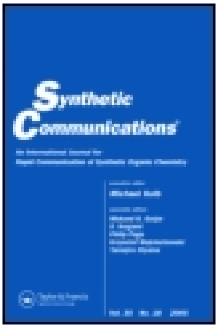

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THE MILD N-NITROSATION OF SECONDARY AMINES WITH TRICHLORO NITROMETHANE

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Summary:Reaction of trichloronitromethane with secondary amine leads to the formation of corresponding carcinogeneous N-nitrosamines under mild conditions.

Trichloronitromethane (also known as chloropicrin) has not until now enter into any chemical synthesis,*since its discovery early this century due to its high toxicity.*

Trichloronitromethane is used principally as a repellent, fumigant, insectiside, parasiticide, and disinfectant[1-11].

In this work we studied the reaction of trichloronitromethane with secondary amine.The reaction of amine with trichloronitromethane was reported first by Werner et al.[12]

They found that trichloronitromethane gave with amine, coloured addition compounds, which resulted from the interaction of subsidiary valencies associated with the NO_2 group with the N-atom.In general ,it appeared that the production of colour,in the case of nitro compounds,is always a consequence of the saturation of the subsidiary valencies of the NO_2 group.In our work we found that the reaction of trichloronitromethane with secondary amine in RT affords the nitrosation of amine (scheme 1) and we could not find this type of reaction in the literature.

$$Cl_3CNO_2 \quad + \quad R^1R^2NH \longrightarrow R^1R^2N{-}NO$$

Scheme 1

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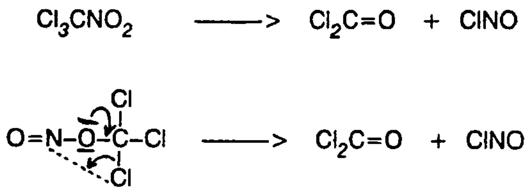
Table 1 . N-nitrosation of amines

Amine	Reaction time (h)	Product[*13]	Yield %
Diisopropylamine	48	N-nitrosodiisopropylamine	52
Morpholine	48	N-nitrosomorpholine	46
Piperidine	36	N-nitrosopiperidine	58
Diethylamine	48	N-nitrosodiethylamine	56
Pyrrolidine	36	N-nitrosopyrrolidine	43
t-Butyl-methylamine	24	t-Butyl-methylnitrosamine	36
Methyl-phenylamine	36	Methyl-phenylnitrosamine	48

[*] Products were characterised by comparison with authentic samples(IR,^{1}HNMR,GLC)[13].

When trichloronitromethane and diisopropylamine were stirred at room temperature for two days in acetonitrile as solvent a crystalline solid was formed.After removing of the solid by filtration,and remaining reaction mixture was evaporated,the crude product after chromatographic separation gave an oil which was identified as a N-nitrosodiisopropyl amine (^{1}H NMR, IR, MS) . We obtained the same results (summarized in table 1) using different secondary amines.

The only source of nitrosation in our reaction should be trichloronitromethane if one wants to think about a reasonable explanation of what goes on.On decomposition, trichloromethane was found to give phosgene and nitrosyl chloride according to scheme 2[14-15].



$$Cl_3CNO_2 \longrightarrow Cl_2C{=}O + ClNO$$

$$O{=}N{-}O{-}CCl_3 \longrightarrow Cl_2C{=}O + ClNO$$

Scheme 2

$$R_2NH \quad + \quad ClNO \quad \longrightarrow \quad R_2N\text{-}NO \quad + \ HCl$$

Scheme 3

It is quite possible that nitrosyl chloride could be the nitrosation agent of the secondary amine as illustrated in scheme 3.

The hydrogen chloride formed reacts with an equivalent amount of the amine to give the amine hydrochloride salt which was noted to separate out as a crystalline solid from the reaction mixture. Because the most nitrosamines are potently carcinogenic[16,17] ,all of the produced nitrosamines were converted into hydrazine and amine using LAH,Zn/HCl and $TiCl_3$ reductions[18-20]. **(NOTE,However,that most nitrosamines are potent carcinogens and must be treated with due caution).**

To conclude, we have found that trichloromethane,which has a large area of use,converts amine into carcinogeneous nitrosamines under mild conditions.

EXPERIMENTAL

Warning: Most nitrosamines are potentially carcinogenic,and should be handled,stored,and discarded with due caution for their toxic potential[16,17].Trichloronitromethane produces severe sensory irritation in upper respiratory passages.It has strong lacrimatory properties,produces increased sensitivity of skin and eyes after frequent exposures. When taken orally,severe nausea, vomiting, colic, diarrhoea result[21].

All reagents were of commercial quality and reagent quality solvents were used without further purification.IR spectra were determined on a Phillips model PU9700.1H-NMR were determined on a Bruker AC 80 MHz FT spectrometer, mass spectra were determined on a VG-TRIO-2 spectrometer.Melting points were determined with a Buchi SMP-20 melting point apparatus and are uncorrected.Elemental analysis were performed at the Middle East Technical Univesity analysis center.

General procedure for the preparation of N-nitroso compounds.

Into a 100 mL flask 30 ml of dry acetonitrile were introduced.Dry nitrogen gas was bubbled trough the solvent and then 20 mmol of amine and 10 mmol of trichloronitromethane were subsequently injected.The mixture was then stirred for 48 h at room temperature,during which white time, needle like crystals were formed. The crystals were separated from the reaction mixture by filtration and were identified as a corresponding amine hydrochloride.From the remaining liquid,the solvent was removed by evaporation and a light yellow crude liquid N-nitroso amine was purified by chromatography and distillation(Kugelrohr).

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