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REARRANGEMENT OF NITRONES TO AMIDES USING CHLOROSULFONYL ISOCYANATE

SAJAN P. JOSEPH and D.N. DHAR*

Department of Chemistry
Indian Institute of Technology
Kanpur 208016, India

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Abstract - Reaction of chlorosulfonyl isocyanate (CSI) with nitrones 1a-n and 5a,b has been studied. α,α,N-Triaryl nitrones 1a-n react with CSI to form the N,N-diaryl arylamides 3a-n and 4i-n in good yields. In the case of α-H,α,N-diaryl nitrones 5a,b however, two compounds viz., the rearranged product 11a,b and the 1,4-dihydro tetrazines 10a,b are formed.

The effect of substituents on the rearrangement has been studied. It is found that the nature of the substituent has got a profound effect on the rearrangement. We have also noted that the rearrangement is independent of the syn or anti configurations of the nitrones.

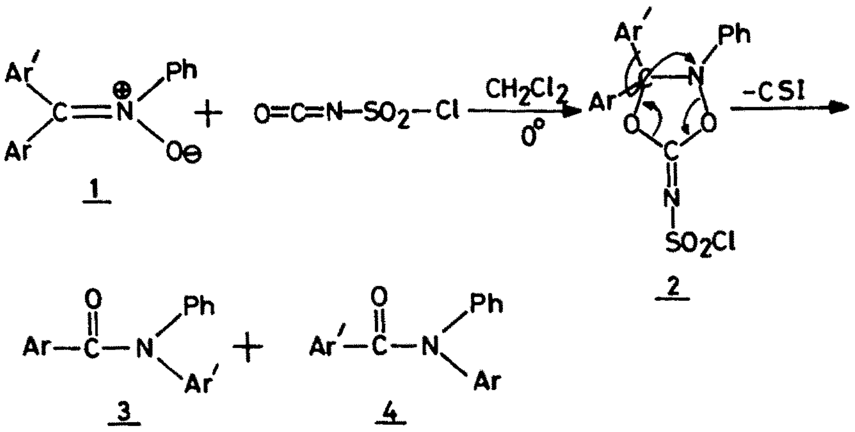
The rearrangement of nitrones to amides is a potentially useful reaction as it provides a viable synthetic route to differently substituted amides and amines. The thermolysis of nitrones gives amides, amines and ketones in poor yields[1]. The nitrone-amide rearrangement has also been achieved by various reagents such as, acetic anhydride, phosphorous oxychloride and p-toluenesulfonylchloride[2]. However, all these studies have been done on α-H, α,N-diphenyl nitrones and α,α,N-triaryl-nitrones are not investigated. In the present work, we have investigated the nitrone-amide rearrangement of α,α,N-triaryl nitrones using chlorosulfonyl isocyanate (CSI) under very mild reaction conditions. The rearrangement should be of considerable synthetic importance, since it can be used for the synthesis of several hitherto inaccessible amides and amines.

Chlorosulfonyl isocyanate is reported to undergo cycloaddition reaction with 1,3-dipolar species[3]. Both the C=O and C=N moieties of CSI can act as dipolarophile in these reactions. 1,3-dipolar additions of isocyanate with nitrones are also reported in the literature[4], where the C=N group of isocyanate acts as the dipolarophile. However, in our studies on the reaction of CSI with triaryl nitrones, we have observed that it is the C=O group of CSI which adds to the dipole. The nitrones studied in the present work include α,α,N-triphenyl nitrone (1a),α,α-di(4-methylphenyl)-N-phenyl nitrone (1b),α,α-di(4-methoxyphenyl)-N-phenyl nitrone (1c),α,α-di(4-chlorophenyl)-N-phenyl nitrone (1d),α-(4-methylphenyl)-α-(4-nitrophenyl)-N-pheyl nitrone (1e),α-(4-methoxyphenyl)-α-(4-nitrophenyl)-N-phenyl nitrone (1g),α,N-diphenyl-α-(4-nitrophenyl) nitrone (1h), α-(4-bromophenyl)-α,N-diphenyl nitrone (1i),α-(4-chlorophenyl)-α,N-diphenyl nitrone (1j), α,N-diphenyl-α-(4-methyl phenyl) nitrone (1k), α-(4-biphenyl)-α,N-diphenyl nitrone (1l), α,N-diphenyl-α-(1-naphthyl) nitrone (1m) and α,N-diphenyl-α-(4-methoxyphenyl) nitrone (1n).

RESULTS AND DISCUSSION

Nitrones 1a-d reacted with CSI to give the corresponding amides 3a-d in yields ranging between 60-97%. Nitrones 1e-h under analogous reaction conditions, gave only one of the two possible rearranged products viz., 3e-h. However, substrates 1i-n gave a mixture of both the amides in 70-90% combined yield. The rearrangement of nitrones 1e-n has been carried out with a view to study the migratory aptitudes of the different groups as well as to have a better understanding of the mechanism involved in these reactions. The migratory aptitudes of substituted aryl groups showed that an electron rich aryl group migrates in preference to an electron deficient aryl group (Table 2). The mixture of amides after hydrolysis was subjected to gas chromatographic analysis so as to quantify the data. In the case of α-(4-methylphenyl)-α,N-diphenyl nitrone, both the syn and anti isomers gave the product mixture of amides with identical composition (Table 2). A mechanism compatible with these observations is given in Scheme 1. The nitrone upon cycloaddition with carbon-oxygen double bond of CSI forms the intermediate 2, which on subsequent decomposition and rearrangement gives 3 and 4.

SCHEME I



1a Ar = C_6H_5; Ar' = C_6H_5

1b Ar = 4 - $CH_3C_6H_4$; Ar' = 4 - $CH_3C_6H_4$

1c Ar = 4 - $CH_3OC_6H_4$; Ar' = 4 - $CH_3OC_6H_4$

1d Ar = 4 - ClC_6H_4; Ar' = 4 - ClC_6H_4

1e Ar = 4 - $NO_2C_6H_4$; Ar' = 4 - $CH_3C_6H_4$

1f Ar = 4 - $NO_2C_6H_4$; Ar' = 4 - $CH_3OC_6H_4$

1g Ar = 4 - $NO_2C_6H_4$; Ar' = 4 - ClC_6H_4

1h Ar = C_6H_5; Ar' = 4 - $NO_2C_6H_4$

1i Ar = C_6H_5; Ar' = 4 - Br C_6H_4

1j Ar = C_6H_5; Ar' = 4 - ClC_6H_4

1k Ar = C_6H_5; Ar' = 4 - $CH_3C_6H_4$

1l Ar = C_6H_5; Ar' = 4 - $C_6H_5C_6H_4$

1m Ar = C_6H_5; Ar' = 1 - Naphth.

1n Ar = C_6H_5; Ar' = 4 - $CH_3OC_6H_4$

Table 1 Physical constants and relevant spectral data of product amides

Product No.	Chromatographic eluent	Yield %	MP °C	IR(KBr) C=O cm^{-1}	MS m/e (M^+)
3b	Petroleum ether-Benzene (1:1)	91	109-110	1655	310
3c	Ether	90	154-155	1605	333
3d	Petroleum ether-Benzene (1:1)	60	121-122	1655	342
3e	Petroleum ether-Ether (17:3)	84	102-103	1660	332
3f	Petroleum ether-Ether (17:3)	92	126-127	1660	348
3g	Petroleum ether-Ether (17:3)	78	128-129	1655	352
3h	Petroleum ether-Ether (1:4)	88	154-154	1665	318
3i+4i	Petroleum ether-Ether (1:1)	87	137-138	1650	351
3j+4j	Petroleum ether-Benzene (1:1)	70	116-117	1650	307
3k+4k	Petroleum ether-Benzene (1:1)	84	(liquid)	1655 (thin film)	287
3l+4l	Petroleum ether-Benzene (1:1)	90	179-181	1650	349
3m+4m	Petroleum ether-Benzene (9:1)	88	150-151	1650	323
3n	Petroleum ether-Ether (4:1)	88	123-124	1650	303
4n	Ether	4	145-146	1610	303

In order to acertain the formation of cycloadduct 2 in these reactions and the subsequent decomposition to 3 and 4 with aryl migration, the reaction was monitored by IR spectroscopy at -20°C and at room temperature. IR spectrum of the reaction mixture at -20°C taken after 15 minutes showed absorption at 1610 cm^{-1} ($\gamma_{C=N}$), 1360 and 1185 cm^{-1} (γ_{SO_2}) respectively. The absence of any absorption at 2220 cm^{-1} indicated that all CSI has reacted. The absence of any carbonyl absorption confirmed that carbon oxygen double bond of CSI has added across 1,3 dipole of the nitrone. However, an IR spectrum recorded after bringing the reaction mixture to room temperature showed absorption at 2220 cm^{-1} indicating that CSI has

Table 2 Relative migratory aptitude of substituted phenyl groups vs phenyl group

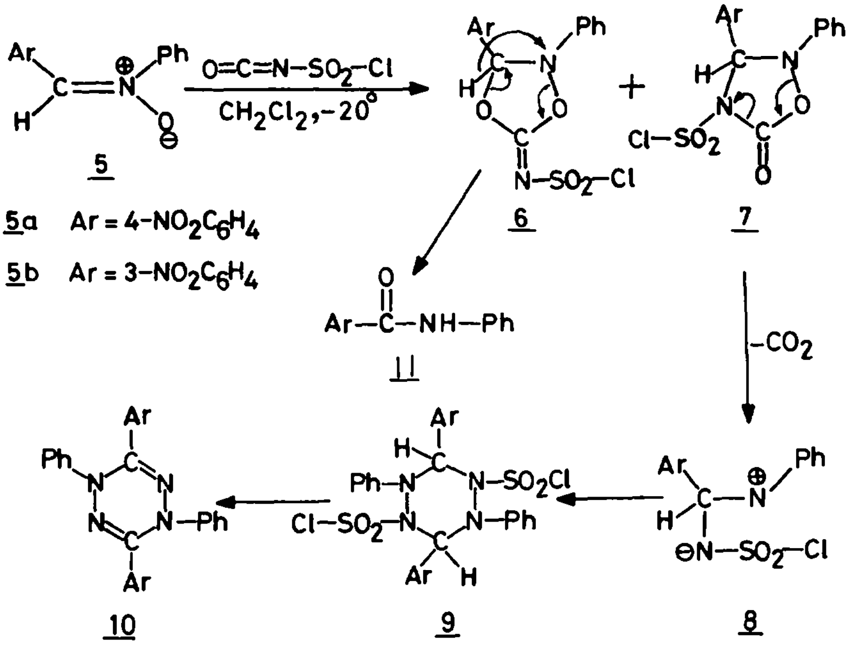
Substrate	Product (percentage) 4	3	Relative migratory aptitude (4:3)
1h	100	0	1:0
1i	64	36	1:0.6
1j	68	32	1:0.5
1k	20	80	1:4.0
1ksyn	20.3	79.7	1;3.92
1kanti	19.5	80.5	1:4.12
1l	11	89	1:8.1
1m	7	93	1:13.3
1n	5	95	1:19.0

been regenerated in the process. The regenerated CSI has been recovered as amino sulfonic acid after the work up.

The fact that syn and anti configurations of the nitrone does not have any effect on the migration of aryl group adds to the above evidence for the formation of cycloadduct 2, compounds similar to intermediate 2 have been isolated in the reaction of CSI with oxiranes[5] and nitrones with carbodiimides[6]. In many of these reported cases the adducts were not very stable. We could not however isolate this intermediate 2, because of its extreme reactivity as far as the amide formation is concerned.

In order to check whether the same mode of addition of CSI occurs with α-H, α-N-diaryl nitrones we have carried out reactions of 5a and 5b with CSI. It is found that the hydrogen atom is preferred over p-nitrophenyl group in the migration. We have also observed that the C=N bond of CSI adds to the dipole to some extent. The reaction proceeds to give the tetrazine derivative (10c and 10d) in 30% and 22% yield. Decomposition of compounds similar to 7 have been reported[4] to give amidines at higher temperature. However under our experimental conditions we do not observe any amidine formation. The structures of 10c and 10d have been arrived at on the basis of analytical data and spectral evidences. A possible mechanism for the formation of the tetrazine derivative is given in Scheme II.

SCHEME II



EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer with KBr discs. Mass spectra were recorded on a Jeol JMS-300D mass spectrometer at 70 eV. The elemental analysis were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser. GC analysis were carried out in Varian GC 3700. Chlorosulfonyl isocyanate was purchased from Fluka AG, Switzerland, and was used as such. Dichloromethane distilled over P_2O_5 and petroleum ether (40-60°) were used in this investigation.

The nitrones were prepared by reported procedure[8,9]. All the reactions were carried out under nitrogen atmosphere.

Melting points of hitherto unknown nitrones are given below.
1c 148-149°, 1d 154-155°, 1e 135-136°, 1f 175-176°, 1g 187-188°, 1i 206-207°, 1m 179-180°, 1n 137-138°.

Rearrangement of nitrone 1a (General method)

To a magnetically stirred solution of 1a (273 mg, 1 mmol) in dichloromethane (5 ml) at 0°, CSI(0.09 mL, 1 mmol) in dichloromethane (3 mL) was added dropwise and stirring was continued for one hour. The reaction mixture was brought to room temperature and extracted with water. The organic layer was separated, dried over sodium sulfate and the solvent evaporated off. The residue obtained was flash chromatographed over silica gel (TLC grade). Elution with a mixture (1:1) of petroleum ether and benzene gave 265 mg (97%) of N,N-diphenyl benzamide 3a, mp 178-179° (mixture melting point)[10].

The aqueous solution was evaporated off to yield (96 mg) (100%) of amino sulfonic acid (the hydrolysis product of CSI) mp 207°.[11]

Same procedure, as described above, was employed for the rearrangement of nitrones 1b-n and the syn and anti form of 1k (vide supra). Results are presented in Table 1.

Hydrolysis of mixture of amides (3 and 4) formed by the rearrangement of nitrones 1i-l

The amides (1 mmol) were refluxed with alcoholic KOH for 4-5 h. The reaction mixture was extracted with dichloromethane, washed with water, dried and analysed by GC for the amine component. The aqueous solution was acidified with dilute HCl. The acids separated were collected by filtration, washed with water, dried and analysed by GC. The results are collected in Table 2.

Reaction of CSI with 5a

The reaction was carried out as described in the case of 1a. Elution with a mixture (1:4) of benzene and petroleum ether gave 10a. It was crystallised from a mixture (1:1) of benzene and petroleum ether, yield 30%; mp 154-155°. IR: 1500, 1335 cm^{-1} (γ_{NO_2}), NMR ($CDCl_3$) 8.2-7.9 (8H,m), 7.1 (10H,m), Mass Spectrum m/e (relative intensity) 478 (M^+,8), 277(7), 275(18), 239(11), 225(10), 150(14), 111(24), 91(100), Anal. ($C_{26}H_{18}N_6O_4$) Found. C(65.16), H(3.80), N(17.60), Calcd. C(65.27), H(3.77), N(17.57). Further elution with ethyl acetate furnished 4-nitrobenzanilide, yield, 24%; mp 211° (mixture melting point)[12].

Reaction of CSI with 6b

Reaction was carried out in an analogous manner (vide supra). Elution of the column with a mixture (1:4) of benzene and petroleum ether gave 10b. It was recrystallized from benzene and petroleum ether. Yield, 22%; mp 122-123°, IR: 1525, 1350 cm^{-1} (γ_{NO_2}) NMR ($CDCl_3$) 8.6(2H,s), 8.1(6H,d), 7.1(10H,m). Mass spectrum, m/e (relative intensity). 478(M^+,24), 277(4), 275(11), 239(14), 225(20), 179(15), 91(100). Anal. ($C_{26}H_{18}N_6O_4$) Found. C(65.09), H(3.68), N(17.60), Calcd. C(65.27), H(3.77), N(17.52). Elution with ethylacetate gave 3-nitrobenzanilide yield, 16%, mp 154° (mixture melting point)[12].

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