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α Elimination of *N*-Chloro-*N*-sodiourethane in Ethers and in Hydrocarbons

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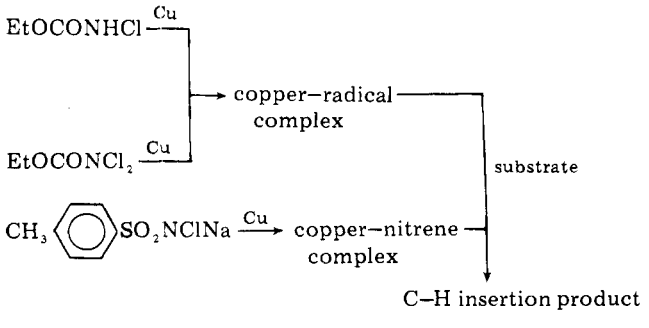
We reported that, in the presence of copper, the reactions of *N*-chloro- and *N,N*-dichlorourethanes with several substrates such as hydrocarbons and ethers proceeded via a copper–radical complex involving no nitrene.[2] Furthermore, Carr et al. reported that the reaction of chloramine-T with dioxane gave the N-substituted sulfonamide in the presence of copper, suggesting that a copper–sulfonylnitrene complex was formed as an intermediate.[3] In these reactions, the presence of copper gave the C–H insertion products, while it was found that the reaction of *N*-chloro-*N*-sodiourethane gave the C–H insertion product in spite of the absence of copper.



Results and Discussion

As shown in Table I, the reactions of *N*-chloro-*N*-sodiourethane (**1**) with ethers and hydrocarbons gave the respective N-substituted urethanes **2** and urethane **3**, whose yields were compared with those of the photolyses of ethyl azidoformate (**4**). In the reactions with cyclic ethers, tetrahydrofuran, tetrahydropyran, and dioxane, the preferential formations of α-substituted derivatives parallel those in the photolyses of **4**.[4,5] The reactions of *cis*- and *trans*-2,5-dimethyltetrahydrofurans were found to proceed nonstereospecifically in the formation of **2**.[6] In the reactions with aromatic hydrocarbons, none of the azepines were detected, contrary to the photolyses of **4**. In the reaction of the azide, the formation of the azepine is explained by the addition of singlet ethoxycarbonylnitrene to an aromatic double bond followed by cleavage of the C–C bond.[7,8] In sharp contrast with the photolyses of **4**, the reaction of **1** with cyclohexene gave preferentially the abstraction product **3** without the cycloadduct. This finding shows that the nitrene mechanism may be ruled out since both the singlet and triplet nitrenes react with olefins to give cycloadducts.[9]

Heating chloramine-T in the presence of copper in dimethyl sulfoxide furnished the sulfoximine in 80% yield.[3] An analogous experiment omitting the copper catalyst gave the sulfoximine in 6% yield.[3] Then, the reaction of **1** was carried out in the presence of copper to know the influence of the catalyst. The results are listed in Table I. The same products as formed in the absence of copper were obtained in slightly higher yields than those in the absence. The azepines were also not detected even under this condition. The findings indicate that the influence of copper is not essential contrary to that in the case of ref 3.

The reactions of **1** with ethanol in the absence and in the presence of copper gave urethane in the yields of 80.6 and 81.8%, respectively, and those with 1-butanol gave urethane in the yields of 73.1 and 96.3%, respectively, accompanied by the corresponding aldehydes. None of the O–H insertion products, *N*-ethoxyurethane and *N*-butoxyurethane, were detected in these reactions, whereas the photolyses of **4** in ethanol and 1-butanol gave the O–H insertion products in the yields of 11.0 and 27.0%, respectively, accompanied by urethane.[5] The O–H insertion products have been formed by singlet nitrene but not by any radicals.[5]

The results mentioned so far can be explained tentatively by a radical-like mechanism. Then **1** was treated with dioxane in the presence of radical inhibitors, nitrobenzene and hydroquinone. The addition of nitrobenzene decreased the yields of both N-substituted urethane (**2C**, 14.3%) and urethane (28.6%), and the addition of hydroquinone gave only urethane in high yield (64.9%). As for the decomposition of **4**, where the singlet nitrene was generated, the effect of the additives such as nitrobenzene and sulfur led to the increased yield of the insertion products and to the decreased yield of the abstraction product.[10]

The influence of copper on the present reaction was not so great as that on the reaction of chloramine-T, where the copper–nitrene complex had been proposed. This difference can be explained as follows. For *N*-chloro-*N*-sodiourethane, a resonance as presented by formula **5** is permitted. Consequently, the nitrogen atom of **1** is not easy to coordinate with copper, while the nitrogen atom of chloramine-T, whose resonance is not considered other than d-orbital expansion of the

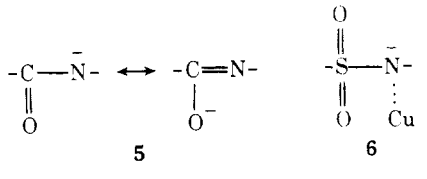


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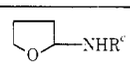
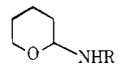
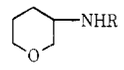
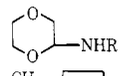
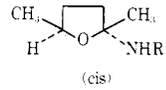
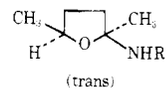
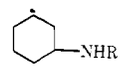
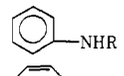
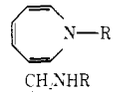
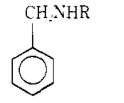
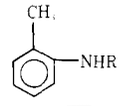
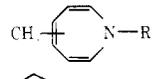
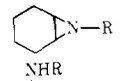
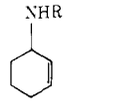
Table I. Reaction of 1 with Ethers and Hydrocarbons

substrate	registry no.	2	registry no.	product, %[a,f] dec of 1 absence of Cu	dec of 1 presence of Cu	dec of 4[b]
tetrahydrofuran	109-99-9	**A** 	13267-68-0	12.0 (65.0)	26.6 (66.2)	25.0 (21.0)
tetrahydropyran	142-68-7	$\mathbf{B_1}$ 	13267-69-1	15.0	28.7	25.0
		$\mathbf{B_2}$ 	68001-56-9	ND[d] (63.7)	ND (61.4)	5.0 (16.0)
dioxane	123-91-1	**C** 	13267-73-7	39.6 (49.0)	44.8 (46.1)	32.8 (22.2)
cis-2,5-dimethyltetrahydrofuran	2144-41-4	$\mathbf{D_1}$  (cis)	68001-57-0		8.2	8.0
		$\mathbf{D_2}$  (trans)	68001-58-1		12.3 (63.8)	13.0 (54.0)
trans-2,5-dimethyltetrahydropyran	2390-94-5	$\mathbf{D_1}$			6.0	8.0
		$\mathbf{D_2}$			12.3 (61.5)	11.0 (53.0)
cyclohexane	110-82-7	**E** 	1541-19-1	1.0 (44.7)	2.0 (50.8)	32.0 (15.0)
benzene	71-43-2	$\mathbf{F_1}$ 	101-99-5	2.0	3.0	1.7
		$\mathbf{F_2}$ 	2955-79-5	ND (33.0)	ND (41.0)	20.8 (7.6)
toluene	108-88-3	$\mathbf{G_1}$ 	10507-52-5	2.6	3.0	1.8
		$\mathbf{G_2}$ 	5255-71-0	1.0	1.0	3.6[e]
		$\mathbf{G_3}$ 	68001-77-4	ND (31.3)	ND (47.6)	21.8[f] (5.0)
cyclohexene	110-83-8	$\mathbf{H_1}$ 	1541-27-1	ND	ND	77.5
		$\mathbf{H_2}$ 	1541-28-2	2.5 (62.5)	1.9 (64.3)	12.5 (4.1)

[a] Calculated on the basis of **1** and **4** used. [b] The values show the data for the photolysis of ethyl azidoformate. The values for the ethers came from ref 4 and 5 and those for hydrocarbons came from ref 2. [c] R = $COOC_2H_5$. [d] ND = not detected. [e] In addition, *N*-(*p*-tolyl)urethane was obtained in the yield of 1.1%. [f] The value shows the total yield of 2- (6.7%), 3- (8.9%), and 4- (6.2%) methyl-*N*-carbethoxyazepines. [f] Parentheses indicates the yield of urethane.

sulfur atom, is able to coordinate with copper to give a complex (**6**).

Experimental Section

Materials. The *N*-chloro-*N*-sodiourethane (**1**) was prepared from monochlorourethane with sodium hydroxide by the method of Saika and Swern.[11] The purity of the urethane was determined by iodometric analysis.[11] The propylene oxide, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, benzene, toluene, cyclohexane, cyclohexene, ethanol, and 1-butanol were used after the commercial reagents had been purified according to the published directions.[12] Analytical grade reagents of copper, nitrobenzene, and hydroquinone were used without further purification. The preparation of *cis*- and *trans*-2,5-dimethyltetrahydrofurans has been described previously.[4]

Authentic Samples. *N*-Cyclohexylurethane (**2E**) was prepared by the method of Lwowski and Mattingly.[13] *N*-Phenylurethane ($\mathbf{2F_1}$), *N*-benzylurethane ($\mathbf{2G_1}$), and *N*-(*o*-tolyl)urethane ($\mathbf{2G_2}$) were prepared from ethyl chloroformate and the corresponding amines in a way similar to that used in the preparation of *N*-cyclohexylurethane.[13] All their IR and NMR data were shown in a previous paper.[2]

Reaction with Hydrocarbons and Ethers. A suspension of **1** (0.02 mol) in a substrate (0.5 mol) was stirred at 50 °C (case of ethers and alcohols) or 70 °C(case of hydrocarbons) under an atmosphere of nitrogen until iodine was no longer liberated on addition of the suspension to a potassium iodide aqueous solution. Next then the reaction mixture was filtrated and the filtrate was concentrated under reduced pressure. The residue was analyzed by VPC. Urethane (**3**) had IR and NMR spectra and a VPC retention time identical with those of the authentic sample.

The reaction in the presence of copper was carried out in the same manner mentioned above using copper powder (0.02 mol). The IR and the NMR spectral data of *N*-(2-tetrahydrofuryl)urethane (**2A**), *N*-(2-tetrahydropyranyl)urethane ($\mathbf{2B_1}$), *N*-(1,4-dioxan-2-yl)urethane (**2C**), *N*-(*cis*-2,5-dimethyl-2-tetrahydrofuryl)urethane ($\mathbf{2D_1}$), *N*-(*trans*-2,5-dimethyl-2-tetrahydrofuryl)urethane ($\mathbf{2D_2}$), *N*-carbethoxyazepine ($\mathbf{2F_2}$), and 2-, 3-, and 4-methyl-*N*-carbethoxyazepines ($\mathbf{2G_3}$) have been described previously.[4,5] The products, **2E**, $\mathbf{2F_1}$, $\mathbf{2G_1}$,

and $2G_2$ had IR and NMR spectra and VPC retention times identical with those of the authentic samples. The IR and NMR data of 7-carbethoxy-7-azabicyclo[4.1.0]heptane ($2H_1$) and 3-cyclohexylurethane ($2H_2$) were identical with those reported by Lwowski and Mattingly.[13]

Reaction with Alcohols. In the absence and in the presence of copper, a suspension of 1 (0.02 mol) in ethanol (0.5 mol) or in 1-butanol (0.5 mol) was stirred at 50 °C under an atmosphere of nitrogen. After the reaction mixture was filtered, the excess substrate and volatile product, aldehyde, were trapped in a flask immersed in a dry ice–methanol bath under reduced pressure. The trapped solution was added to a 2,4-dinitrophenylhydrazine solution and the aldehyde was converted to the hydrazone.

Reaction in the Presence of Radical Inhibitors. The reaction was carried out in the same manner mentioned above in the addition of radical inhibitor (0.02 mol).

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Registry No.—**1**, 17510-52-0; **3**, 51-79-6.

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(6) The reaction of **1** with either *cis*- or *trans*-1,4-dimethylcyclohexane gave a mixture of *N*-(*cis*-1,4-dimethylcyclohexyl)urethane and *N*-(*trans*-1,4-dimethylcyclohexyl)urethane (stereoisomers). The total yields of isomers in each reaction were less than 1%, though the yield of **3** was over 60%. In the photolyses of **4**, however, only one product isomer (14% yield in the cis isomer and 11% yield in the trans isomer) was isolated in each reaction: T. Shingaki, M. Inagaki, N. Torimoto, and M. Takebayashi, *Chem. Lett.*, 155 (1972).
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Trimethylsulfonium Hydroxide: A New Methylating Agent

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Trimethylsulfonium hydroxide (Me_3SOH) may be considered an analogue of *S*-adenosylmethionine, which serves as a methyl group donor in biomethylation reactions.[1] In this paper we describe methylation of various kinds of compounds using Me_3SOH. We prepared Me_3SOH[2] in methanol–water (50:1 v/v) by a reaction of trimethylsulfonium iodide and silver oxide. The reagent solution is strongly basic and stable for months with negligible decomposition when stored below 10 °C.

In general, methylation reactions were carried out by concentrating a mixture of substrate and the reagent solution followed by treating the residue at 70–120 °C for 5–30 min. In a few cases, such as deoxyguanosine, when the residue forms a hard solid mass, dimethylformamide (DMF) was used as a solvent. Since the byproducts of Me_3SOH are water and dimethyl sulfide (bp 38 °C), methylated products could be isolated easily by direct distillation or recrystallization of the reaction mixture, after removal of DMF if used. Examples of methylation are shown in Table I.

Me_3SOH is well suited for methylation of COOH, SH, aromatic OH, ring –NH– groups in aromatic heterocycles, etc., which have pK_a values smaller than approximately 12. An aliphatic amido group undergoes methylation in a satisfactory yield by the employment of a large excess of Me_3SOH, but the reagent is not practical for methylation of aliphatic and aromatic NH_2 and aliphatic OH groups. The reactions can be represented by the following scheme.

$$NuH + (CH_3)_3S^+ OH^- \rightarrow Nu^- \xrightarrow{H_2O} CH_3\text{-}S^+(CH_3)_2 \rightarrow Nu\text{-}CH_3 + (CH_3)_2S$$

The main advantages of Me_3SOH as a methylating agent are easy separation and purification of products and nearly quantitative and rapid methylation with 10–30% excess of Me_3SOH. When the product is soluble in water, Me_3SOH is particularly advantageous with regard to product isolation, since most of the other methylating agents generate water-soluble byproducts, for instance, HI and $(CH_3O)SO_3H$ or their Na or K salts from CH_3I and $(CH_3O)_2SO_2$, respectively.[3,4] Methylation of deoxyguanosine illustrates a typical example; e.g., with Me_3SOH, 1-methyldeoxyguanosine (m^1dG) was isolated easily in a yield of 70%, whereas, with CH_3I,[5] m^1dG was obtained in a poor yield (29%) although the thin-layer chromatography of the reaction mixture suggested the formation of the product in >85% yield.

Diazomethane may be as useful as Me_3SOH. Its preparation and handling, however, must be conducted carefully since diazomethane and its starting materials (*N*-nitroso compounds) are carcinogens.[6]

Taking the above advantages of Me_3SOH, we have been examining methylation of nucleosides and nucleotides; the results will be reported later.

Experimental Section

Preparation of Trimethylsulfonium Hydroxide (Me_3SOH). Trimethylsulfonium iodide (10.2 g, 50.0 mmol) was dissolved in a warm mixture of methanol and water (200–1 mL) and the solution was treated by silver oxide (7.2 g, 31.1 mmol) with stirring. Occasionally a few drops of the supernatant was checked for iodide by nitric acid–silver nitrate solution. After completion of the reaction, the reaction mixture was filtered and concentrated to 50 mL. The concentration of Me_3SOH in the solution was determined by titration with 0.1 N hydrochloric acid to be 0.86 N. (The yield of Me_3SOH was 86%.) When the titrated solution was concentrated, trimethylsulfonium chloride was obtained as crystals quantitatively. The NMR of the solution was δ 3.02 [s, $(CH_3)_3S^+$]. The electron impact mass spectrum was (75 eV) *m/e* (rel intensity) 76 ($M - H_2O$, 30), 62 (CH_3SCH_3, 100), 61 (CH_3SCH_2, 85), and 47 (CH_3S, 97).

General Methylation Procedure. Reaction conditions and results are summarized in Table I. A mixture of the Me_3SOH solution and a substrate was concentrated by a rotatory evaporator and heated with stirring. The unpleasant order of dimethyl sulfide can be avoided by extending rubber tubing from the exit of the reaction flask to a sink or to a trap immersed in an acetone–dry ice bath. When methylation of the compound was incomplete as in the case of ε-caprolactam, the reaction mixture was mixed again with the Me_3SOH solution, concentrated, and heated. The similar procedure was repeated till a product was formed in a substantial yield. For methylation of deoxyguanosine, the concentrated mixture of the nucleoside and the Me_3SOH solution was heated in DMF (4 mL). The reaction mixture was occasionally analyzed by gas and thin-layer chromatographies as well as NMR spectrometry. Products were isolated by direct distillation or recrystallization of the reaction mixture. 1-Methyldeox-

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