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Nitrosation of 1,3-Diarylureas with Nitrosyl Chloride, Dinitrogen Trioxide and Dinitrogen Tetroxide in Dimethylformamide

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Nitrosation of 1,3-diarylureas (Ia—f) with nitrosyl chloride or dinitrogen trioxide in dimethylformamide gave 1,3-diaryl-1-nitrosoureas (IIa—f) in 59—96% yields, and nitrosation of 1,3-diarylureas (Ia, c—f) with dinitrogen tetroxide also gave 1,3-diaryl-1-nitrosoureas (IIa, c—f) in 75—91% yields. However, nitrosation of 1,3-bis(4-methoxyphenyl)urea (Ib) with dinitrogen tetroxide in dimethylformamide resulted in the formation of 1-(4-methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)urea (III) in 60% yield, and nitrosation with a large excess of dinitrogen tetroxide gave 1,3-bis(4-methoxy-2-nitrophenyl)urea (IV) in 42% yield.

Keywords——nitrosation; nitration; dinitrogen trioxide; dinitrogen tetroxide; nitrosyl chloride; 1,3-diarylurea; 1,3-diaryl-1-nitrosourea

1-Alkyl-1-nitrosoureas [$RN(NO)CONH_2$] are well known as potent carcinogens, and some of them have been used to obtain experimental tumors for pathological studies. In contrast, some nitrosoureas having a 3-(2-chloroethyl)-3-nitrosoureido group [$-NHCON(NO)CH_2CH_2Cl$] are effective antitumor agents against some solid tumors as well as leukemia.[1] However, the chemical and biological activities of 1,3-diarylnitrosoureas [ArN(NO)CONHAr'] have not been clarified because of the difficulty of nitrosation due to the decrease in the basicity of the urea nitrogens and to their instability.

This paper describes the nitrosation of 1,3-diarylureas with three gaseous nitrosating agents, nitrosyl chloride, dinitrogen trioxide and dinitrogen tetroxide, in dimethylformamide.

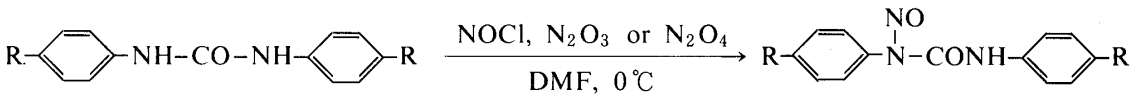
1,3-Diarylureas (Ia—f) were prepared by the reaction of aryl isocyanates with the appropriate anilines. 1,3-Bis(4-nitrophenyl)urea (Ie) was prepared by heating 4-nitrophenyl isocyanate in pyridine.

A combination of sodium nitrite and acids is generally used for the nitrosation of 1-alkyl- and 1,3-dialkylureas.[2] Dinitrogen trioxide, dinitrogen tetroxide and nitrosyl chloride are also used in some special cases. Since most 1,3-diarylureas (Ia—f) are poorly soluble in several nitrosating systems for alkylureas, these nitrosating systems could not be used. After several trials, we were able to prepare 1,3-diaryl-1-nitrosoureas (IIa—f) with such gaseous nitrosating agents as nitrosyl chloride (NOCl), dinitrogen trioxide (N_2O_3) and dinitrogen tetroxide (N_2O_4), in dimethylformamide.

A solution of nitrosyl chloride or dinitrogen trioxide in dimethylformamide was added to a solution of a 1,3-diarylurea (Ia—f) in dimethylformamide at 0°C. The 1,3-diaryl-1-nitrosourea (IIa—f) produced was extracted with ether from the reaction mixture. Since most of the resulting nitrosoureas were unstable at room temperature, they could not be subjected to elemental analysis, and their structures were confirmed by means of infrared (IR) and ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectroscopy,[3] and also by converting them to the corresponding 1-arylazo-2-naphthols. They could be preserved in a refrigerator for a few days. The yields and some physical data are tabulated in Table I.

The nitrosation of the 1,3-diarylureas was then tried with a combination of dinitrogen tetroxide and dimethylformamide. Treatment of Ia, Ic, Id, Ie and If with dinitrogen tetroxide in dimethylformamide at 0°C also gave the corresponding *N*-nitrosoureas (IIa, IIc, IId, IIe, IIf) in 75—91% yields (Table I). However, the same treatment of 1,3-bis(4-

TABLE I. 1,3-Diarylnitrosoureas (IIa—f)



Ia—f IIa—f

Compd. No.	R	mp (°C)	IR (C=O) (Nujol, cm^{-1})	^{1}H-NMR (NH) (Acetone-d_6, ppm)	Yield (%) NOCl	N_2O_3	N_2O_4
IIa	CH_3	105	1730	9.75	94	96	85
IIb	CH_3O	101	1720	9.50	83	75	—[a]
IIc	F	118	1715	8.88	91	81	78
IId	Cl	134	1740	10.08	75	59	80
IIe	NO_2	138	1725	—[b]	78	68	91
IIf	H	107	1725	9.80	96	70	75

a) Formation of 1-(4-methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)urea (III).
b) Not identified.

methoxyphenyl)urea (Ib) gave an unstable product. When the ethereal solution of this unstable product was allowed to stand at room temperature overnight, it changed to a ring *C*-nitro compound, 1-(4-methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)urea (III), in a yield of 60% calculated from the starting urea Ib (Chart 1). When a large excess of dinitrogen tetroxide was used, a ring *C*-dinitro compound, 1,3-bis(4-methoxy-2-nitrophenyl)urea (IV), was produced in 42% yield. The structure of III was confirmed by comparing its IR spectrum with that of an authentic sample which was prepared by the reaction of 4-methoxy-2-nitroaniline (V) and 4-methoxyphenyl isocyanate, and that of IV was confirmed by means of NMR spectroscopy.

The IR spectrum of 1,3-bis(4-methoxyphenyl)urea (Ib) showed a peak at 1625 cm^{-1} due to a ureido carbonyl group [–NHCONH–], while that of 1,3-bis(4-methoxyphenyl)-1-nitrosourea (IIb) showed a peak at 1720 cm^{-1} due to a nitrosoureido carbonyl group [–N(NO)CONH–]. However, the IR spectrum of the unstable intermediate showed a peak at 1745 cm^{-1}. This remarkable shift (1625 $cm^{-1} \rightarrow$ 1745 cm^{-1}) as compared with the case of the *N*-nitrosourea IIb (1625 $cm^{-1} \rightarrow$ 1720 cm^{-1}) suggested that the intermediate was an *N*-nitrourea, 1,3-bis(4-methoxyphenyl)-1-nitrourea (VI), which, in the ethereal solution, rearranged to a ring *C*-nitro compound III. In the IR spectra of *N*-nitrocarbamates and *N*-nitrosocarbamates, the peaks due to the carbonyl group of nitrocarbamates were also recorded at much higher wave numbers than in the case of nitrosocarbamates.[4,5] If *C*-nitroso compounds were formed and then oxidized to give *C*-nitro compounds, the IR peak of the urea carbonyl of the intermediate should be almost the same as that of the starting urea (Ib).

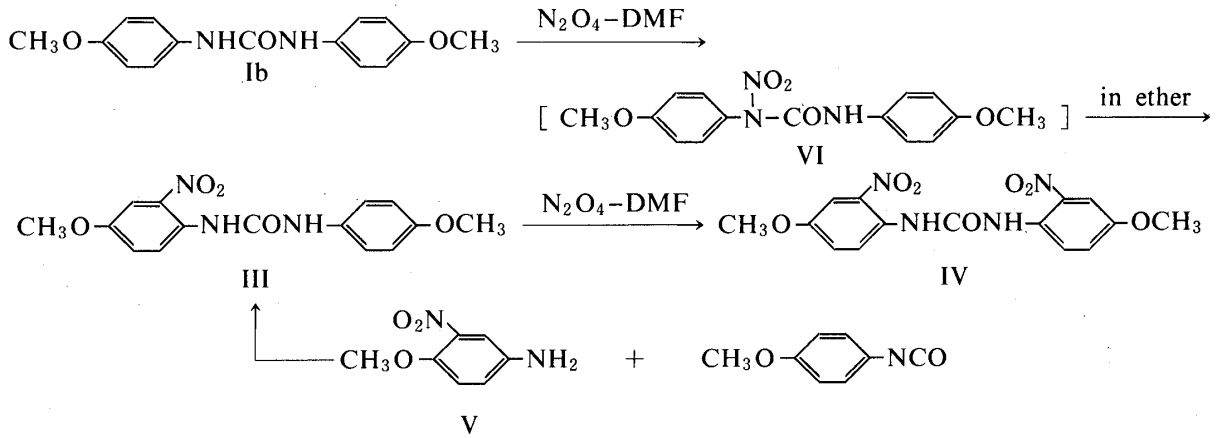


Chart 1

As shown in Table I, when nitrosyl chloride and dinitrogen trioxide were used, a slight tendency for lower yields could be observed for the 1,3-diarylureas having electron-withdrawing groups. With the combination of dinitrogen tetroxide and dimethylformamide, no significant difference in the yields due to the substituents, except for the methoxy group, was observed. The nitrosating abilities of these three reagents therefore seem to be similar.

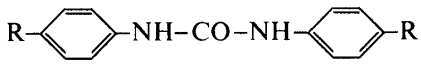
Experimental[6]

Gaseous Nitrosating Reagents——Nitrosyl chloride, dinitrogen trioxide and dinitrogen tetroxide were purchased from Matheson Gas Products and were used without further purification.

1,3-Diaryureas (Ia—f)——A typical preparation of 1,3-diarylureas is described for the case of 1,3-bis(4-methoxyphenyl)urea (Ib). A solution of 4-methoxyaniline (1.5 g, 12 mmol) in benzene (50 ml) was added dropwise to a solution of 4-methoxyphenyl isocyanate (1.5 g, 10 mmol) in benzene (100 ml) with stirring. The stirring was continued for 1.5 h. The solution was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol. Colorless needles, mp 254°C. IR ν_{max}^{Nujol} cm^{-1}: 1625 (NCON), 3300 (NH), 1210 (CH_3O). ^{1}H-NMR (DMSO-d_6, δ): 8.31 (NH), 7.35, 6.85 (ring CH), 3.71 (CH_3O).Yield, 2.8 g (90%). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H,5.92; N, 10.29. Found: C, 65.97; H, 5.75; N, 10.38.

The spectral data and elemental analysis data for 1,3-diarylureas (Ia—f) are tabulated in Table II.

TABLE II. Diarylureas (Ia—f)



Compd. No.	R	mp (°C)	IR (C=O) (Nujol, cm^{-1})	^{1}H-NMR (DMSO-d_6, ppm)	Formula	Analysis, (%) Calcd (Found) C	H	N
Ia	CH_3	245—250[a]	1635	8.45	$C_{15}H_{16}N_2O$			
Ib	CH_3O	245[b]	1625	8.31	$C_{15}H_{16}N_2O_3$	66.16	5.92	10.29
						(65.97	5.75	10.39)
Ic	F	235[c]	1620	8.65	$C_{13}H_{10}F_2N_2O$	62.88	4.02	11.29
						(63.04	4.14	11.49)
Id	Cl	255[d]	1620	8.71	$C_{13}H_{10}Cl_2N_2O$	55.32	3.55	9.92
						(55.63	3.54	10.13)
Ie	NO_2	306[e]	1645	9.65	$C_{13}H_{10}N_4O_3$	51.66	3.34	18.54
						(51.88	3.37	18.69)
If	H	230[f]	1625	8.61	$C_{13}H_{12}N_2O$			

a) Lit., mp 252,[7] 253—254°C.[8]
b) Lit., mp 231,[9] 235—237°C.[10]
c) Lit., mp 255°C.[8]
d) Lit., mp 289,[11] 307°C.[8]
e) Lit., mp 364°C.[11]
f) Lit., mp 235°C.[12]

Nitrosation of 1,3-Diarylureas (Ia—f) with Nitrosyl Chloride——A typical experiment is described for the case of 1,3-bis(4-tolyl)-1-nitrosourea (IIa). A solution of nitrosyl chloride (500 mg, 6.7 mmol) in dimethylformamide (10 ml) was added dropwise to a solution of 1,3-bis(4-tolyl)urea (Ia) (240 mg, 1 mmol) in dimethylformamide (1 ml) under cooling to below 0°C, with stirring. The reaction mixture was further stirred at 0°C for 2 h and diluted with ice-water (100 ml). The mixture was extracted twice with ether (200 ml), then the combined extracts were washed with cold water, dried over anhyd. sodium sulfate, and evaporated to dry-ness under reduced pressure. The residue was recrystallized from ether. Pale yellow needles, mp 105°C. IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO). ^{1}H-NMR (acetone-d_6, δ): 8.76 (NH). Yield, 288 mg (85%). *Anal.* Calcd for $C_{15}H_{15}N_3O_2$: C, 66.20; H, 5.61; N, 15.61. Found: C, 66.83; H, 5.56; N, 15.91.

Nitrosation of 1,3-Diarylureas (Ia—f) with Dinitrogen Trioxide——The procedure of this nitrosation was similar to that in the case of nitrosyl chloride. A typical experiment is described for 1,3-bis(4-chlorophenyl)urea (Id). A solution of dinitrogen trioxide (500 mg, 6.6 mmol) in dimethylformamide (30 ml) was added dropwise to a solution of 1,3-bis(4-chlorophenyl)urea (Id) (282 mg, 1 mmol) in dimethylformamide (5 ml) under cooling to below 0°C with stirring. The reaction mixture was further stirred at 0°C for 2 h, and diluted with ice-water (100 ml). The mixture was extracted twice with ether (250 ml), then the combined

extracts were washed with cold water, dried over anhyd. sodium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized from ether. Yield, 182 mg (59%). mp 134°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1740 cm^{-1} *Anal.* Calcd for $C_{13}H_9Cl_2N_3O_2$: C, 50.32; H, 2.90; N 13.55. Found: C, 50.44; H, 2.86; N: 14.00.

Nitrosation of 1,3-Diarylureas (Ia—f) with Dinitrogen Tetroxide——The procedure of this nitrosation was similar to that in the case of nitrosyl chloride. A typical experiment is described for 1,3-bisphenyl-1-nitrosourea (IIf). A solution of 1,3-bisphenylurea (If) (210 mg, 1 mmol) in dimethylformamide (5 ml) was cooled to 0°C, and was stirred. Cooled dinitrogen tetroxide (500 mg, 5.4 mmol) was added dropwise to the stirred solution maintained at 0°C. The reaction mixture was stirred for 2 h, diluted with ice-water (100 ml), and extracted twice with ether (200 ml). The combined extracts were washed with cold water, dried over anhyd. sodium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized from ether. Yellow fine needles, mp 107°C. Yield, 170 mg (71%). IR ν_{max}^{Nujol} cm^{-1}: 1725. ^{1}H-NMR (acetone-d_6, δ): 9.1 (NH), 7.4—7.8, 7.0—7.3 (ring CH).

Nitrosation of 1-Bis(4-methoxyphenyl)urea (Ib)——Dinitrogen tetroxide (500 mg, 5.4 mmol) was added dropwise to the cooled solution of 1,3-bis(4-methoxyphenyl)urea (Ib) (272 mg, 1 mmol) in dimethylformamide (5 ml), under cooling to below 0°C. The reaction mixture was stirred for 2 h, poured into ice-water (100 ml), and extracted with ether. The combined extracts were washed with cold water, dried over anhyd. sodium sulfate, and allowed to stand at room temperature overnight. The ether was evaporated off under reduced pressure, and the residue was recrystallized from ethanol to give 1-(4-methoxy-2-nitrophenyl)-3-(4-methoxyphenyl)urea (III), yellow crystalline powder, mp 226°C Yield, 190 mg (60%). IR ν_{max}^{Nujol} cm^{-1}: 1635 (C=O), 3220 (NH). ^{1}H-NMR (DMSO-d_6, δ): 9.74 (NH), 7.23—8.34 (ring CH). This compound was identical with an authentic sample prepared from 4-methoxy-2-nitroaniline and 4-methoxyphenyl isocyanate.

Similar treatment of 1,3-bis(4-methoxyphenyl)urea (Ib) using 1.8 g (19.5 mmol) of dinitrogen tetroxide gave 1,3-bis(4-methoxy-2-nitrophenyl)urea (IV) in 42% yield. Yellow crystalline powder, mp 241°C. IR ν_{max}^{Nujol} cm^{-1}: 1645 (C=O), 3320 (NH). ^{1}H-NMR (DMSO-d_6, δ): 3.82 (CH_3O), 7.30 (H_5), 7.50 (H_3), 7.70 (H_6), 9.65 (NH). ^{13}C-NMR (DMSO-d_6, δ) 126.22 (C_1), 140.86 (C_2), 108.65 (C_3), 154.00 (C_4), 121.23, 126.00 (C_5, C_6). *Anal.* Calcd for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.87; N, 15.43. Found: C, 49.42; H, 3.95; N, 15.13.

The Reaction of 1,3-Diarylnitrosoureas and 2-Naphthol in Alkaline Solution——Naphthol solution (0.1 M, 1 ml) in ethanol and 1 N sodium hydroxide (1 ml) were added to a solution of 1,3-diarylnitrosourea (5 mg) in ethanol (1 ml). The reaction mixture was allowed to stand for 5 min at room temperature, and diluted with ethanol to a suitable concentration for photometric determination. The absorption was measured at the λ_{max} (480—500 nm) of the resulting 1-arylazo-2-naphthol. The yields were as follows: 1-(4-tolylazo)-2-naphthol (55%); 1-(4-methoxyphenylazo)-2-naphthol (56%); 1-(4-fluorophenylazo)-2-naphthol (60%); 1-(4-chlorophenylazo)-2-naphthol (65%); 1-(4-nitrophenylazo)-2-naphtol (64%); 1-phenylazo-2-naphthol (58%).

References and Notes

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