaction of 1 with Methanol in the Presence of NCS——Compound **1** (10 mmol), triethylamine (10 mmol), and MeOH (10 mmol) were added in turn with stirring to a solution of NCS (10 mmol) in dichloromethane (30 ml) at room temperature under nitrogen. The solution was stirred for 2 hr at room temperature, washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and then dried over anhyd. Na_2SO_4. On distilling off the solvent, **3** was obtained in 62% yield.

Reaction of 1 with Morpholine in the Presence of NCS——Compound **1** (10 mmol), triethylamine (10 mmol) and morpholine (10 mmol) were added in turn with stirring to a solution of NCS (10 mmol) in dichloromethane (30 ml) at room temperature under a nitrogen stream. After being stirred for 2 hr, the solution was washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and then dried over anhyd. Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was recrystallized from MeOH to give **6** in 70% yield.

***p*-Toluenesulfonyl Chloride (7)**——1) Triethylamine (10 mmol) and **1** (10 mmol) were added with stirring to a solution of NCS (10 mmol) in dichloromethane (30 ml) at room temperature under a nitrogen atmosphere.

After being stirred for 2 hr, the solution was washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and then dried over anhyd. Na_2SO_4. The solvent was distilled off under reduced pressure and the residue was dissolved into Et_2O. Insoluble precipitates were collected by filtration. This compound was identical with an authentic sample of di-*p*-tolyldisulfone (**4**).[9] Yield, 6%. The ethereal extract was concentrated to give **7** in 60% yield.

2) *t*-Butylhypochlorite (10 mmol) was added dropwise with stirring to a solution of **1** (10 mmol) in dichloromethane (30 ml) at room temperature under a nitrogen atmosphere. After being stirred for 2 hr, the solution was washed with 1% $NaHCO_3$ (30 ml) and then with H_2O (30 ml), dried over anhyd. Na_2SO_4, and distilled off to give **7** in 81% yield.

3) Chloramine-T (5 mmol) was added with stirring to a solution of **1** (5 mmol) in dichloromethane (20 ml) at room temperature under a nitrogen stream. Stirring was continued for 3 hr, then the solution was washed with H_2O (20 ml). The precipitates were recrystallized from a mixture of $CHCl_3$ and *n*-hexane (1: 1) to give di-*p*-toluene sulfonylamine (**12**) in 3% yield. mp 169—170°. MS *m/e*: 325 (M^+). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1360, 1175 (SO_2). The organic layer was dried over anhyd. Na_2SO_4, and concentrated. The residue was taken up with benzene. Insoluble precipitates of *p*-toluenesulfonamide (**13**), which originated from chloramine-T, were filtered off, and the extract was concentrated to give **7** in 57% yield. mp 69°.

Di-*p*-tolyldisulfone (4)——Triethylamine (10 mmol) and **1** (10 mmol) were added in turn to a stirred solution of **7** (10 mmol) in dichloromethane (30 ml) under a nitrogen atmosphere, and the solution was stirred for 2 hr at room temperature. The solution was washed with H_2O (30 ml), 0.1 N HCl (30 ml), 1% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), and dried over anhyd. Na_2SO_4. The solvent was distilled off, and the residue was dissolved in Et_2O. The insoluble precipitates were collected. Yield, 12%. mp 190—195° (dec.). This compound was identical with an authentic sample[9] as judged from the IR spectra.

Phenyl-*p*-tolyldisulfone (10)——Triethylamine (10 mmol) and **1** (10 mmol) were added in turn with stirring to a solution of benzenesulfonyl chloride (10 mmol) in dichloromethane (30 ml) and the mixture was stirred for 2 hr at room temperature. The mixture was treated by the procedure described above to give the product in 4.5% yield. mp 159—162°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1345, 1130 (SO_2). MS *m/e*: 296 (M^+). *Anal.* Calcd for $C_{13}H_{12}O_4S_2$: C, 52.69; H, 4.08. Found: C, 53.04; H, 4.04.

Reaction of 1 with Chloramine-T in the Presence of Triethylamine——Chloramine-T (5 mmol) was gradually added to a stirred mixture of **1** (5 mmol) and triethylamine (6 mmol) in dichloromethane (30 ml) under a nitrogen atmosphere. Stirring was continued for 4 hr at room temperature, then solution was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (45 g, 2.5 cm × 16 cm). Elution with $CHCl_3$–acetone (5: 1 v/v, 250 ml) provided **13**. The product packed on top of the silica gel column was extracted with ethyl acetate. The extract was washed with 0.5 N HCl and then with H_2O, and evaporated to dryness. The residue was recrystallized from *n*-hexane–$CHCl_3$ (1: 1) to give **12** in 11% yield. mp 171—172°. *Anal.* Calcd for $C_{14}H_{15}NO_4S_2$: C, 51.67; H, 4.65; N, 4.31. Found: C, 52.05; H, 4.48; N, 4.35.

Reaction of 14 with Chloramine-T in the Presence of Triethylamine——Compound **14** (5 mmol) was treated with chloramine-T (5 mmol) in the presence of triethylamine (6 mmol) by the procedure described above, and **15** was obtained in 13% yield. mp 169—170°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1365, 1170 (SO_2). MS *m/e*: 311 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_4S_2$: C, 50.14; H, 4.21; N, 4.50. Found: C, 50.27; H, 3.98; N, 4.45.

Reaction of 7 with 13——Compound **7** (5 mmol) was added to a stirred solution of **13** (5 mmol) and triethylamine (6 mmol) in dichloromethane (30 ml), and the solution was stirred for an additional 12 hr at room temperature. After distilling off the solvent, the residue was chromatographed on silica gel (20 g, 2 cm × 11 cm). The column was eluted with $CHCl_3$–acetone (10: 1 v/v), and the product packed on top of the column was extracted with ethyl acetate. The extract was washed with 0.5 N HCl and then with H_2O, and evaporated to dryness. The residue was recrystallized from *n*-hexane–$CHCl_3$ (1: 1) to give **12** in 37% yield.

Reaction of 1 with Methanol in the Presence of Chloramine-T——Chloramine-T (9 mmol) was added gradually with stirring to a mixture of **1** (10 mmol), MeOH (12 mmol), and triethylamine (12 mmol) in dichloromethane (30 ml) at 2—5° under a nitrogen stream. The mixture was stirred for an additional 3.5 hr at room temperature, washed with 0.5 N HCl, 1% $NaHCO_3$, and finally with H_2O, then dried over anhyd. Na_2SO_4. The solvent was distilled off and the residue was taken up in *n*-hexane. The insoluble precipitates of **13** (73%) were filtered off and the extract was distilled to give **3** in 56% yield.

Reaction of 1 with Morpholine in the Presence of Chloramine-T——A solution of **1** (5 mmol), morpholine (6 mmol), and triethylamine (6 mmol) in dichloromethane (30 ml) was treated with chloramine-T (4.5 mmol) by the procedure described above. The reaction mixture was washed and evaporated to dryness, then the residue was extracted with benzene. The insoluble part of **13** was filtered off and the extract was evaporated to dryness. The residue was washed with a small amount of EtOH to give **6** in 86% yield.

Reaction of 1 with Methanol in the Presence of NCS-Triphenylphosphine——Triphenylphosphine (10 mmol), **1** (10 mmol), and MeOH (20 mmol) were added in turn to a stirred solution of NCS (10 mmol) in dichloromethane (40 ml) below −15° under a nitrogen atmosphere. Stirring was continued for an additional 24 hr at room temperature. The mixture was washed with H_2O (30 ml), 1 N HCl (30 ml), 5% $NaHCO_3$ (30 ml), and finally with H_2O (30 ml), then dried over anhyd. Na_2SO_4, and evaporated to dryness. The residue was dissolved in a suitable amount of *n*-hexane. The insoluble precipitates consisted of triphenylphosphine oxide. The filtrate was concentrated and chromatographed on silica gel to give **2** in 63% yield.

References and Notes

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