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REACTION OF CHLOROSULFONYL ISOCYANATE WITH NITRONES: AN EFFICIENT METHOD FOR THE SYNTHESIS OF CYCLIC ENAMIDES AND 2H-PYRROLES

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Abstract-Reaction of chlorosulfonyl isocyanate (CSI) with nitrones (derived from cyclic conjugated ketones), 1-7 and 3,4-dihydro-2H-pyrrole-1-oxides, 15a-f, has been studied. Nitrones, 1-7, react with CSI to form the enamides, 8, 10-14, and the cyclic amide, 9, in yields ranging from 33 to 72 %. However, the 3,4-dihydro-2H-pyrrole-1-oxides, 15a-e, on reaction with CSI gave the 2H-pyrroles, 16a-e, in good yields. The 3,4-dihydro-2H-pyrrole-1-oxide, 15f, under similar experimental conditions gave the pyrrolidone, 17f, in 40% yield. Plausible mechanisms for the above mentioned rearrangement and conversions have been proposed with experimental evidences.

Beckmann and Schmidt[1] ring expansion reactions are the two common methodes used to convert a cyclic ketone into the corresponding ring expanded lactam. Prager has reported[2] a method for the ring expansion of N-methyl nitrones of conjugated ketones by employing p-toluene sulfonylchloride in aqueous-pyridine. The same reagent has been used by Barton et al[3] for the rearrangement of N-methyl nitrones of steroidal enones and showed that only one of the two possible products is formed. An extension of this reaction to nitrones derived from simple enones is reported[4] to give low yields of the enamides.

The other member of the nitrone family ie., 3,4-dihydro-2H-pyrrole-1-oxides is reported[5-9] to give various products depending upon the reaction conditions. The reaction of alkynes with 3,4-dihydro-2H-pyrrole-1-oxides is known[10] to afford 4-isoxazolines, which readily isomerize to the corresponding pyrrolidines. Phenyl isocyanate[11] and phenyl isothiocyanate[12] react with 3,4-dihydro-2H-pyrrole-1-oxides to give 1:1 cycloadducts. Conversion of 3,4-dihydro-2H-pyrrole-1-oxide to 2H-pyrrole has not been reported [13] in literature except[14] for the side product in the reaction of benzoyl chloride with 3,4-dihydro-2,2-dimethyl-4,5-diphenyl-2H-pyrrole-1-oxide.

CSI is found[15] to react with 1,3-dipolar compounds to form 1:1 cycloadducts. Earlier we have reported[16] the rearrangement reactions of α,α,N-triaryl nitrones to amides using CSI, in which we have shown that the rearrangement does not depend on the initial configuration of the nitrone but it depends on the migratory aptitude of the substituents. Herein we give an account of our investigation on the reaction of CSI with nitrones (derived from cyclic conjugated ketones) and 3,4-dihydro-2H-pyrrole-1-oxides.

RESULTS AND DISCUSSION

Nitrone, 1, on treatment with CSI at -15°C in dichloromethane gave the amide, 8, in 72% yield (Scheme I). Nitrone, 2, derived from adamantanone under similar conditions gave the amide, 9, in 64% yield. Similarly the nitrones, 3-7, gave the corresponding enamides, 10-14, in yields ranging from 33 to 51% (Table). All the products were identified by comparing with authentic samples. It is interesting to note that if the above reaction was carried out at ambient temperature (~30°C), a mixture of products was formed, which could not be resolved. However, if the reaction was carried out at low temperature (-15°C) followed by quick workup (ie., pouring the reaction mixture onto silicagel followed by flash chromatography) the enamides were obtained in good yields. To

Scheme I

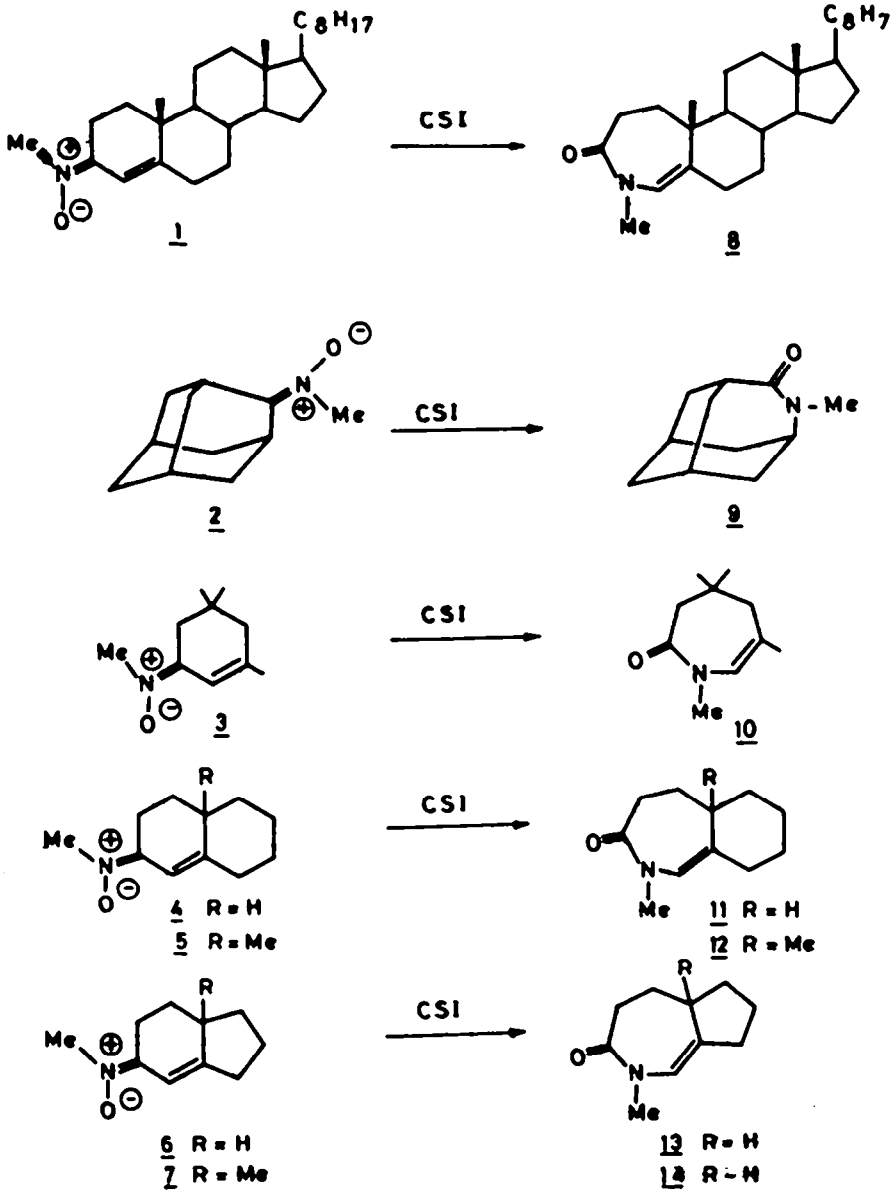


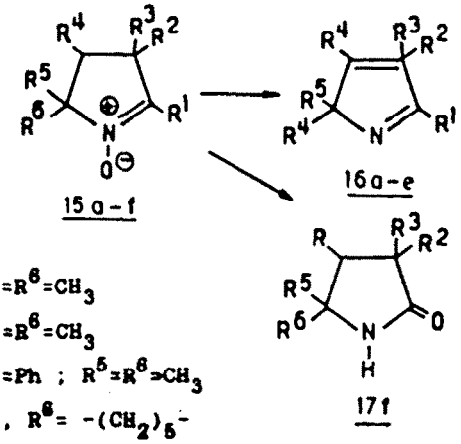
Table-Reaction of CSI with nitrones derived from conjugated ketones and 3,4-dihydro-2H-pyrrole-1-oxides.

Starting material No.	Product No.	Yield %	MP/BP°C (mm)[ref] Observed
1	8	72	98[3]
2	9	64	67[3]
3	10	42	49-50/(0.05)[2]
4	11	33	90-91/(0.5)[2]
5	12	38	79/(0.05)[2]
6	13	51	69-70/(0.02)[2]
7	14	44	69-70/(0.01)[2]
15a	16a	70	60-61[6]
15b	16b	65	66-68[7]
15c	16c	52	93-94[9]
15d	16d	63	112-114[20]
15e	16e	60	55/(3)[21]
15f	17f	40	140-141

study the mechanism, the reaction was monitored by IR spectroscopy. The IR spectrum (recorded at -15°C) of the reaction mixture did not show any carbonyl absorption, but it showed absorptions at 1615 cm^{-1} (C=N) and 1365, 1185 cm^{-1} (SO_2).

However, 3,4-dihydro-2H-pyrrole-1-oxides, 15a-e, (Scheme II) upon reaction with CSI gave the 2H-pyrroles, 16a-e, in satisfactory yields (52-70%) (Table). On the contrary 3,4-dihydro-2,2,4,4-tetramethyl pyrrole-1-oxide, 15f, under the similar experimental conditions furnished 3,3,5,5-tetramethyl pyrrolidin-2-one,

Scheme II



15 a-f

16a-e

17f

a. $R^1=R^4=Ph$; $R^2=R^3=H$; $R^5=R^6=CH_3$

b. $R^1=R^2=Ph$; $R^3=R^4=H$; $R^5=R^6=CH_3$

c. $R^1=C_5H_4N$; $R^2=R^3=H$; $R^4=Ph$; $R^5=R^6=CH_3$

d. $R^1=R^4=Ph$; $R^2=R^3=H$; R^5, R^6= $-(CH_2)_5-$

e. $R^1=Ph$; $R^2=R^3=R^4=H$; $R^5=R^6=CH_3$

f. $R^1=R^4=H$; $R^2=R^3=R^5=R^6=CH_3$

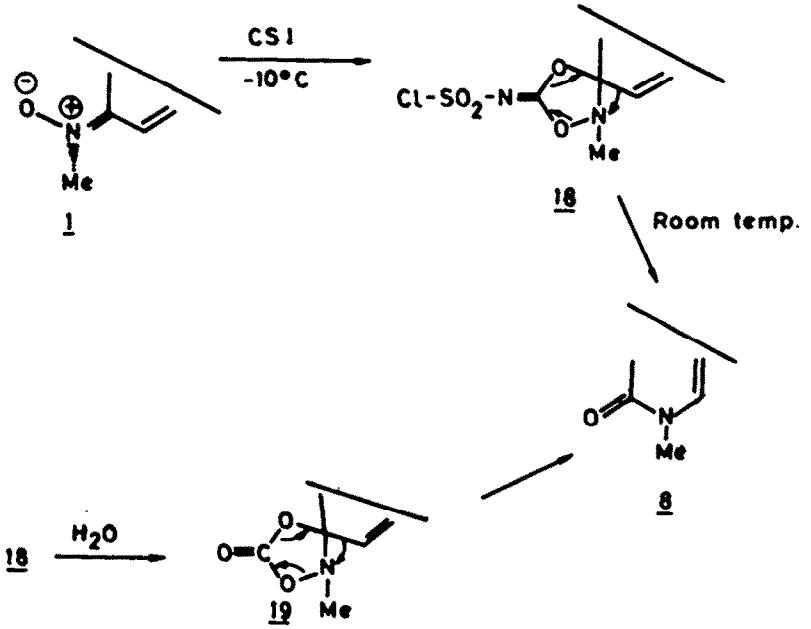
17f, in 40% yield (Scheme II). All the products were identified by comparison with authentic samples.

A Plausible mechanism for the rearrangement of N-methyl nitrones (derived from conjugated ketones) is depicted in Scheme III. Thus, the C=O of CSI adds across the 1,3-dipole of the nitrone resulting in the formation of 18. The formation of 18 is supported by the absence of carbonyl function in the IR spectrum of the reaction mixture (recorded at -15°C). The formation of a single product (ie., due to the migration of the vinylic carbon) also supports the formation of the cyclic intermediate, 18. The intermediate, 18, is similar to the product obtained in the reaction of CSI with epoxides[17]. The intermediate, 18, on decomposition and rearrangement gives the amide (Scheme III). Since the reaction mixture is poured onto silicagel at low temperature itself the possibility of the hydrolysis of 18 to 19 (in silica gel) and subsequent elimination of carbon dioxide and rearrangement can not be ruled out (Scheme III).

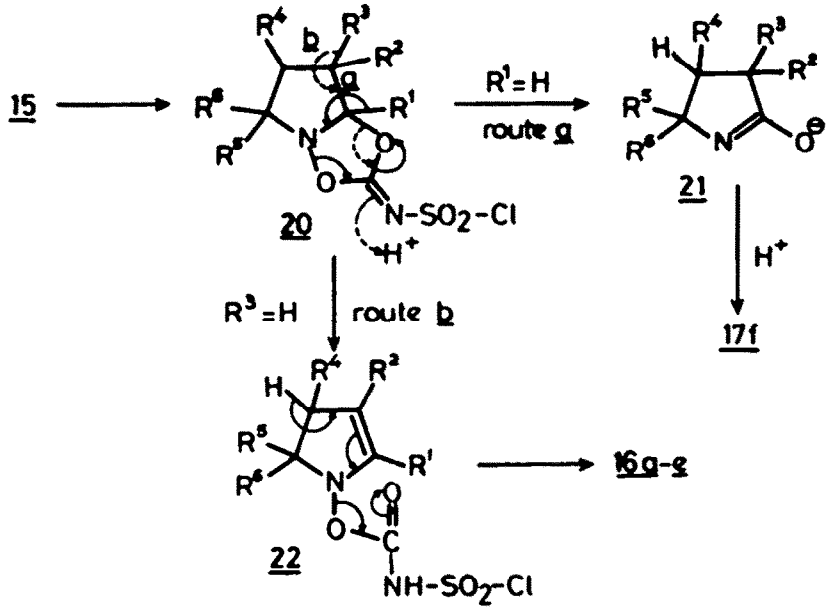
The proposed mechanism explains the formation of several products when the reaction was carried out at ambient temperature. Under these conditions CSI gets eliminated from 18 and causes secondary reactions, leading to the formation of several products. To prevent the secondary reaction, the reaction mixture was poured onto silica gel so that the generated CSI undergo immediate hydrolysis with the water present in the silica gel.

We propose a mechanism for the conversion of 3,4-dihydro-2H-pyrrole-1-oxides, 15a-f, to 2H-pyrroles, 16a-e, and pyrrolidin-2-one, 17f, as shown in Scheme IV. Thus CSI reacts with 3,4-dihydro-2H-pyrrole-1-oxide to form the cycloadduct, 20, Which can open up in two possible pathways (route a and b, Scheme IV). Elimination of a proton from C-3 with the C-O cleavage (route b, Scheme IV) will give the intermediate, 22, Which on further elimination of a

Scheme III



Scheme IV



proton from C-4 and subsequent N-O bond cleavage give the 2H-pyrroles, 16a-e. This mechanism has an analogy with the one proposed[14] for the reaction of benzoyl chloride with 3,4-dihydro-2,2-dimethyl-4,5-diphenyl-2H-pyrrole-1-oxide. On the otherhand if the C-3 is disubstituted, the cyclic intermediate, 20, opens up by cleaving the N-O bond (route a, Scheme IV) to give the intermediate, 21, which will accept a proton to yield the product, 17f. The mechanism operating in the reaction is similar to that described[18] in the reaction of CS_2 with 3,4-dihydro-2H-pyrrole-1-oxide.

The difference in the reactivity of the 3,4-dihydro-2,2,4,4-tetramethyl-2H-pyrrole-1-oxide towards CSI may be due to the disubstitution at C-3, which will prevent the opening of the cycloadduct by route b.

From the results mentioned above it is apparent that CSI can be used effectively for the rearrangement of nitrones (derived from conjugated ketones) to the corresponding enamides. This method is superior to the other methods[4] in terms of the better yield and mild reaction conditions. The reaction of CSI with 3,4-dihydro-2H-pyrrole-1-oxide gives an easy route to 2H-pyrroles.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus. Chlorosulfonyl isocyanate was purchased from Fluka AG Switzerland and was used as such. Dichloromethane, distilled over Phosphorous pentoxide, was used in the present investigation. The nitrones were prepared using the reported proce-dure[2,3], from their corresponding ketones and methyl hydroxylamine. 3,4-Dihydro-2H-pyrrole-1-oxides, 15a[19], 15b[14], 15c,d[9], 15e[11] and 15f[12] were prepared from suitable nitro compounds using known methods. All the reactions were carried out under nitrogen atmosphere.

Rearrangement of 3-methylimino cholest-4-ene-N-oxide, 1. (General method)

To a magnetically stirred solution of 3-methylimino cholest-4-ene-N-oxide, 1, (0.413 g, 0.001 mol) in dichloromethane (5 mL), CSI (0.09 mL, 0.001 mol) in dichloromethane (5 mL) was added dropwise at -15°C. Stirring was continued for 1.5 h. The reaction mixture was poured onto silicagel and flash chromatographed. The amide was eluted with benzene-chloroform mixture (3:2) to yield 0.300 g of the product, 8.

The reaction of nitrones, 2-7, with CSI was carried out as described above and the results obtained are collected in Table I.

Reaction of 3,4-dihydro-2,2-dimethyl-3,5-diphenyl-2H-pyrrole-1-oxide, 15a, with CSI. (General method)

A solution of CSI (0.09 mL, 0.001 mol) in dichloromethane (5 mL) was added dropwise to a magnetically stirred solution of 15a (0.265 g, 0.001 mol) in dichloromethane (5 mL), at -10°C. The stirring was continued for 0.5 h. The solvent was evaporated off under reduced pressure. The residue was dissolved in aqueous acetone (2:3, 5 mL) and stirred for ten minutes. The reaction mixture was neutralized (5% KOH), diluted with water and extracted with dichloromethane (3x10 mL). The organic layer was washed with water, dried (Na_2SO_4) and the solvent evaporated off. The residue on silicagel (Merck grade 1) column chromatography using the eluent ether-petroleum ether (40-60°C) mixture (3:7) furnished the 2,2-dimethyl-3,5-diphenyl-2H-pyrrole, 16a.

Similarly, the reactions of 15b-f with CSI was carried out and the results obtained are collected in Table II. 17f was eluted with a mixture (1:1) of ether-petroleum ether (40-60°C).

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