1,3-Nitroso Rearrangement and Transnitrosation of 1-Aryl-3-benzyl-1-nitrosoureas Which Decompose to Liberate Nitrosyl Radical under Mild Conditions[1)]

Masayuki TANNO,* Shoko SUEYOSHI and Shozo KAMIYA

National Institute of Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 185, Japan. *Received June 9, 1989*

Thermolysis of 1-aryl-3-benzyl-1-nitrosoureas (1c, d) was carried out in CCl_4 at 33 °C under an atmosphere of air or argon. Decomposition of 1c, d under aerobic conditions gave mainly benzyl isocyanate (4b) *via* a diazoester intermediate, whereas under anaerobic conditions, decomposition gave 1-aryl-3-benzyl-3-nitrosoureas (5c, d) as 1,3-shifted products, and 3-benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (8c, d) as transnitrosated products *via* N–NO bond cleavage. 3-Benzyl-1-(4-substituted 2-nitrophenyl)ureas (6c, d) were also produced by N–NO bond cleavage. The 1,3-nitroso shift and transnitrosation under these conditions were assumed to involve a nitrosyl radical fission pathway. The nitrosated nitro compounds (8c, d) were also obtained together with 6c, d by nitration of the ureas (7c, d) with a mixture of fuming nitric acid and acetic acid. The *N*-nitrosourea (1c) acted as a nitrosating agent on 3-methyl-1-(4-tolyl)urea (7a) to convert it into nitrosoureas (1a and 5a).

From our results, we presumed that the *O*-nitrosoisourea (11) or its isomer (12) was an intermediate in the 1,3-nitroso shift and also an ultimate nitrosating agent in the transnitrosation reaction.

Keywords nitrosourea; *O*-nitrosoisourea; nitrosyl radical; 1,3-nitroso shift; transnitrosation; radical reaction; diazoester rearrangement; Chapman rearrangement

Many reports on *N*-nitrosoureas have dealt with the biological activities of aliphatic *N*-nitrosoureas such as 1,3-dialkylnitrosoureas.[2,3)] While studying the preparation of aryl-1-nitrosoureas (**1**). We also examined the decomposition of 3,3-dialkyl-1-aryl-1-nitrosoureas (**2**)[5)] under mild conditions.

composition of 3,3-dialkyl-1-aryl-1-nitrosoureas (**2**)[5)] under mild conditions.

As shown in Chart 1, 1-aryl-3-methyl-1-nitrosoureas (**1a, b**) in carbon tetrachloride at 33 °C decomposed to give aryl diazohydroxides (**3a,b**), methyl isocyanate (**4a**), 1-aryl-3-methyl-3-nitrosoureas (**5a,b**), 3-methyl-1-(4-substituted 2-nitrophenyl)ureas (**6a,b**) and 1-aryl-3-methylureas (**7a,b**). The possibility of producing aryl diazohydroxides (**3**) and alkyl isocyanates (**4**) in the decomposition of 1-aryl-1-nitrosoureas (**1**) was decribed in our previous paper.[1)] The antitumor activities of 1-aryl-3-methyl-3-nitrosoureas (**5**) have been investigated by Yano *et al.*[6)]

The decomposition mechanism and the biological properties of *N*-aryl-*N*-nitroso type ureas (**1**) are not known in detail. The thermolysis of *N*-nitrosoureas (**1a,b**) was considered[1,5)] to proceed by both a diazoester rearrangement and an N–NO bond cleavage. Aryl diazohydroxides (**3a,b**) and methyl isocyanate (**4a**) were produced *via* the corresponding diazoester intermediate.[1)] Other compounds (**6—8**) were also produced from the N–NO bond cleavage.[5,7,8)] The 3-nitrosoureas (**5a,b**) were formed from the 1-nitrosoureas (**1a,b**) by thermal 1,3-rearrangement of the nitroso group.[1)]

It is known[1,9,10)] that the disubstituted 1-nitrosoureas isomerize to the corresponding 3-nitrosoureas in the presence of acids. Despite the absence of acids, 1-aryl-3-methyl-1-nitrosoureas (**1a,b**) isomerized to the corresponding 3-nitrosoureas (**5a,b**). Migration of a nitroso group is formally similar to the isomerization of **1a** under acidic conditions. However, the mechanism of the 1,3-nitroso

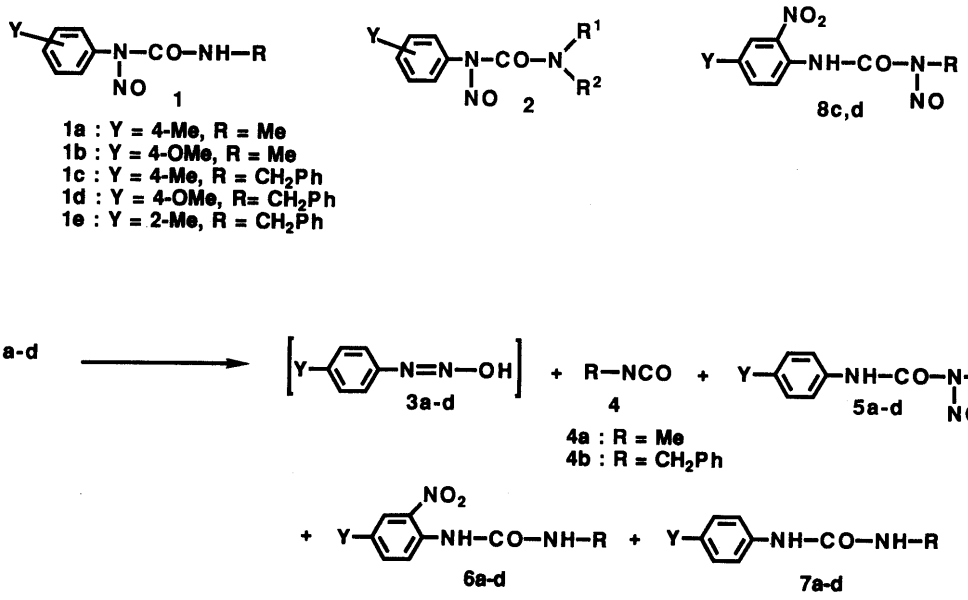


Chart 1

shift reaction in an aprotic solvent such as carbon tetrachloride may differ from that seen under the acidic conditions.

We studied the thermolysis of 1-aryl-3-benzyl-1-nitrosoureas (**1c—e**). The decomposition of 3-benzyl-1-(4-tolyl or 4-methoxyphenyl)-1-nitrosoureas (**1c,d**) under an atmosphere of argon, which is also described in this paper, also gave 3-benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (**8c,d**) as new products. The 3-nitrosoureas (**8**) are the eventual transnitrosated products of **6** arising from **1**. The mechanisms of the formation of the 3-nitrosoureas (**5**, **8**) in the decomposition of **1** are not well known; it is not clear whether nitrosyl radical liberation is involved or not. We wish to report here on the decomposition mechanism of 1-aryl-1-nitrosoureas (**1c—e**) in connection with a Fisher–Hepp rearrangement[11] in an acid-catalyzed reaction.

Results and Discussion

1-Nitrosoureas (**1**) and their 3-nitroso isomers (**5**), with 1-(4-tolyl), 1-(4-methoxyphenyl) and 1-(2-tolyl) substituents, were prepared by nitrosation of the corresponding ureas (**7**) using a method described in a previous paper.[1] Their analytical and spectral data are shown in Tables I and II.

When the 4-substituted phenyl derivatives of *N*-nitrosoureas (**1c,d**) were dissolved in carbon tetrachloride and allowed to stand at 33 °C for 6 h under aerobic conditions or under an atmosphere of argon, they decomposed to give products (**4b**, **5c,d—8c,d**) as shown in Chart 1. These products were identified by comparison with authentic samples. Their yields were determined by high-performance liquid chromatography (HPLC) with the aid of an internal standard, and are shown in Table III. The isocyanates (**4**) were preferentially formed in air. In contrast, the 1,3-nitroso-shifted products (**5**) and the transnitrosated compounds (**8**) were preferred in argon. The yields of nitro compounds (**6**) were somewhat better in air.

A detailed examination of the thermolysis of 4-substituted phenylnitrosoureas (**1**) using HPLC was performed with **1c**. Time courses of product yields are displayed in Fig. 1, with first-order rate plots for the decomposition of **1c**. The rate constant under aerobic conditions was $4.85 \times 10^{-5}\,s^{-1}$, and a major product was benzyl isocyanate (**4b**) (40% yield) obtained *via* a diazoester rearrangement.[12]

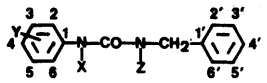
When **1c** was dissolved in carbon tetrachloride and the solution was permitted to stand overnight at room temperature, the infrared (IR) spectrum of the resulting decompostion mixture showed a strong N=C=O group absorption at $2250\,cm^{-1}$. The 1,3-rearranged compound (**5c**) was found in an 8% yield in air. Formation of the transnitrosated compound (**8c**) could not be detected. On the other hand, the first-order plot in argon was curved and appeared to be composed of two linear components. The rate constant for the initial stage was $5.27 \times 10^{-5}\,s^{-1}$, and was close to the value of the rate constant under aerobic conditions. The second stage had a rate constant of $3.36 \times 10^{-4}\,s^{-1}$. In the second stage, the main products were the 1,3-nitroso-shifted compound (**5c**) (55% yield) with the transnitrosated compound (**8c**) (3% yield). The isocyanate (**4b**) was not observed. In the decomposition of nitrosourea (**1c**), the nitro compound (**6c**) and the denitrosated compound (**7c**) were minor products, and their yields were less than 12% under both air and argon. In spite of the argon atmosphere, the nitro compound (**6c**) derived by oxidation was always

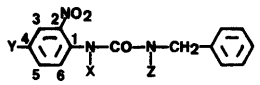
TABLE I. Physicochemical Properties and Analytical Data of 1-Aryl-3-benzylureas

Compd.	Yield[a] (%)	mp (°C)[b]	Formula	Analysis (%) Calcd (Found)			IR[c] ν cm^{-1}	
				C	H	N	N^{1}H N^{3}H	Ring CO
1c	10	85.5—86.5[e]	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61	—	1600w
				(66.65	5.65	15.64)	3430	1720
1d	10	90.5—91.5[e]	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73	—	1605m
				(63.24	5.56	14.36)	3430	1715
1e	12	91—92[e]	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61	—	1605w
				(66.73	5.61	15.48)	3430	1725
5c	80	100—101[e]	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.61	3390	1590s
				(66.79	5.61	15.69)	—	1725
5d	65	95—96[e]	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73	3400	1595s
				(62.95	5.31	14.86)	—	1720
5e	70	77.5—78.5[e]	$C_{15}H_{15}N_3O_2$	66.96	5.61	15.61	3410	1585s
				(67.02	5.69	15.72)	—	1720
6c	70	176—177	$C_{15}H_{15}N_3O_3$	63.15	5.30	14.73	3340	1575s
				(63.09	5.31	14.69)	3440	1690
6d	65	193.5—194.5	$C_{15}H_{15}N_3O_4$	59.79	5.02	13.95	3300	1575m
				(59.28	4.94	13.97)	3440	1685
7c	97	168—169	$C_{15}H_{16}N_2O$	74.97	6.71	11.66	3025[d]	1610sh
				(74.84	6.78	11.63)	3300[d]	1615
7d	98	166.5—167.5	$C_{15}H_{16}N_2O_2$	70.39	6.29	10.93	3060[d]	1605s
				(70.19	6.33	10.88)	3300[d]	1620
7e	88	134.5—135.5	$C_{15}H_{16}N_2O$	74.97	6.71	11.66	3025[d]	1605m
				(74.86	6.81	11.57)	3310[d]	1625
8c	13	96—97	$C_{15}H_{14}N_4O_4$	57.32	4.49	17.83	3280	1575s
	(80)			(57.12	4.44	17.89)	—	1725
8d	12	100—101	$C_{15}H_{14}N_4O_5$	54.54	4.27	16.96	3300	1580s
	(85)			(54.07	4.26	16.75)	—	1730

a) Isolated yields. Yields from **6** are given in parentheses. *b*) Compounds **1** and **5** were recrystallized from a mixture of *n*-hexane and ether, and **6—8** were from acetone. *c*) Compounds **7** were measured in Nujol mull and others in $CHCl_3$. Abbreviation: s, strong; w, weak; m, moderate; sh, shoulder. *d*) Two NH stretching bands were indistinguishable. The bands at $3300\,cm^{-1}$ were strong and broad. *e*) Decomposition points.

TABLE II. ^{13}C-NMR Chemical Shifts (ppm)[a] of *N*-Nitrosoureas (**1**, **5**, **8**), Nitro Compounds (**6**) and Ureas (**7**)





1: X=NO, Z=H **5**: X=H, Z=NO **7**: X=Z=H **6**: X=Z=H **8**: X=H, Z=NO

Compd.	Y	C-1 C-1′	C-2 C-2′	C-3 C-3′	C-4 C-4′	C-5 C-5′	C-6 C-6′	CO	CH_2	Me	OMe
1c	4-Me	129.4	127.6	130.0	140.2	130.0	127.6	153.4		21.3	
		137.3	127.9	128.8	127.8	128.8	127.9		44.6		
1d	4-OMe	124.3	129.1	114.6	110.3	114.6	129.1	153.5			55.4
		137.4	128.0	128.8	127.8	128.8	128.0		44.7		
1e	2-Me	131.9	136.2	130.3	127.7	130.9	126.9	153.1		17.4	
		137.5	127.8	128.7	128.0	128.7	127.8		44.5		
5c	4-Me	134.1[b]	120.4	129.8	134.8[b]	129.8	120.4	150.6		20.9	
		134.5	128.6	128.8	127.9	128.8	128.6		42.8		
5d	4-OMe	129.7	122.2	114.5	157.1	114.5	122.2	150.8			55.5
		134.6	128.6	128.7	127.9	128.7	128.6		42.8		
5e	2-Me	129.4	134.8[b]	130.7	125.6	127.0	122.6	150.8		17.6	
		134.5[b]	128.6	128.8	127.9	128.6	128.7		42.9		
6c	4-Me	131.6	138.3	125.3	134.6	136.9	121.6	154.2		20.3	
		135.6	127.7	128.8	127.6	128.8	127.7		44.7		
6d	4-OMe	130.9	138.3	108.0	153.9	123.4	124.2	154.3			55.9
		136.2	127.7	128.8	127.6	128.8	127.7		44.7		
7c	4-Me	134.4[b]	122.5	130.0	135.6[b]	130.0	122.5	155.1		20.8	
		139.0	127.5	128.7	127.4	128.7	127.5		44.5		
7d	4-OMe	130.8	125.2	114.8	157.4	114.8	125.2	156.6			55.6
		139.1	127.5	128.7	127.4	128.7	127.5		44.4		
7e	2-Me	133.0	136.0	131.1	126.3	127.6[b]	125.9	156.4		17.8	
		139.1	127.5[b]	128.7[b]	127.4[b]	128.7[b]	127.5[b]		44.5		
8c	4-Me	131.4	137.2	125.9	134.4[b]	136.7	121.9	151.1		20.6	
		134.3[b]	128.7[c]	128.7[c]	128.0	128.7[c]	128.7[c]		42.8		
8d	4-OMe	127.2	138.1	109.2	155.6	123.2	123.6	151.1			56.0
		134.4	128.6	128.7	128.0	128.7	128.6		42.8		

a) Measured in $CDCl_3$ with TMS as an internal standard. Measured at −10 °C for **1c**—**d** and at room temperature for other compounds. *b*) Assignments may be reversed. *c*) Overlapping.

TABLE III. Yields of Decomposition Products of Nitrosoureas (**1**) in CCl_4 at 33 °C

Conditions	Compd.	Products (%)[a]				
		4	**5**	**6**	**7**[c]	**8**[c]
Air[b]	**1c**	40	5	8	12	—
	1d	31	8	29	11	—
Argon[b]	**1c**	—	55	6	3	3
	1d	—	34	15	15	0.2

a) Determined by HPLC. *b*) The extent of decomposition of **1** was 60% in air and 80% in argon. *c*) Final yields.

observed, presumably due to air contamination caused by small leaks in the reaction system.

The formation of the 1,3-shifted compound (**5c**), the oxidized product (**6c**), and the transnitrosated compound (**8c**) *via* a pathway of N–NO bond cleavage proceed more smoothly under argon than under aerobic conditions. The slow decomposition in the first stage under argon proceeds in a similar manner under aerobic conditions because of a small amount of oxygen in the reaction system. Formation of the nitro compounds (**6**) as oxidation products consumed oxygen in the reaction system. Consequently, more rapid decomposition during the second, oxygen-free stage gave the 3-nitroso isomer (**5**) *via* the N–NO bond cleavage.

Benzyl isocyanate (**4b**) was preferentially formed in air, and was not observed in argon. Currently, it is not clear

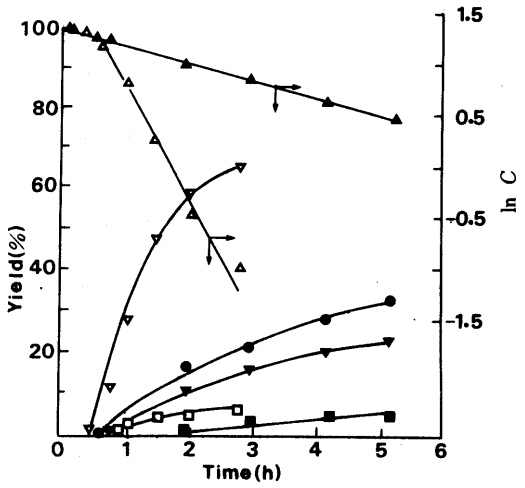


Fig. 1. Relationship between ln *C* (*C*; Concentration of **1c**) and Time for the Decomposition of 3-Benzyl-1-(4-tolyl)-1-nitrosourea (**1c**) in CCl_4 at 33 °C, and Percent Yields of Benzyl Isocyanate (**4b**), 3-Benzyl-1-(4-tolyl)-3-nitrosourea (**5c**), and 3-Benzyl-1-(2-nitro-4-tolyl)urea (**6c**) *vs.* Time as Determined by HPLC

Air: **1c**, ▲; **4b**, ●; **5c**, ▼; **6c**, ■. Argon: **1c**, △; **5c**, ▽; **6c**, □.

why the formation of benzyl isocyanate (**4b**) *via* a diazoester intermediate (**9**) is favored in the presence of oxygen. However, the following mechanism is suggested to account for the decomposition of compound **1** (Chart 2). Thermal cleavage of the N–NO bond generates a nitrosyl (NO) and a

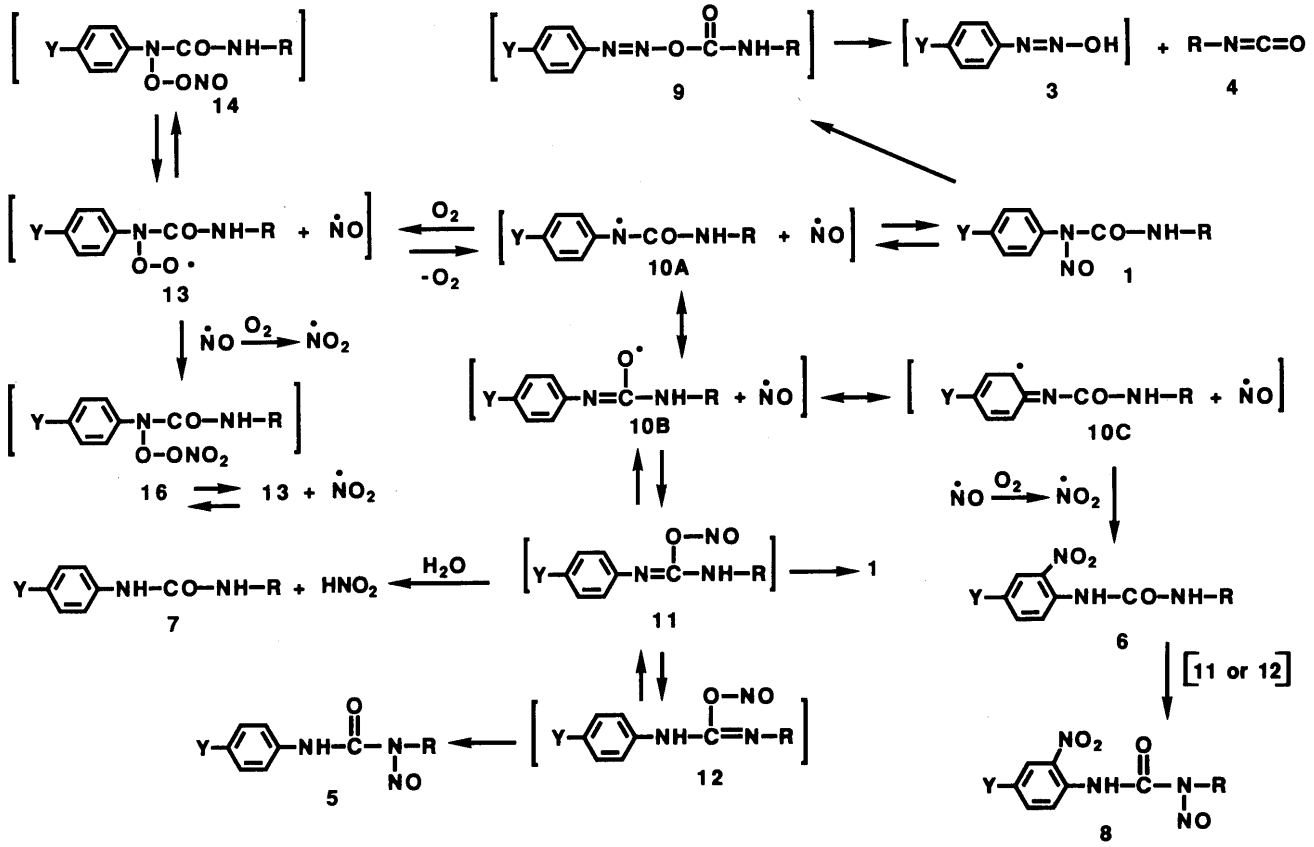


Chart 2

ureidyl radical (**10**). Recombination of these two partially regenerates the starting nitrosourea (**1**) or yields *O*-nitrosoisourea (**11**) through a resonance hybrid of the ureidyl radical (**10A**—C). The *O*-nitrosoisourea (**11**), or its proton-transformed isomer (**12**), is thought to be an intermediate in the decomposition of **1** to give the 3-nitrosourea (**5**).

It is widely known that *O*-alkylimidates undergo Chapman rearrangement[13,14] to *N*-alkylamides by a thermodynamically controlled process. Therefore, the resulting intermediate (**10**) reverts to the parent nitrosourea (**1**), or after the proton has shifted, the intermediate (**12**) rearranges to the thermodynamically stable 3-nitrosourea (**5**) by an analogous Chapman rearrangement. When oxygen is present in the reaction system, a nitrosyl radical is oxidized to a nitro radical (NO_2). The nitro radical reacts with the ureidyl radical to form the nitro compound (**6**). In addition, oxygen also reacts with the ureidyl radical to give a ureidyl-oxygen radical (**13**), followed by a nitrosyl radical to give an adduct (**14**). Formation of these oxygen adducts (**13**, **14**) competes with formation of *O*-nitroso intermediates (**11**, **12**). Oxygen prevents the 1,3-nitroso transfer *via* an *O*-nitroso intermediate and reduces the yield of the 3-nitrosourea (**5**).

In the decomposition of 3-benzyl-1-(4-methoxyphenyl)-1-nitrosourea (**1d**), the rate constant was $k = 3.80 \times 10^{-5}\,s^{-1}$ in air. Furthermore, $k = 5.43 \times 10^{-5}\,s^{-1}$ in the first stage, and $k = 1.08 \times 10^{-4}\,s^{-1}$ in the second stage in argon. The nitro compound (**6d**) was formed in good yield compared with the 4-tolyl derivative (**1c**). This is significant since the ureidyl radical (because of the contribution of **10C** due to a resonance effect of the *p*-MeO group) is likely to produce the nitro compound (**6d**).

The Fisher–Hepp rearrangement involves transformation from *N*-nitroso to *C*-nitroso compounds under acidic conditions, for example, from *N*-nitroso-*N*-methylaniline to *N*-methyl-4-nitrosoaniline in hydrochloric acid.[11] It is believed that the attacking entity is nitrosyl chloride.[15,16]

In our study, the conversion of compound **1** to 3-alkyl-1-(2-nitroso-4-tolyl)ureas (**15**) failed under our experimental conditions. The 1,3-nitroso rearrangement *via* an *O*-nitroso intermediate (**11**) occurs preferentially because *O*-nitrosation is more rapid than phenyl-*C*-nitrosation. In this regard, the nitrophenyl compound (**6**) is believed to be produced by air oxidation of a nitrosyl radical,[8] and not by oxidation of the *C*-nitroso compound (**15**). In general, oxidation of the *C*-nitroso (**15**) to the *C*-nitro compound (**6**) requires an oxidizing agent such as $K_2Cr_2O_7$[17] or NO^+[18] under acidic conditions.

The transnitrosated products (**8**) were finally obtained in 0.2—3% yields only under an atmosphere of argon. It is worth noting that thermal transnitrosation of *N*-nitroso compounds took place in the absence of acids, because this is rarely seen, except with *N*-nitrosodiphenylamine,[19] *N*-nitrosocarbazole[20] and 3-isopropyl-1-(4-tolyl)-1-nitrosourea.[1] Usually, the presence of acids and nucleophilic reagents in the reaction accelerates the transfer of a nitroso group of *N*-nitrosoureas to secondary amines.[21] However, the compounds (**8c,d**) are believed to be derived by the reaction of the nitro compounds (**6c,d**) with **1c,d**.

In our case, the intermediate (**11** or **12**) acted as a nitrosating agent, and nitrosated the resulting nitro compounds (**6c,d**) to give 3-nitrosoureas (**8c,d**). Formation of **8** *via* the *O*-nitrosoisourea (**11**) is also inhibited by the

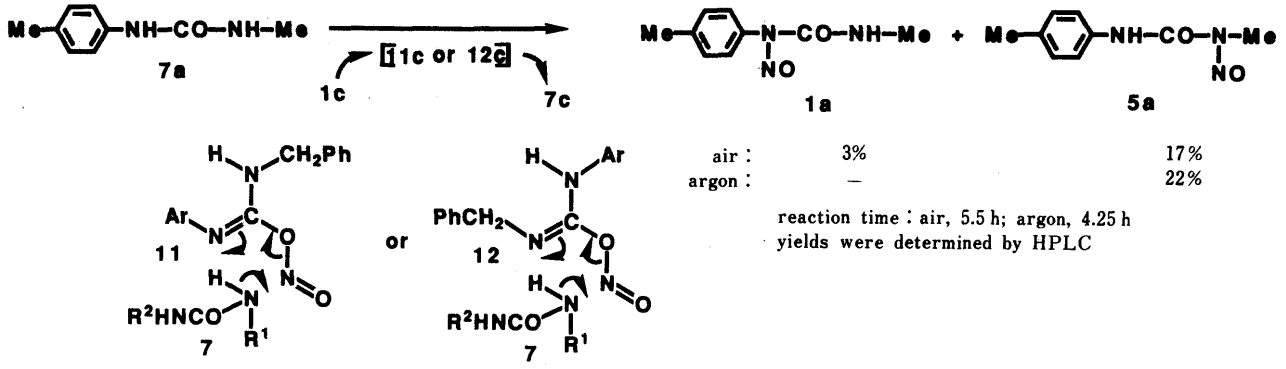


Chart 3

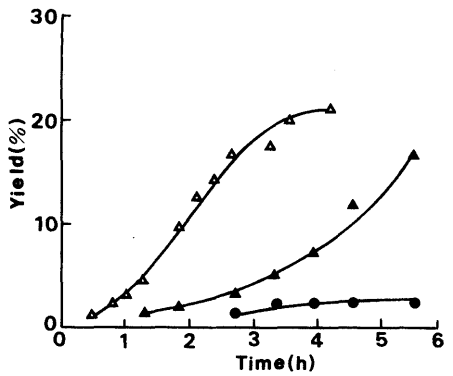


Fig. 2. Transnitrosation of 3-Benzyl-1-(4-tolyl)-1-nitrosourea (**1c**) to 3-Methyl-1-(4-tolyl)urea (**7a**)

Yields of the products, 3-methyl-1-(4-tolyl)-1-nitrosourea (**1a**) and 3-methyl-1-(4-tolyl)-3-nitrosourea (**5a**), were determined by HPLC. Air: **1a**, ●; **5a**, ▲. Argon: **5a**, △.

presence of oxygen. Thus, the *O*-nitroso intermediate (**11** or **12**) nitrosates other ureas similarly to the nitro compounds (**6**).

In order to clarify further the transnitrosation process, we performed transnitrosation using the *N*-nitrosourea (**1c**) and 3-methyl-1-(4-tolyl)urea (**7a**) in carbon tetrachloride at 33 °C under aerobic or anaerobic conditions (Chart 3). The formation curve of the transnitrosated products is shown in Fig. 2. Both transnitrosated products, 3-methyl-1-(4-tolyl)-1-nitrosourea (**1a**) (3% yield) and 3-methyl-1-(4-tolyl)-3-nitrosourea (**5a**) (17% yield), were formed under aerobic conditions. Compound **5a** (22% yield) was produced faster in argon than in air. This may be attributed to competition between formation of the *O*-nitrosoisourea intermediate (**11**) and the radical species (**13**). Perhaps, the *O*-nitrosoisourea (**11** or **12**) nitrosates the urea (**7a**) through the interaction shown in Chart 3. The transnitrosated product, 1-nitrosourea (**1a**) was not observed in argon. This shows that the compound (**1a**) is also converted into its isomer (**5a**) *via* a 1,3-nitroso shift in the same manner as the isomerization from **1c** to **5c** in argon.

Thermolysis of 3-benzyl-(2-tolyl)-1-nitrosourea (**1e**) was very slow at 33 °C (in air, $k = 3.47 \times 10^{-6}\,s^{-1}$; in argon, $k = 4.91 \times 10^{-6}\,s^{-1}$), and its kinetic behavior in argon was linear, different from the decomposition of the 4-tolyl derivative (**1c**).

Benzyl isocyanate (**4b**), related to a diazoester rearrangement, was observed by IR spectroscopy. The corresponding nitro compound and the denitrosated product (**7e**) of N–NO bond cleavage were rarely observed. The cause seems to be the difference in degree of twisting about the phenyl–N^1 bond in the aryl-N^1(NO)CON^3(alkyl)$_2$ moiety between the 4-tolyl derivative (**1c**) and the 2-tolyl derivative (**1e**) as described previously.[4] The twisting (**1e**) deactivates N–NO bond cleavage, and activates a diazoester rearrangement.

We found during the preparation of the authentic samples of the nitro compounds (**6**) that nitration of the ureas (**7**) in a mixture of fuming nitric and acetic acid at room temperature gave the nitrosated nitro compounds (**8**) in about 13% yield, together with the nitro compounds (**6**) in about 70% yield. In spite of the nitrative conditions, nitrosation occurred. This is due to reaction of N_2O_4 contained in fuming nitric acid with the nitro compounds (**6**) produced by nitration, because N_2O_4 is known to have the ability to nitrosate.[22] Currently, we are attempting to detect the presence of an *O*-nitrosoisourea intermediate, and hope to publish our results in the near future.

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. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU chromatograph with a ultraviolet (UV) detector (JASCO 875-UV) operating at 254 nm, using a TSK-Gel LS 310K column (4 × 300 mm i.d., Toyo Soda) with *n*-hexane–ethyl acetate (80 : 20 and 87 : 13, v/v) as a mobile phase. Peak areas were determined with a Shimadzu C-R3A Chromatopac. The internal standard employed was 4-methyl-2-nitroacetanilide. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a Varian EM 360-A spectrometer and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were measured with a JEOL FX-200 spectrometer, with tetramethylsilane (TMS) as an internal standard. The abbreviations are as follows: s, singlet; d, doublet; br, broad.

1-Aryl-3-benzylureas (7c—e) Aryl isocyanate (aryl = 4-tolyl, 4-methoxyphenyl, 2-tolyl) (75 mmol) was added dropwise to an ice-cooled solution of benzylamine (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. Yield, 88—98%. ^{1}H-NMR (DMSO-d_6) δ: **1c**: 2.22 (3H, s, CH_3), 4.30 (2H, d, J = 7 Hz, CH_2), *ca.* 6.5 (1H, br, NH), 6.97, 7.26 (4H, d, J = 9 Hz, tolyl-H^{2,3}), 7.30 (5H, s, phenyl-H), *ca.* 8.4 (1H, br, NH). The spectral and analytical data of the ureas (**7**) are listed in Tables I and II.

***N*-Nitrosoureas (1c—e, 5c—e)** *N*-Nitrosoureas (**1**, **5**) were prepared by nitrosation of the ureas (**7**) in $CHCl_3$ at 5 °C using isoamyl nitrite as described in a previous paper.[1] A typical method is described below for **1c** and **5c**. Isoamyl nitrite (0.06 mol) was added dropwise to a suspension of 3-benzyl-1-(4-tolyl)urea (**7c**) (0.04 mol) in $CHCl_3$ (200 ml) at 0—5 °C and the mixture was stirred for 10 h. The unreacted urea was filtered off and the filtrate was evapoated 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. The first and the second fractions gave the 3-nitrosourea (**5c**) and the 1-nitroso isomer (**1c**) in 80% and 10% yields, respectively. ^{1}H-NMR ($CDCl_3$) δ: **1c**: 2.37 (3H, s, CH_3), 4.70 (2H,

d, $J=7$ Hz, CH_2), 6.84, 7.26 (4H, dd, $J=9$ Hz, tolyl-$H^{2,3}$), 7.38 (5H, s, phenyl-H), *ca.* 7.3 (1H, br, NH). **5c**: 2.35 (3H, s, CH_3), 5.05 (2H, s, CH_2), 7.20, 7.45 (4H, d, $J=9$ Hz, tolyl-$H^{2,3}$), 7.30 (5H, s, phenyl-H), *ca.* 8.75 (1H, br, NH).

Nitrosation of the ureas (**7d,e**) was carried out according to the method described for **7c**. When the urea (**7e**) was nitrosated, the 1-nitrosourea (**1e**) and its 3-nitroso isomer (**5e**) were obtained 71% and 12% yields, respectively. In the case of **7d**, the first fraction gave the 3-nitrosourea (**5d**) (65% yield). The second fraction was a mixture containing the desired *N*-nitrosourea (**1d**) and the nitro compound (**6d**). To separate **1d** and **2d** by column chromatography was difficult. The mixture was crystallized in a freezer, and pale yellow crystals of **1d** and yellow crystals of **6d** were separated by the use of tweezers. **1d**: Yield, 10%. The physicochemical, analytical and spectral data are listed in Tables I and II.

3-Benzyl-1-(4-substituted 2-nitrophenyl)ureas (6c,d) and 3-Benzyl-1-(4-substituted 2-nitrophenyl)-3-nitrosoureas (8c,d) A typical experiment is described. Fuming nitric acid ($d=1.52$, 1.5 ml) was added to a suspension of 3-benzyl-1-(4-tolyl)urea (**7c**) (1.2 g, 5 mmol) in acetic acid (10 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 $NaHCO_3$ solution and with water, and was 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 chromatographed on a column of silica gel with $CHCl_3$ as an eluting solvent. The first fraction gave 0.2 g (12.7%) of 3-benzyl-1-(2-nitro-4-tolyl)-3-nitrosourea (**8c**), which was identical with an authentic sample produced by the nitrosation of **6c**. The second fraction gave 1.0 g (69.9%) of 3-benzyl-1-(2-nitro-4-tolyl)urea (**6c**). ^{1}H-NMR ($CDCl_3$) δ: **6c**: 2.35 (3H, s, CH_3), 4.48 (2H, d, $J=7$ Hz, CH_2), *ca.* 5.7 (1H, br, NH), 7.38, 7.96 (2H, dd, $J=9$, 2 Hz, tolyl-$H^{3,5}$), 8.55 (1H, d, $J=9$ Hz, tolyl-$H^{1,6}$), 7.34 (5H, s, phenyl-H), *ca.* 9.7 (1H, br, NH).

3-Benzyl-1-(4-methoxyphenyl)urea (**7d**) gave 3-benzyl-1-(2-nitro-4-methoxyphenyl)-3-nitrosourea (**8d**) from the first fraction and 3-benzyl-1-(4-methoxy-2-nitrophenyl)urea (**6d**) from the next fraction. The yields of **6d** and **8d** were 65% and 12%, respectively. Their physicochemical, analytical and spectral data are listed in Tables I and II.

The Nitrosation of 6c,d with Isoamyl Nitrite Isoamyl nitrite (0.7 g, 6.0 mmol) was added dropwise to a suspension of 3-benzyl-1-(2-nitro-4-tolyl)urea (**6c**) (1.43 g, 5.0 mmol) in $CHCl_3$ (50 ml) at 0—5 °C and stirred for 10 h. The unreacted **6c** was filtered off and the filtrate was evaporated to dryness under reduced pressure in an ice-water bath. The residue was chromatographed on a column of silica gel with $CHCl_3$ as an eluting solvent. The eluate gave 0.126 g (80%) of 3-benzyl-1-(2-nitro-4-tolyl) urea (**8c**). Yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: **8c**: 2.44 (3H, s, CH_3), 5.10 (2H, s. CH_2), 7.55, 8.10 (2H, dd, $J=9$, 2 Hz, tolyl-$H^{3,5}$), 8.78 (1H, d, $J=9$ Hz, tolyl-$H^{1,6}$), 7.3 (5H, s, phenyl-H), *ca.* 7.3 (1H, br, NH).

3-Benzyl-1-(2-nitro-4-methoxyphenyl)urea (**6d**) gave 3-benzyl-1-(2-nitro-4-methoxyphenyl)-1-nitrosourea (**8d**) in a similar manner. Yield, 85%. The physicochemical, analytical and spectral data are listed in Tables I and II.

Decomposition of *N*-Nitrosoureas (1c,d) The *N*-nitrosoureas (**1c,d**) (0.035 mmol) were dissolved in CCl_4 (exactly 10 ml) containing 4-methyl-2-nitroacetanilide[4] as an internal standard. The solutions were kept at 33 ± 0.5 °C for 6 h under an atmosphere of argon or air. The decomposition products were determined by the HPLC method. These results are shown in Fig. 1 and Table III. A similar experiment was performed on **1e**, but no product was observed.

Transnitrosation of *N*-Nitrosourea (1c) to the Urea (7a) 3-Benzyl-1-(4-tolyl)-1-nitrosourea (**1c**) (9.4 mg, 0.035 mmol) was added to a suspension of 3-methyl-1-(4-tolyl)urea (**7a**) (5.74 mg, 0.035 mmol) in CCl_4 solution (10 ml) containing an internal standard. The solution was kept at 33 ± 0.5 °C for 6 h under an atmosphere of argon or air. The yields of 3-methyl-1-(4-tolyl)-1-nitrosourea (**1a**) and 3-methyl-1-(4-tolyl)-3-nitrosourea (**5a**) were also determined by the HPLC method. The results are shown in Fig. 2 and Chart 3.

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