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The Reaction of Primary Nitro Compounds with Dipolarophiles in the Presence of *p*-Toluenesulfonic Acid

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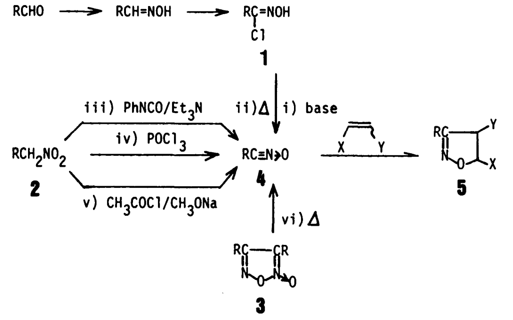
3-Substituted 2-isoxazolines or isoxazoles were obtained from the reaction of primary nitro compounds [methyl nitroacetate, 2-nitro-1-phenylethanone, (nitromethyl)benzene, 1-nitropropane, and (phenylsulfonyl)-nitromethane] with dipolarophiles in refluxing mesitylene in the presence of a small amount of *p*-toluenesulfonic acid. The formation of these products can be explained in terms of 1,3-dipolar cycloaddition of nitrile oxide generated by a dehydration of the primary nitro compounds. On the other hand, 4,5-decamethylene-3-phenylsulfonyl-2-isoxazoline *N*-oxide was obtained from a similar reaction of (phenylsulfonyl)nitromethane with cyclododecene. The formation of the isoxazoline *N*-oxide can be explained on the basis of the intermediacy of 3,4-bis(phenylsulfonyl)furazan 2-oxide.

1,3-Dipolar cycloaddition reactions using nitrile oxides were one of versatile methods for the preparation of five-membered heterocycles. Many preparative methods of nitrile oxides have been known so far[1—7] (see Scheme 1) but each of these methods possesses at least one disadvantage; the method (i) is the most familiar one,[2] but several troublesome steps are necessary for the preparation of hydroximoyl chlorides (**1**), a precursor of nitrile oxides (**4**). On the other hand, one-step methods (iii—v)[4—6] using primary nitro compounds (**2**) which are more easily available than **1** appear to be an attractive one. However, an equimolar or an excess amount of reagents is required for the dehydration of **2**, and consequently, separation of the desired compounds from the reaction mixture is troublesome and considerable amounts of undesired by-products are formed in some cases. The present paper describes a new effective and simple method for the generation of nitrile oxides by the dehydration of **2** using a small amount of *p*-toluenesulfonic acid and the preparation of cycloadducts in the presence of dipolarophiles.

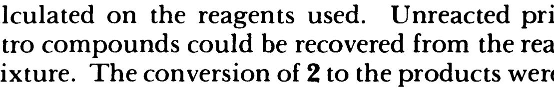


Scheme 1.

Results and Discussion

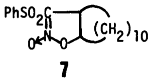
Removal of a proton from an aliphatic primary nitro compound gives a carbanion which can be alkylated (or acylated) at oxygen or carbon atom. *O*-Alkylation (or -acylation) gives nitronic esters (or anhydrides), which are generally unstable to heat and break down to a nitrile oxide, while *C*-alkylation (or acylation) gives by-products for the purpose of generation of a nitrile oxide. Acid catalyzed enolization and acid catalyzed dehydration of a hydroxyl group are well known. It is expected that a primary nitro compound would give a nitrile oxide in the presence of a trace of acid and it is shown to be the case.

The reactions between an equimolar mixture of several primary nitro compounds (**2a**—**e**) bearing various types of substituents and dipolarophiles were carried out in refluxing xylene or mesitylene for 6—20 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. (see Eq. 1) 2-Isoxazolines (**5**) or isoxazoles (**6**) were obtained from the reaction of **2a**—**e** with ethylenic or acetylenic dipolarophiles, respectively, in the yields shown in Table 1. The isolated yields in Table 1 are calculated on the reagents used. Unreacted primary nitro compounds could be recovered from the reaction mixture. The conversion of **2** to the products were over 80% in all cases shown in the Table. Though the reaction of **2a** with dipolarophiles proceeded slowly at the temperature of xylene refluxing, those of **2b**—**e** with dipolarophiles were too slow to be observed at this temperature. However, all of **2** reacted rapidly with dipolarophiles at the temperature of mesitylene refluxing. Formation of water was observed as the reaction proceeded. No remarkable improvement in the yields of the cycloadducts was observed after removing the water from the reaction system. On the other hand, 4,5-decamethylene-3-phenylsulfonyl-2-isoxazoline *N*-oxide (**7**) was the only isolable cycloadduct from the reaction mixture of **2e** and cyclododecene.



(1)

2a; R = CO$_2$Me
2b; R = COPh
2c; R = Ph
2d; R = Et
2e; R = SO$_2$Ph



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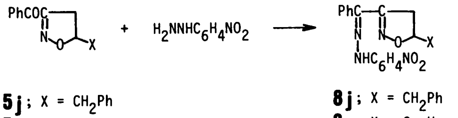
The structure of the cycloadducts (**5**, **6**, and **7**) was established on the basis of elemental analyses and spectral data (see Table 2). Physical properties of **5r**, **5s**, and

TABLE 1. REACTIONS OF **2** AND DIPOLAROPHILES IN THE PRESENCE OF *p*-TOLUENESULFONIC ACID

Nitro Compound	Dipolarophile	Solvent	Product	Yield /%	Mp (Bp) /°C
2a	*N*-Phenylmaleimide	Xylene	**5a** [R=CO_2Me, X, Y=-CON(Ph)CO-]	70	223—225
2a	*N*-Butylmaleimide	Xylene	**5b** [R=CO_2Me, X, Y,=-CON(Bu)CO-]	36	Oil
2a	Diethyl fumarate	Xylene	**5c** (R=CO_2Me, X=Y=CO_2Et)	36	Oil
2a	Allylbenzene	Xylene	**5d** (R=CO_2Me, X=CH_2Ph, Y=H)	15	60—61
2a	1-Decene	Mesitylene	**5e** (R=CO_2Me, X=C_8H_{17}, Y=H)	18	44—45
2a	1-Tetradecene	Mesitylene	**5f** (R=CO_2Me, X=$C_{12}H_{25}$, Y=H)	25	66—68
2a	Allyl *p*-nitrophenyl ether	Mesitylene	**5g** (R=CO_2Me, X=$CH_2OC_6H_4NO_2$, Y=H)	22	87—88
2b	*N*-Phenylmaleimide	Mesitylene	**5h** [R=COPh, X, Y=-CON(Ph)CO-]	85	167—170
2b	Diethyl fumarate	Mesitylene	**5i** (R=COPh, X=Y=CO_2Et)	75	(180—187/ 0.8 mmHg)
2b	Allylbenzene	Mesitylene	**5j** (R=COPh, X=CH_2Ph, Y=H)	70	Oil
2b	Cyclododecene	Mesitylene	**5k** (R=COPh, X, Y=-$C_{10}H_{20}$-)	38	83—84
2b	1-Tetradecene	Mesitylene	**5m** (R=COPh, X=$C_{12}H_{25}$, Y=H)	53	Oil
2b	Allyl *p*-nitrophenyl ether	Mesitylene	**5n** (R=COPh, X=$CH_2OC_6H_4NO_2$, Y=H)	35	116—119
2b	DMAD[a]	Mesitylene	**6p** (R=COPh, X=Y=CO_2Me)	60	88—89 (160—172/ 5 mmHg)
2b	Phenylacetylene	Mesitylene	**6q** (R=COPh, X=Ph, Y=H)	46	79—80 (170—177/ 0.7 mmHg)
2c	*N*-Phenylmaleimide	Mesitylene	**5r** [R=Ph, X, Y=-CON(Ph)CO-]	54	170—172[b]
2c	Allylbenzene	Mesitylene	**5s** (R=Ph, X=CH_2Ph, Y=H)	29	64—65[c]
2c	1-Tetradecene	Mesitylene	**5t** (R=Ph, X=$C_{12}H_{25}$, Y=H)	45	72—73
2c	Allyl *p*-nitrophenyl ether	Mesitylene	**5u** (R=Ph, X=$CH_2OC_6H_4NO_2$, Y=H)	42	152—153
2d	*N*-Phenylmaleimide	Mesitylene	**5v** [R=Et, X, Y=-CON(Ph)CO-]	58	85—87
2d	*N*-Propylmaleimide	Mesitylene	**5w** [R=Et, X, Y=-CON(Pr)CO-]	35	(180—184/ 5 mmHg)
2d	DMAD[a]	Mesitylene	**6x** (R=Et, X=Y=CO_2Me)	15	(120—128/ 6 mmHg)
2e	Allylbenzene	Mesitylene	**5y** (R=SO_2Ph, X=CH_2Ph, Y=H)	39	114—115
2e	Allyl *p*-nitrophenyl ether	Mesitylene	**5z** (R=SO_2Ph, X=$CH_2OC_6H_4NO_2$, Y=H)	21	159—160
2e	Cyclododecene	Mesitylene	**7**	60	90—93[d]

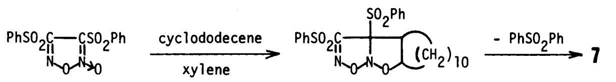
a) DMAD; Dimethyl acetylenedicarboxylate. b) Lit,[8a] mp 174 °C. c) Lit,[8b] mp 72—73 °C. d) Lit,[9] mp 90—91 °C.

7 agreed well with those of known compounds.[8,9] The structure of oily cycloadducts (**5j** and **5m**) was further supported by conversion into crystalline hydrazones (**8**) by the reaction with *p*-nitrophenylhydrazine. (Eq. 2)

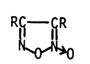


(2)

5j; X = CH_2Ph **8j**; X = CH_2Ph
5m; X = $C_{12}H_{25}$ **8m**; X = $C_{12}H_{25}$



3e (3)



3a; R = CO_2Me
3b; R = COPh
3c; R = Ph
3d; R = Et
3e; R = SO_2Ph

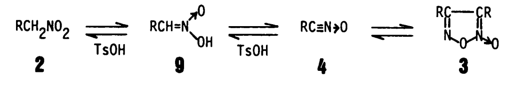
Though the formation of **5** and **6** may be ascribed to the results of a direct cycloaddition reaction of nitrile oxides (**4**), generated by the dehydration of **2**, with dipolarophiles, the isolation of **7** in a particular reaction may suggest an alternative reaction mechanism for these reactions. Recently, we reported that **7** was obtained from a nitrone-type cycloaddition reaction of 3,4-bis(phenylsulfonyl)furazan 2-oxide (furoxan) (**3e**) with cyclododecene.[9] Furthermore, furazan *N*-oxides (furoxan) bearing appropriate substituents are known to undergo dissociation into to moles of nitrile oxides and give isoxazolines or isoxazoles by the following cycloaddition with dipolarophiles at the temperatures over 200 °C[7] (see route vi in Scheme 1). In view of these facts, it is necessary to examine the possibility of the intervention of furoxans in the reactions reported here. Although none of pure furoxans were isolated from the reaction mixture, we examined the reaction of furoxans (**3a**—**e**) with dipolarophiles in mesitylene at the refluxing temperature. It was found that **3c** and **3d** were quite stable under the reaction conditions and were recovered quantitatively and that **3a** and **3b**

TABLE 2. NMR SPECTRAL DATA[a)] OF **5** AND **6**

Adduct	Chemical shift/δ
5a	3.87(s, 3H), 4.95(d, 1H, J=10 Hz), 5.82(d, 1H, J=10 Hz), 7.0—7.8(m, 5H)
5b	0.7—1.9(m, 7H), 3.5(t, 2H, J=7 Hz), 3.95(s, 3H), 4.75(d, 1H, J=10 Hz), 5.6(d, 1H, J=10 Hz)
5c	1.28(t, 3H, J=7 Hz), 1.32(t, 3H, J=7 Hz), 3.9(s, 3H), 4.25(q, 4H, J=7 Hz), 4.62(d, 1H, J=6.5 Hz), 5.35(d, 1H, J=6.5 Hz)
5d	2.6—3.45(m, 4H), 3.8(s, 3H), 4.7—5.3(m, 1H), 7.2(s, 5H)
5e	0.7—2.0(m, 17H), 2.8(dd, 1H, J=9 and 18 Hz), 3.28(dd, 1H, J=10 and 18 Hz), 3.87(s, 3H), 4.5—5.1(m, 1H)
5f	0.7—2.0(m, 25H), 2.77(dd, 1H, J=9 and 18 Hz), 3.27(dd, 1H, J=11 and 18 Hz), 3.87(s, 3H), 4.5—5.1(m, 1H)
5g	3.2—3.6(m, 2H), 3.9(s, 3H), 4.25(d, 2H, J=4.5 Hz), 5.0—5.5(m, 1H), 7.0(d, 2H, J=9 Hz), 8.2(d, 2H, J=9 Hz)
5h	5.2(d, 1H, J=10 Hz), 5.85(d, 1H, J=10 Hz), 7.2—7.9(m, 8H), 8.0—8.3(m, 2H)
5i	1.23(t, 3H, J=7 Hz), 1.35(t, 3H, J=7 Hz), 4.27(q, 2H, J=7 Hz), 4.33(q, 2H, J=7 Hz), 4.9(d, 1H, J=6.5 Hz), 5.4(d, 1H, J=6.5 Hz), 7.3—7.8(m, 3H), 8.1—8.4(m, 2H)
5j	2.6—3.6(m, 4H), 4.7—5.25(m, 1H), 7.2(s, 5H), 7.1—7.6(m, 3H), 7.9—8.2(m, 2H)
5k	0.8—2.2(m, 20H), 3.4—3.85(m, 1H), 4.6—5.0(m, 1H), 7.25—7.7(m, 3H), 8.0—8.35(m, 2H)
5m	0.7—2.1(m, 25H), 2.9(dd, 1H, J=9 and 17 Hz), 3.4(dd, 1H, J=11 and 17 Hz), 4.5—5.0(m, 1H), 7.2—7.7(m, 3H), 8.0—8.3(m, 2H)
5n	3.27(dd, 1H, J=9 and 18 Hz), 3.63(dd, 1H, J=10 and 18 Hz), 4.32(d, 2H, J=4.5 Hz), 5.25(ddt, 1H, J=4.5, 9, and 10 Hz), 7.1(d, 2H, J=9 Hz), 7.3—7.8(m, 3H), 8.17(d, 2H, J=9 Hz), 8.0—8.4(m, 2H)
6p	3.9(s, 3H), 4.03(s, 3H), 7.3—7.8(m, 3H), 8.0—8.3(m, 2H)
6q	7.05(s, 1H), 7.25—7.8(m, 6H), 7.8—8.0(m, 2H), 8.3—8.5(m, 2H)
5r	5.25(d, 1H, J=10 Hz), 5.75(d, 1H, J=10 Hz), 7.1—7.8(m, 8H), 7.8—8.2(m, 2H)
5s	2.6—3.55(m, 4H), 4.65—5.2(m, 1H), 7.25(s, 5H), 7.1—8.0(m, 5H)
5t	0.7—2.0(m, 25H), 2.9(dd, 1H, J=8 and 17 Hz), 3.4(dd, 1H, J=10 and 17 Hz), 4.4—5.0(m, 1H), 7.2—7.8(m, 5H)
5u	3.3(dd, 1H, J=8 and 17 Hz), 3.65(dd, 1H, J=10 and 17 Hz), 4.3(d, 2H, J=5 Hz), 4.8—5.4(m, 1H), 7.15(d, 2H, J=9 Hz), 7.3—7.9(m, 5H), 8.2(d, 2H, J=9 Hz)
5v	1.26(t, 3H, J=7 Hz), 2.3—2.9(m, 2H), 4.4(d, 1H, J=10 Hz), 5.4(d, 1H, J=10 Hz), 7.1—7.6(m, 5H)
5w	0.9(t, 3H, J=7 Hz), 1.25(t, 3H, J=7 Hz), 1.2—1.8(m, 2H), 2.2—2.7(m, 2H), 3.5(t, 2H, J=7 Hz), 4.35(d, 1H, J=10 Hz), 5.35(d, 1H, J=10 Hz)
6x	1.3(t, 3H, J=7 Hz), 2.9(q, 2H, J=7 Hz), 3.9(s, 3H), 4.0(s, 3H)
5y	2.7—3.6(m, 4H), 4.8—5.3(m, 1H), 7.2(s, 5H), 7.3—7.8(m, 3H), 7.8—8.1(m, 2H)
5z	3.2(dd, 1H, J=8 and 18 Hz), 3.6(dd, 1H, J=11 and 18 Hz), 4.0—4.5(m, 2H), 5.1—5.6(m, 1H), 6.9(d, 2H, J=9 Hz), 7.7—8.4(m, 7H)

a) **5a**, **5h**, **5n**, **5r**, **5u**, and **5z** were dissolved in DMSO-d_6, the other substances were dissolved in CDCl$_3$.

underwent other types of cycloaddition reactions[9)] and any trace of 3-methoxycarbonyl-2-isoxazolines or 3-benzoyl-2-isoxazolines could not be isolated from the reaction mixture. However, **5y**, **5z**, and **7** were obtained from the reaction of the furoxan **3e** with allylbenzene, allyl *p*-nitrophenyl ether, or cyclododecene, respectively, in yields similar to those from the reactions of the nitro compound **2e**. From these results, the most probable mechanism of the reaction of **2** with dipolarophiles in the presence of *p*-toluenesulfonic acid is as follows; acid-catalyst accelerates enolization of nitro compounds (**2**) into nitronic acid (**9**). Acid-catalyzed dehydration (or tosylation of the nitronic acid (**9**) followed by acid-catalyzed detosylation) gives nitrile oxides (**4**). The nitrile oxides undergo either a dimerization to furoxans (**3**) or a 1,3-dipolar cycloaddition with dipolarophiles depending on the nature of the substituents R. 1,3-Dipolar cycloadditions occur preferentially in the cases of R=CO_2Me, PhCO, Ph, and Et, and, on the other hand, a dimerization precedes the cycloaddition in the case of R=SO_2Ph. Bis(phenylsulfonyl)furoxan (**3e**) was known to undergo two types of reactions (Eq. 3 or thermoreversion into the nitrile oxide) depending on the nature of dipolarophiles.[9)]



2 **9** **4** **3** (4)

p-Toluenesulfonic acid was the best catalyst among the examined acids, CH_3CO_2H, CF_3CO_2H, and TsOH.

It is concluded that isoxazolines or isoxazoles can be easily obtained from primary nitro compounds in a moderate yield and the method is especially effective in the reaction with dipolarophiles which have a poor reactivity toward nitrile oxides at low temperature below 100°C because our method can apply at arbitrary high temperature.

Experimental

Measurements. All melting and boiling points are uncorrected. ^{1}H NMR spectra were measured on Varian T-60 A instrument with Me_4Si as an internal standard. All new crystalline products gave correct elemental analyses (±0.3% for C, H, and N).

Materials. Methyl nitroacetate,[10] 2-nitro-1-phenylethanone,[11] (nitromethyl) benzene,[12] (phenylsulfonyl)nitromethane,[13] bis(ethoxycarbonyl)furoxan,[14] dibenzoylfuroxan,[14] diphenylfuroxan,[15] diethylfuroxan,[4] and bis(phenylsulfonyl)furoxan[16] were prepared according to the method described in the literatures. 1-Nitropropane and *p*-toluenesulfonic acid monohydrate were commercially available and were used without further purification.

Reactions of Primary Nitro Compounds with Dipolarophiles. General Procedure. A mixture of an equimolar amount (20 mmol) of primary nitro compounds and dipolarophiles and a small amount of *p*-toluenesulfonic acid monohydrate (*ca.*~100 mg) was heated to reflux in mesitylene (50 ml) for 6 h. When xylene was used for the solvent instead of mesitylene, the mixture was refluxed for 20 h. In the case of the reaction with maleimides, a small amount (*ca.* 40 mg) of hydroquinone was also added. Evaporation of the solvent and other low-boiling products from the reaction mixture in a rotary evaporator gave the crude products. Crystalline crude products were recrystallized from appropriate solvents several times and some oily crude products were chromatographed (silica gel) with chloroform to give the crystalline products or pure oily products. The other oily crude products were purified by fractional distillation. Yields and melting (or boiling) points are shown in Table 1 and the NMR spectral data are shown in Table 2; 1 mmHg≈133.322 Pa.

*Reaction of 5-Benzyl (or -Dodecyl)-3-benzoyl-2-isoxazoline (**5j** or **5m**) with p-Nitrophenylhydrazine.* An ethanol solution (60 ml) of **5j** (or **5m**) (5 mmol) and *p*-nitrophenylhydrazine (5 mmol) was refluxed for 4 h. The subsequent evaporation of the solvent yielded a viscous oily material which solidified upon scratching with a glass rod. Recrystallization from ethanol gave yellow crystals (**8j** or **8m**). **8j**; 54% yield, mp 165—167 °C, NMR (DMSO-d_6) δ=2.8—3.6 (m, 4H), 4.7—5.2 (m, 1H). 7.2—7.5 (m, 12H), 8.15 (d, 2H, J=9 Hz), 11.5 (s, 1H, NH). Calcd for $C_{23}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.43%. Found: C, 67.95; H, 5.17; N, 14.50%. **8m**; 63% yield, mp 92.5—93 °C, NMR ($CDCl_3$) δ=0.7—2.0 (m, 25H), 2.75 (dd, 1H, J=9 and 16 Hz), 3.25 (dd, 1H, J=9 and 16 Hz) 4.3—5.0 (m, 1H), 7.23 (d, 2H, J=9 Hz), 7.43 (s, 5H), 8.15 (d, 2H, J=9 Hz), 12.0 (s, 1H, NH). Calcd for $C_{28}H_{38}N_4O_3$: H, 8.00; C, 70.26; N, 11.71%. Found: H, 8.10; C, 70.47; N, 11.80%.

*Reactions of Furoxans (**3a**—**e**) with Dipolarophiles.* The reaction was carried out according to the method previously reported[9] except for the use of mesitylene as the solvent. From the reaction of **3e** with allylbenzene, *p*-nitrophenyl allyl ether, or cyclododecene, **5y**, **5z**, and **7** were obtained in 35, 22, and 54% yield, respectively.

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