Thermolysis of *N*-Aryl-*N*-nitrosoureas to Afford Aryl Isocyanates and Nitrosamines *via* *O*-Nitrosoisourea Intermediates

Masayuki TANNO,* Shoko SUEYOSHI, and Shozo KAMIYA

National Institute of Hygienic Sciences, 1–18–1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan. *Received March 26, 1990*

Nitrosation of 3,3-dialkyl-1-(4-tolyl)ureas (9) with sodium nitrite in formic acid under ice-cooling gave 3,3-dialkyl-1-(4-tolyl)-1-nitrosoureas (10). In the nitrosation of the ureas with a benzyl group, small amounts of dealkylated nitrosourea, 3-benzyl-1-(4-tolyl)-3-nitrosourea, were formed as a by-product. Decomposition of 10 in CCl_4 at 33 °C under an argon atmosphere gave 4-tolyl isocyanate (11) and *N*-nitrosodialkylamines (12) besides ureas (9), 3,3-dialkyl-1-(2-nitro-4-tolyl)ureas (13) and 3,3-dialkyl-1-(4-tolyl)triazenes (14). Formation of 11 and 12 suggests the involvement of an *O*-nitrosoisourea intermediate (15) in the decomposition of 10. In the thermolysis of 10 involving radical decomposition, nitric oxide generated from 10 was trapped as an NO_3 complex of *N*,*N*′-ethylenebis-(salicylideneiminato)iron (Fe(III)-salen-NO_3).

Keywords nitrosourea; nitrosoisourea; nitrosamine; nitrosyl radical; nitric oxide; thermolysis; diazoester rearrangement; dealkylation

There are many reports[1] on thermolysis of acyl-type *N*-nitroso compounds in organic solvents. Nearly all of these investigations show that *N*-nitrosamides or *N*-nitrosoureas decompose *via* the corresponding diazoester intermediates that are formed by intramolecular reaction. On the other hand, thermal decomposition *via* homolytic N–NO bond cleavage of *N*-aryl-*N*-nitroso compounds has been studied in the case of *N*-aryl-*N*-nitrosamines such as *N*-nitrosodiphenylamine and *N*-nitrosocarbazole.[2] However, the decomposition of *N*-aryl-*N*-nitrosoureas and *N*-aryl-*N*-nitrosamides *via* N–NO bond cleavage is not so well known. It has been reported[3] that thermolysis of aliphatic trialkylnitrosoureas in the presence of cuprous chloride as a catalyst at 87 °C gave *N*-nitrosodialkylamines and denitrosated ureas. Such thermal decomposition involving the N–NO bond cleavage of aliphatic *N*-nitrosoureas rarely occurs without a catalyst.

We recently reported[4,5] on the thermolysis of 3-alkyl-1-aryl-1-nitrosoureas in nonpolar solvents. In the thermolysis, diazoester rearrangement (path a) and N–NO bond cleavage (path b) took place competitively. For example, 3-benzyl-1-(4-tolyl)-1-nitrosourea (**1**) gave 4-tolyldiazohydroxide (**2**) and benzyl isocyanate (**3**) *via* path a, while 3-benzyl-1-(4-tolyl)-3-nitrosourea (**4**), 3-benzyl-1-(2-nitro-4-tolyl)urea (**5**), 3-benzyl-1-(4-tolyl)urea (**6**) and 3-benzyl-1-(2-nitro-4-tolyl)-3-nitrosourea (**7**) were formed *via* path b[5] (Chart 1).

The decomposition rate of **1** was affected by oxygen. 1-Nitrosourea (**1**) isomerized to 3-nitrosourea (**4**) by a 1,3-nitroso shift, but the NO migration reaction was inhibited under aerobic conditions. Since the mechanism of the 1,3-nitroso shift could be explained by analogy to the thermal rearrangement of *O*-alkylimidates to *N*-alkylamides under neutral conditions, which is known as the Chapman rearrangement,[6] we proposed an *O*-nitrosoisourea intermediate (**8A** or **8B**)[5] in the decomposition of the disubstituted nitrosoureas (**1**). Further, we considered that 1-(2-nitro-4-tolyl)-3-nitrosourea (**7**) was formed by the reaction of the nitro compound (**5**) with the intermediate (**8**) generated from **1**. In the chemistry of denitrosation with sulfuric acid of aliphatic *N*-nitrosamides, formation of an *O*-nitrosoimidate intermediate from *N*-nitrosamide has been suggested.[7]

The thermolysis of the trisubstituted nitrosoureas (**10**) was compared to that of the disubstituted nitrosoureas (**1**). Under anaerobic conditions, we found that **10** produced 4-tolyl isocyanates (**11**) and *N*-nitrosodialkylamines (**12**) besides 3,3-dialkyl-1-(4-tolyl)ureas (**9**), 3,3-dialkyl-1-(2-nitro-4-tolyl)ureas (**13**), and 3,3-dialkyl-1-(4-tolyl)triazenes (**14**). In this report, we describe firstly the isolation of 4-tolyl isocyanates (**11**) and *N*-nitrosodialkylamines (**12**) in order

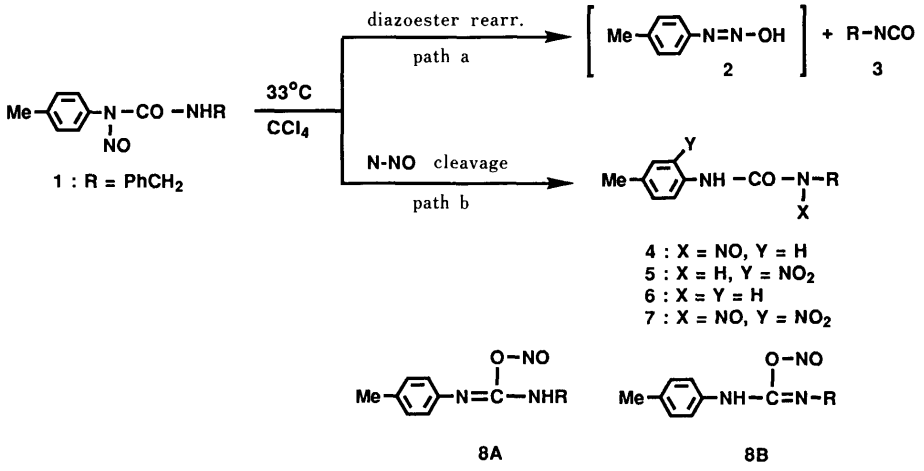


Chart 1

to demonstrate the involvement of *O*-nitrosoisourea intermediates (**15**), and secondly the trapping of nitric oxide as an iron complex to prove that radical N–NO bond cleavage occurs in the trisubstituted nitrosoureas (**10**).

Results and Discussion

Nitrosation of 3,3-Dialkyl-1-arylureas 3,3-Dialkyl-1-(4-tolyl)-1-nitrosoureas (**10a—c**) were prepared by nitrosation of the corresponding ureas (**9a—c**) with sodium nitrite in formic acid by the method described previously[8] (Chart 2). The yields and physicochemical properties are listed in Table I. In the nitrosation of ureas (**9**) with a benzyl group at the N^3 position, such as 3,3-dibenzyl-1-(4-tolyl)urea (**9a**) and 3-benzyl-3-methyl-1-(4-tolyl)urea (**9c**), dealkylation at N^3 occurred to produce 3-benzyl-1-(4-tolyl)-3-nitrosourea (**4**) as a by-product of **10a, c** in about 5% yield. We reported nitrosation of disubstituted ureas (**6**) with isoamyl nitrite in chloroform without using an acid.[4] Nitrosation of trisubstituted ureas (**9**) was similarly tried with isoamyl nitrite in the absence of acid. Nitrosoureas (**10**) were formed in low yields compared with the method using sodium nitrite and formic acid, and then the nitrosative dealkylation was not observed. This result shows that the dealkylation occurs only in acidic solution.

There is no information in the literature on the nitrosative dealkylation mechanism of the ureas. Dealkylation of *N,N*-dialkylanilines by nitrosyl cation (NO^+) was reported to occur by a Leoppky–Tomasik mechanism,[9] in which the reaction proceeds *via* a nitrosammonium ion. The mechanism for nitrosative dealkylation of trisubstituted ureas is considered to be similar to that of *N,N*-dialkylanilines. A nitrosammonium ion derivative is produced at first by the reaction of the 1-arylurea (**9**) with NO^+ as shown in Chart 2. When R^1 in **9** is benzyl, this ammonium ion must decompose to an imminium ion, and successively give the disubstituted urea (**6**) by the addition of water. 3-Nitrosourea (**4**) is finally formed by the reaction of NO^+. In the nitrosation of 3,3-diisopropyl- (**9b**) and 3,3-diethyl-1-(4-tolyl)urea (**9d**) using sodium nitrite and formic acid, only trisubstituted nitrosoureas (**10b, d**) were obtained, but no dealkylated product was found. We consider that the inductive effect of the benzyl group in the nitrosammonium ion is an important factor for selective dealkylation by the nitrosation, and a hydrogen atom of the benzyl or methyl group tends to be releasable owing to the inductive effect of the residual benzyl group. In the

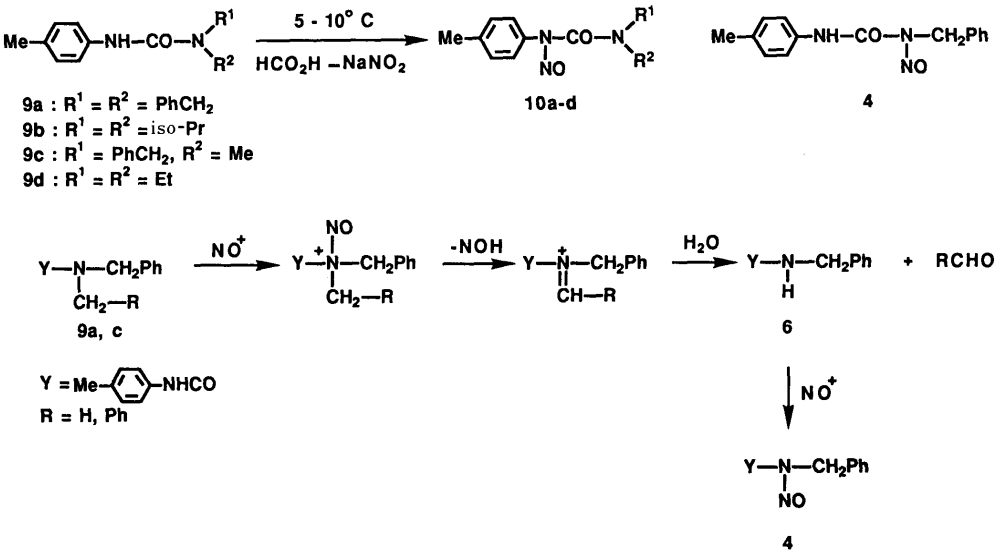


Chart 2

TABLE I. Physicochemical Properties and Analytical Data[a] for 3,3-Dialkyl-1-(4-tolyl)ureas (**9**), 3,3-Dialkyl-1-(4-tolyl)-1-nitrosoureas (**10**), 3,3-Dialkyl-1-(2-nitro-4-tolyl)ureas (**13**), and 3,3-Dialkyl-1-(4-tolyl)triazenes (**14**)

Compd.	Yield (%)	mp (°C)	Formula	*Anal.* (%) Calcd			Found			IR ($CHCl_3$) cm^{-1} NH/CO
				C	H	N	C	H	N	
9a	85	172.5—173.5	$C_{22}H_{22}N_2O$	79.97	6.71	8.48	79.86	6.85	8.43	3425, 1650
9b	80	145—146	$C_{14}H_{22}N_2O$	71.75	9.46	11.96	71.67	9.65	11.91	3475, 1650
9c	90	111—112	$C_{16}H_{18}N_2O$	75.56	7.13	11.02	75.85	7.19	11.12	3460, 1655
10a	42	64.5—65.5[b]	$C_{22}H_{21}N_3O_2$	73.51	5.89	11.69	73.87	6.01	11.78	— , 1700
10b	20	56.0—56.5[b]	$C_{14}H_{21}N_3O_2$	63.85	8.04	15.96	63.95	8.14	16.06	— , 1695
10c	60	50—51[b]	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	67.87	6.12	15.08	— , 1700
13a	73	111—112	$C_{22}H_{21}N_3O_3$	70.38	5.64	11.19	69.93	5.76	11.15	3350, 1665
13c	64	75—76	$C_{16}H_{17}N_3O_3$	64.20	5.72	14.04	63.99	5.63	14.24	3360, 1660
14a	93	65.5—66.5	$C_{21}H_{21}N_3$	79.96	6.71	13.32	79.77	6.76	13.25	
14c	88	Oil	$C_{15}H_{17}N_3$	75.28	7.16	17.56	75.39	7.21	17.78	

a) Data for **9d**, **10d** and **12d—14d** were described in a previous paper.[8] *b*) Decomposition points.

nitrosation of 3-benzyl-3-methyl-1-(4-tolyl)urea (**9c**), 3-methyl-1-(4-tolyl)-3-nitrosourea is actually not produced. Moreover, the nitrosation of **9a, c** did not give 3-benzyl-1-(4-tolyl)-1-nitrosourea (**1**), though its formation was expected by the reaction of the produced 3-benzyl-1-(4-tolyl)urea intermediate (**6**) with NO^+. 1-Nitrosourea (**1**) is presumed to isomerize to its 3-nitrosourea (**4**), for it is well known that acids promote the isomerization of disubstituted nitrosoureas by acid-catalyzed 1,3-nitroso shift.[4,10]

The Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) of Nitrosoureas (10) ^{13}C-NMR spectral data for the nitrosoureas (**10a—c**) at low temperature are shown in Table II. In a recent paper,[11] we reported that three conformers I—III were observed as two sets of signals in the spectra of 1-aryl-1-nitrosoureas (Fig. 1). Conformers I and II are twisted between phenyl-C^1 and ureido-N^1, and conformer III has a coplanar form in which a conjugated system is present between the phenyl and N^1 nitrogen. Conformers II and III are effective for the occurrence of diazoester rearrangement and N–NO bond cleavage, respectively, in the decomposition of *N*-aryl-*N*-nitrosoureas.

The nitrosoureas (**10a, b**) show conformers I and III. In **10c** having unsymmetrical dialkyl groups at the N^3 nitrogen, two kinds of conformer III, that is, conformers III_1 and III_2 are observed besides conformer I. These conformers are reflected in the chemical shifts at the C^2 carbon of the aryl group by conjugation between phenyl-C^1 and ureido-N^1.[11] The phenyl-C^2 signal of conformer III appears at a higher field than that of conformer I, which has weak conjugation. We feel that the coplanar conformation is also reflected in the ease of N–NO bond fission of trisubstituted nitrosoureas.[11]

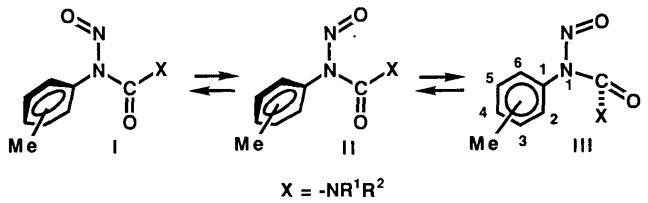


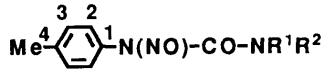
Fig. 1. Conformation of *N*-Aryl-*N*-nitrosoureas

4-Tolyl nitrosourea derivatives (**10**) take conformers I and III, and 2-tolyl derivatives adopt conformers I and II at −40 °C.[11]

Liberation of NO Radical The decomposition of 3,3-diethyl-1-(4-tolyl)-1-nitrosourea (**10d**) in carbon tetrachloride was reported in our previous paper.[8] 3,3-Diethyl-1-(2-nitro-4-tolyl)urea (**12d**) and 3,3-diethyl-1-(4-tolyl) triazene (**14d**) were produced *via* the N–NO bond cleavage and the diazoester rearrangement, respectively. The N–NO bond cleavage which formed the nitro compound (**12d**) seemed to be a radical reaction.[8,11] Therefore, we tried to trap the nitrosyl radical (NO) during the decomposition of 3,3-dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**). The NO radical was trapped as a metal complex of NO_3. An *N,N'*-ethylenebis(salicylideneiminato)iron (III)-NO_3 complex (Fe-salen-NO_3) was formed by mixing μ-oxo dimer (Fe-salen)$_2$O[12] with **10a** at room temperature. The complex was identical with an authentic sample[13] which was prepared by bubbling nitric oxide then oxygen through a methylene chloride solution of the μ-oxo dimer (Fe-salen)$_2$O. Formation of the complex was confirmed by mass spectroscopy. We consider that the Fe-salen-NO_3 is not directly formed by reaction of the μ-oxo dimer with **10a** or its intermediate (**15**), because the Fe-salen-NO_3 is obtained by reaction of the μ-oxo dimer with N_2O_3 which is produced from NO and oxygen.[13] Consequently, formation of the metal-NO_3 complex in the thermolysis of **10** involves a homolytical cleavage at the N–NO bond.

Decomposition of Nitrosoureas (10) in CCl_4 We examined the mode of decomposition of the trisubstituted nitrosoureas (**10**) by infrared (IR) spectroscopy. When a carbon tetrachloride solution of **10a** was allowed to stand in a closed cell at room temperature, it showed characteristic absorption bands at 2320 and 2260 cm^{-1} due to CO_2 and the N=C=O group, respectively. The generation of CO_2 with the formation of the triazene (**14a**) is caused by decom-

TABLE II. ^{13}C-NMR Chemical Shifts (ppm)[a] of *N*-Nitrosoureas (**10**)



Compd.	Form[b]	Tolyl C-1	C-2,6	C-3,5	C-4	*C*-Me	CO	*N*-Me	*N*-iso-Pr CH	Me	*N*-Et CH_2	Me	N-CH_2Ph CH_2	C-1	C-2,6	C-3,5	C-4
10a	I	131.0	127.1	130.0	140.0	21.3	155.9						51.8[c]	134.6	*d*)	*d*)	127.9
	III	135.1	118.3	130.3	138.0	21.1	153.0						50.4	135.8	128.2	128.8[e]	128.0[e]
													48.4	133.6	128.1	128.8[e]	128.0[e]
10b	I	131.6	126.1	130.0	139.6	21.2	152.9		*d*)	20.1							
	III	135.4	117.4	130.3	137.4	20.9	150.0		51.2	20.7							
									46.7	20.4							
										19.5							
										19.4							
10c	I	131.1	126.9	130.0	140.0	21.3	155.7	33.6					53.7	133.9[f]	128.1	*d*)	*d*)
	III_1	135.7	118.1	130.3	138.0	21.0	153.1	34.2					52.2	135.0	127.8	128.8	128.0
	III_2	*d*)	118.2	*d*)	*d*)	*d*)	152.3	37.3[c]					53.2[c]	134.8[f]	*d*)	*d*)	*d*)
10d[g]	I	131.3	126.6	130.0	139.8	21.7	154.5				44.2[c]	*d*)					
											42.2[c]	*d*)					
	III	135.2	117.5	130.3	137.7	21.0	151.6				42.8	13.7					
											41.4	12.4					

a) Measured at −40 °C in $CDCl_3$ with TMS as an internal standard. *b*) Forms I—III are shown in Fig. 1. *c*) Broad peak. *d*) Not observable under the experimental conditions, since the signal intensities of conformer III_1 are overwhelmingly stronger than those of conformer III_2. *e*) Coincidences. *f*) Assignments may be reversed. *g*) Data were described in a previous paper.[8]

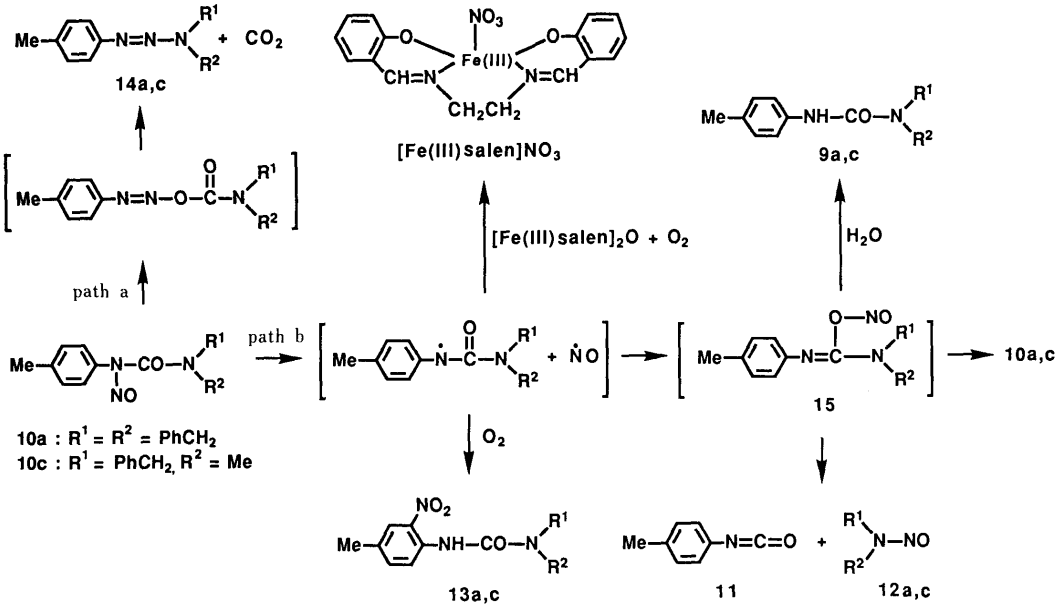


Chart 3

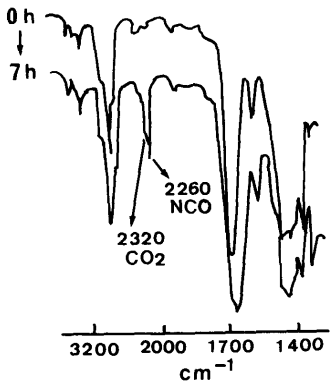


Fig. 2. Infrared Spectra Illustrating the Decomposition of 3,3-Dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**) in CCl_4

TABLE III. Products of the Thermal Decomposition[a] of 3,3-Dialkyl-1-(4-tolyl)-1-nitrosoureas (**10a, c**)

	Nitrosourea		Product yield (%)[b]				
	R^1	R^2	**9**	**11**[c]	**12**	**13**	**14**
10a	CH_2Ph	CH_2Ph	23	4	19	16	15
10c	CH_2Ph	Me	24	3	21	8	24

a) Reactions were carried out in CCl_4 at 33 °C for 24 h under argon. *b*) Isolated yields. Compounds **9**, ureas; **12**, nitrosamines; **13**, nitro compounds; **14**, triazenes. *c*) Yields of 4-tolyl isocyanate (**11**) were determined by GC.

position of the diazoester intermediate.[8] These two peaks increased with the passage of time, and only the CO_2 band at 2300 cm^{-1} disappeared when the solution was degassed (Fig. 2). The formation of 4-tolyl isocyanate (**11**) was also determined by gas chromatography (GC).

Next, we isolated the decomposition products. 3,3-Dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**) was dissolved in carbon tetrachloride and allowed to stand at 33 °C for 24 h under an argon atmosphere. The decomposition products (Chart 3) were isolated by chromatography on a column of silica gel with a mixture of *n*-hexane–ether (4 : 1) as an eluting solvent. *N*-Nitrosodibenzylamine (**12a**), 3,3-dibenzyl-1-(2-nitro-4-tolyl)urea (**13a**) and 3,3-dibenzyl-1-(4-tolyl)triazene (**14a**) were obtained in 19%, 16% and 15% yields, respectively. The urea (**9a**) was found in 23% yield (Table III). These products were identified by comparison with authentic samples as described in the experimental section. Formation of the triazene (**14a**) is considered to occur *via* diazoester rearrangement (path a), and other products (**9a**, **12a**, **13a**) *via* N–NO bond cleavage (path b). Similar treatment of 3-benzyl-3-methyl-1-(4-tolyl)-1-nitrosourea (**10c**) gave the corresponding products (**9c**, **12c**—**14c**), as shown in Chart 3 and Table III.

4-Tolyl isocyanate (**11**) was also derived *via* path b. The yield of **11** was determined by GC after a carbon tetrachloride solution of each nitrosourea (**10a, c**) was kept at 33 °C for 24 h under an argon atmosphere. The isocyanate (**11**) was obtained in 3—4% yields (Table III). The low yields of **11** compared with those of *N*-nitrosodialkylamines (**12**) may be attributed to its chemical activity. 4-Tolyl isocyanate transforms easily to the corresponding carbamic acid by reaction with water present as a contaminant in the solution.

No evidence for the involvement of *O*-nitrosoisoureas is available in the literature. However, it can be considered that 4-tolyl isocyanate (**11**) and *N*-nitrosodialkylamines (**12**) are produced from *O*-nitrosoisoureas intermediates (**15**) which are formed by reaction of the nitrosyl radical and ureidyl radical generated in the decomposition of 3,3-dialkyl-1-(4-tolyl)-1-nitrosoureas (**10**) (Chart 3). The presence of such intermediates (**15**) is possible in acyl-type nitroso compounds, because the NO radical generated from N–NO bond cleavage attacks the oxygen in the carbonyl group and forms the *O*-nitroso compounds by a kinetically controlled process. Intramolecular rearrangement of the *O*-nitroso group to the N^3 nitrogen in the intermediates (**15**) gives aryl isocyanates and nitrosamines, while that to the N^1 nitrogen gives the original *N*-nitrosoureas (**10**) by a process analogous to the Chapmann rearrangement.[7]

Conclusion

Since the disubstituted nitrosourea (**1**) has a mobile

hydrogen atom at the N^3 nitrogen, the thermodynamically stable 3-nitrosourea (**4**) is produced *via* the *O*-nitroso intermediate (**8**).[5] In the case of the trisubstituted nitrosourea (**10**), it gives 4-tolyl isocyanate (**11**) and nitrosamine (**12**) instead of the 1,3-nitroso-shifted product (**4**) found in the case of the disubstituted derivative (**1**), because the *O*-nitroso intermediate (**15**) has no mobile hydrogen atom at the N^3 nitrogen, different from the case of **8**. We conclude from these results that *O*-nitrosoisourea intermediates are produced in the thermolysis of *N*-aryl-*N*-nitrosoureas.

Experimental

All melting points were determined with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a JASCO A-102 spectrophotometer. A Shimadzu model GC-7A gas chromatograph equipped with flame ionization detectors was used. ^{13}C-NMR spectra were measured with a JEOL FX-200 spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded with a JEOL DX-300 mass spectrometer.

Preparation of Ureas (9a—c) A typical experiment is described for 3,3-dibenzyl-1-(4-tolyl)urea (**9a**) as an example. 4-Tolyl isocyanate (**11**) (10.0 g, 75 mmol) was added dropwise to an ice-cooled solution of dibenzylamine (14.8 g, 75 mmol) in 100 ml of ether, and the mixture was allowed to stand at room temperature with stirring for 3 h. The resulting crystals were filtered off, and recrystallized from acetone. mp 172.5—173.5 °C. Yield, 21 g (85%). 3,3-Diisopropyl-1-(4-tolyl)urea (**9b**): mp 145—146 °C. Yield, 80%. 3-Benzyl-3-methyl-1-(4-tolyl)urea (**9c**): mp 111—112 °C. Yield, 90%. 3,3-Diethyl-1-(4-tolyl)urea (**9d**) was prepared according to our previous paper.[8] The analytical and spectral data for **9a—c** are shown in Tables I and IV, respectively.

Nitrosation of 3,3-Dialkyl-1-(4-tolyl)ureas (9a—d) A typical experiment is described for 3,3-dibenzyl-1-(4-tolyl)urea (**9a**) as an example. The urea (**9a**) (3.3 g, 10 mmol) was dissolved in 99% formic acid (20 ml). Sodium nitrite (0.83 g, 12 mmol) was added to the solution at 0—5 °C. The reaction mixture was stirred for 30 min, maintaining the temperature below 5 °C, and was poured into cold $CHCl_3$. A small amount of cold water was added, and the whole was extracted with cold $CHCl_3$. The $CHCl_3$ layer was washed with a cold solution of saturated sodium bicarbonate and cold water until the washings were neutral. The $CHCl_3$ layer was filtered through a silicon-treated filter paper (1 ps phase separator, Whatman Ltd.) and evaporated under reduced pressure in an ice-water bath. The residue was chromatographed on a column of silica gel with a mixture of *n*-hexane and ether (7 : 3) under cooling.[8] The first fraction gave the dealkylated nitrosourea, 3-benzyl-1-(4-tolyl)-3-nitrosourea (**4**), which was identical with an authentic sample.[5] Recrystallization from a mixture of *n*-hexane and ether gave pale yellow needles, mp 100—101 °C (dec.). Yield, 0.13 g (4.8%). The second fraction gave 3,3-dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**) as pale yellow needles (from ether), mp 64.5—65.5 °C (dec.). Yield, 1.51 g (42%). The starting urea (**9a**) was recovered from the last fraction. The reaction mixture should not be permitted to stand in the column for a long time, because 3,3-dibenzyl-1-(2-nitro-4-tolyl)urea (**13a**) is produced as a decomposition product of **10a**.

Nitrosation of other ureas (**9b—d**) was also performed by this procedure. 3-Benzyl-3-methyl-1-(4-tolyl)-1-nitrosourea (**10c**) and the demethylated 3-nitrosourea (**4**) were obtained by nitrosation of 3-benzyl-3-methyl-1-(4-tolyl)urea (**9c**) in 60% and 4.5% yields, respectively.

Nitrosation of 3,3-diisopropyl-1-(4-tolyl)urea (**9b**) and 3,3-diethyl-1-(4-tolyl)urea (**9d**), which have no benzyl group, gave the corresponding trisubstituted 1-nitrosoureas (**10b** and **10d**[8]), but no dealkylated nitrosourea was produced. 3,3-Diisopropyl-1-(4-tolyl)-1-nitrosourea (**10b**) was obtained from the urea (**9b**) in 20% yield. The analytical and spectral data for the nitrosoureas (**10a—c**) are listed in Tables I and II.

Thermolysis of 3,3-Dialkyl-1-(4-tolyl)-1-nitrosoureas (10a, c) Isolation of Decomposition Products (**9a, c, 12a, c—14a, c**): 3,3-Dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**) (100 mg, 0.28 mmol) was dissolved in CCl_4 (10 ml), and the solution was kept at 33 °C for 24 h under argon. The resulting precipitate of the denitrosated urea (**9a**) was filtered off. The filtrate was concentrated under reduced pressure. A small amount of $CHCl_3$ was added to the residue, and the solution was chromatographed on a column of silica gel with a mixture of *n*-hexane–ether (4 : 1) as an eluting solvent. The first fraction gave 3,3-dibenzyl-1-(4-tolyl)triazene (**14a**). Yield, 13 mg (15%). Dibenzylnitrosamine (**12a**) and 3,3-dibenzyl-1-(2-nitro-4-tolyl)urea (**13a**) were obtained from the second and third fractions in 19% (12 mg) and 16% (17 mg) yields, respectively. The urea (**9a**) was also found in the last fraction, and the total yield of **9a** was 23% (21 mg).

Similar treatment of **10c** gave the corresponding products (**9c**, **12c—14c**). All products gave spectral data identical with those of authentic samples described below. Their yields are listed in Table III.

Formation of 4-Tolyl Isocyanate (**11**): When 3,3-dibenzyl-1-(4-tolyl)-1-nitrosourea (**10a**) was dissolved in CCl_4 and the solution was permitted to stand at room temperature, the IR spectrum of the solution showed a strong N=C=O group absorption at 2260 cm^{-1} together with a CO_2 absorption band at 2320 cm^{-1} (Fig. 2). The absorption at 2260 cm^{-1} increased with the passage of time, and was identical with the N=C=O group absorption of 4-tolyl isocyanate (commercial material, Wako Ltd.).

Moreover, a solution of each nitrosourea (**10a, c**) (0.28 mmol) in 2 ml of CCl_4 was kept at 33 °C for 24 h under an atmosphere of argon. The solution was then diluted to exactly 10 ml with acetone. The yields of 4-tolyl isocyanate (**11**) were determined by GC using tetralin as an internal standard. A 2 m OV-1 stainless steel column was used with a nitrogen carrier flow of 60 ml/min. The detector, column and injector port temperature were 120, 120 and 140 °C, respectively. The results are listed in Table III.

Preparation of *N*-Nitrosodialkylamines (12a, c) Dibenzylamine (2.0 g, 10 mmol) was dissolved in 99% formic acid (20 ml). Sodium nitrite (0.9 g, 13 mmol) was added to the solution at 0—5 °C. The reaction mixture was stirred for 30 min, maintaining the temperature below 5 °C, then added to $CHCl_3$ and water, and the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was filtered through a silicon-treated filter paper (1 ps phase separator, Whatman Ltd.) and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel with a mixture of ether and *n*-hexane (1 : 9). The first fraction gave *N*-nitrosodibenzylamine (**12a**). Colorless crystals were obtained by recrystallization from ether. mp 58—59 °C (dec.) [lit.,[14] mp 58—59 °C (dec.)]. Yield, 1.26 g (55%). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.16; H, 6.23; N, 12.29. ^{13}C-NMR ($CDCl_3$) δ: 134.6, 129.0, 128.5, 128.8, 128.5, 129.0 (*E*-isomer, phenyl C^1-C^6), 55.0 (*E*-isomer, CH_2); 134.0, 128.4, 129.0, 127.9, 129.0, 128.4 (*Z*-isomer, phenyl C^1-C^6), 44.9 (*Z*-isomer, CH_2). Dibenzylamine was recovered from the second fraction. *N*-Nitroso-*N*-methylbenzylamine (**12c**) was prepared by the same procedure as in the case of **12a** as an oily product.[14,15] *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.76; H, 6.86; N, 18.36. ^{13}C-NMR ($CDCl_3$) δ: 134.7, 128.7, 128.0, 128.3, 128.0, 128.7 (*E*-isomer, phenyl C^1-C^6), 57.4 (*E*-isomer, CH_2), 30.8 (*E*-isomer, *N*-Me); 133.9, 127.9, 128.8, 129.0, 128.8,

TABLE IV. ^{13}C-NMR Chemical Shifts (ppm)[a] of Ureas (**9**), Nitro Compounds (**13**), and Triazenes (**14**)

Compd.	Tolyl							CO	*N*-Me	*N*-iso-Pr		*N*-CH_2Ph				
	C-1	C-2	C-3	C-4	C-5	C-6	*C*-Me			CH	Me	CH_2	C-1	C-2,6	C-3,5	C-4
9a	132.6	120.2	129.2	136.5	129.2	120.2	20.7	156.1				52.7	137.4	127.4	128.9	127.7
9b	132.0	120.0	129.3	137.0	129.3	120.0	20.7	154.8		45.5	21.6					
9c	132.5	120.5	129.2	136.7	129.2	120.0	20.7	156.1	34.6			52.4	137.7	127.3	128.7	127.4
13a	131.6	135.8	125.2	134.8	136.6	121.8	20.3	155.0				50.4	136.7	127.3	128.8	127.7
13c	131.5	135.7	125.5	135.3	136.9	121.5	20.3	154.9				52.4	137.1	127.5	128.8	127.6
14a	148.3	120.8	127.4	135.4	127.4	120.8	21.0					50.4[b]	136.8	128.3	128.5	129.5
14c	148.7	120.6	128.7	135.3	128.7	120.6	21.0		35.0[b]			58.0[b]	137.0	127.6	128.0	129.5

a) Measured in $CDCl_3$ with TMS as an internal standard. *b*) Broad peak.

127.9 (*Z*-isomer, phenyl C^1-C^6), 47.7 (*Z*-isomer, CH_2), 38.3 (*Z*-isomer, *N*-Me).

Preparation of 3,3-Dialkyl-1-(2-nitro-4-tolyl)ureas (13a, c) Fuming nitric acid (*d*: 1.52, 1.5 ml) was added to a suspension of 3,3-dibenzyl-1-(4-tolyl)urea (**9a**) (1.65 g, 5 mmol) in acetic acid (15 ml) at 5—10 °C with stirring, and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into crushed ice and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated sodium bicarbonate solution and water, and filtered through a silicon-treated filter paper (1 ps phase separators, Whatman Ltd.). The solvent was evaporated off in an ice-water bath. The residue was chromatographd on a column of silica gel with $CHCl_3$ as an eluting solvent. Yellow crystals of 3,3-dibenzyl-1-(2-nitro-4-tolyl)urea (**13a**) were obtained by recrystallization from acetone–ether. mp 111—112 °C. Yield, 1.37 g (73%).

3-Benzyl-3-methyl-1-(2-nitro-4-tolyl)urea (**13c**) was obtained by the same procedure. mp 75—76 °C. Yield, 64%. Their physicochemical, analytical and spectral data are listed in Tables I and IV.

Preparation of Triazenes (14a, c) A solution of sodium nitrite (1.4 g, 20 mmol) in water (3.5 ml) was added to a solution of *p*-toluidine (2.14 g, 20 mmol) in a mixture of 36% HCl (3.0 ml) and water (20 ml) at 0 °C with stirring, and the mixture was stirred for a further 30 min, then was added to a solution of dibenzylamine (4.0 g, 20 mmol) in water (50 ml) at 0—5 °C with stirring. After being stirred for 2 h, the reaction mixture was extracted with ether, and the ether layer was filtered through a silicon-treated filter paper (1 ps phase separators, Whatman Ltd.). The solvent was evaporated off and the residue was chromatographed on a column of silica gel with *n*-hexane as an eluting solvent. Colorless crystals from ether. mp 65.5—66.5 °C. Yield, 5.9 g (93%).

3-Benzyl-3-methyl-1-(4-tolyl)triazene (**14c**) was prepared by the same procedure as a yellow oily product. Yield, 88%. Their physicochemical, analytical and spectral data are listed in Tables I and IV.

Trapping of Nitrosyl Radical by Metal Complex A μ-oxo dimer of *N*,*N*′-ethylenebis(salicylideneiminato)iron(III), $(Fe\text{-salen})_2O$ was prepared by the published method.[12] The prepared $(Fe\text{-salen})_2O$ (0.01 g, 0.015 mmol) was added to a solution of nitrosourea (**10a**) (0.018 g, 0.05 mmol) in CCl_4–$CHCl_3$ (4:1, 10 ml). The reaction mixture was allowed to stand overnight at room temperature. The resultant precipitate was filtered off, washed with ether and methanol, and dried at room temperature to give the NO_3 complex of *N*,*N*′-ethylenebis(salicylideneiminato)iron(III).[13] The spectral data of this compound agreed with those of Fe-salen-NO_3 that was prepared from $(Fe\text{-salen})_2O$ by bubbling of nitric oxide (Sumitomo Seika Ltd.) and oxygen in CH_2Cl_2 at room temperature. The obtained black powder of Fe-salen-NO_3 showed the formula $C_{14}H_{14}FeN_3O_5$. Mass peaks at 384 (M^+), 338 ($M^+ - NO_2$), and 322 ($M^+ - NO_3$) were identical with those in the literature.[13] It forms a purple solution in $CHCl_3$.

Acknowledgement The authors are grateful to Mrs. H. Kitamura, the Analytical Center, School of Pharmaceutical Sciences of Shizuoka, for elemental analysis.

References

1) R. Huisgen and L. Krause, *Justus Liebigs Ann. Chem.*, **574**, 157 (1951); D. H. Hey, J. Stuart-Webb, and G. H. Williams, *J. Chem. Soc.*, **1952**, 4657; M. Miyahara and S. Kamiya, *Chem. Pharm. Bull.*, **30**, 3466 (1982); E. H. White, T. J. Ryan, B. S. Hahn, and R. H. Erickson, *J. Org. Chem.*, **49**, 4860 (1984).
2) P. Welzel, *Chem. Ber.*, **104**, 808 (1971).
3) S. S. Singer, *J. Org. Chem.*, **47**, 3839 (1982).
4) M. Tanno and S. Sueyoshi, *Chem. Pharm. Bull.*, **35**, 1360 (1987).
5) M. Tanno, S. Sueyoshi, and S. Kamiya, *Chem. Pharm. Bull.*, **38**, 49 (1990).
6) B. C. Challis and J. A. Challis, "The Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers, John Wiley & Sons, London, 1970, p. 744.
7) C. N. Berry and B. C. Challis, *J. Chem. Soc., Perkin Trans. 2*, **1974**, 1638.
8) S. Sueyoshi and M. Tanno, *Chem. Pharm. Bull.*, **33**, 488 (1985).
9) R. N. Leoppky and W. Tomasik *J. Org. Chem.*, **48**, 2751 (1983).
10) S. Kamiya and S. Sueyoshi, *Chem. Pharm. Bull.*, **29**, 1267 (1981).
11) M. Tanno and S. Sueyoshi, *Chem. Pharm. Bull.*, **35**, 1353 (1987).
12) A. Nakahara and Y. Nakao, "Shin-Jikkenkagakukouza," Col. Vol. 8, ed. by Nippon Kagakukai, Maruzen Shuppan, Inc., Tokyo, 1975, p. 1549.
13) A. F. Croisy, J. C. Fanning, L. K. Keefer, B. W. Slavin, and S. J. Uhm, *IARC. Sci. Publ.*, **31**, 83 (1980).
14) J. W. Pensabene, W. Fiddler, C. J. Dooley, R. C. Doerr, and A. E. Wasserman, *J. Agr. Food. Chem.*, **20**, 274 (1972).
15) J. P. Gouesnard and G. J. Martin, *Org. Magn. Reson.*, **12**, 263 (1979).