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NOTE

N-Chloroisonicotinamide-A New, Mild, Effective, Efficient and Less Expensive Oxidant for Organic Substrates

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A new N-halo compound, N-chloroisonicotinamide is prepared by the chlorination of isonicotinamide. The physical constant, the formal redox potential, elemental analysis and spectral characterization (IR and ^{1}H NMR) confirm the presence of nitrogen-halogen bond. It is found to be a fairly stable and mild oxidant of low cost. The possibility of the compound acting as an effective source of positive halogen is well established. It is screened for antimicrobial activity against bacteria and fungi at various concentrations using disc diffusion method.

Key Words: N-Chloroisonicotinamide, Oxidant, N-halo compound.

The kinetic study of oxidation of organic compounds is a useful and powerful method in physical organic chemistry. The role of N-halo compounds in this field is very wide. They are being used in kinetics, analytical[1] and organic structural investigation. N-Halo compounds are particularly useful in synthesizing organic substrates[2]. The electro negativities of halogens, except fluorine, are less than that of nitrogen. Hence they acquire a positive charge when linked with nitrogen. The electro negativity of nitrogen is further enhanced by linking it with certain electron withdrawing groups such as acyl group. Thus N-halo compounds are referred as positive halogen compounds.

Recently, considerable attention has been focused on the chemistry of N-halo compounds. The diverse nature of the compounds is due to their ability to act as sources of halo cations, hypo halite species and nitrogen anions which act both as base and nucleophiles. Some of the N-halo compounds are N-chloronicotinamide[3], N-bromonicotinamide[4], N-chlorosuccinimide[5], N-bromosuccinimide[6], N-bromoacetamide[7], N-chlorosaccharin[8], N-chlorobenzotriazole[9], N-chloroacetanilide[10], N-bromophthalimide[11] and so on.

Among the N-halo compounds, N-chloronicotinamide (NCN) has been used as the oxidant for amino acids[12], alcohols[13,14], aldehydes[15], S-phenyl mercapto acetic acid[16] and benzyl ethers[17]. N-Chloronicotinamide is also reported to act as a chlorinating agent for phenols[18]. In the search of new halo compounds, the latest development involves the study of synthesis, characterization and antimicrobial activities of another oxidant, N-chloroisonicotinamide (NCIN).

In this communication, a detailed method of preparing NCIN, its characterization by means of elemental analysis, IR and ^{1}H NMR, formal redox potential and its antimicrobial activities are reported.

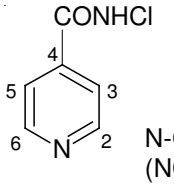
N-Chloroisonicotinamide (m.p. 214 ºC) was prepared by passing a slow stream of chlorine into a solution of isonicotinamide (15 g in 30 mL 3 N HCl) at 32 ºC for 1 h. The NCIN formed as white crystals was filtered and the process of passing chlorine into the filtrate and filtering off the precipitate was repeated till no more precipitate was obtained. N-Chloroisonicotinamide was found to be soluble in water, dimethyl sulphoxide, acetic acid, but insolube in chloroform and carbon tetrachloride.

A digital potentiometer (Equiptronics dual channel potentiometer EQ-603) with a smooth platinum electrode and a saturated aqueous calomel electrode was used for the determination of formal redox potential of NCIN/INA couple. The formal redox potential of NCIN/INA couple was determined by measuring the potential in mixtures containing varying concentration ratios of NCIN and INA in 80 % acetic acid and 0.1 M HCl. Since dilute solutions of both NCIN and INA (isonicotinamide) were used, the activities were replaced by concentration terms in the Nernst equation.

$$E_{obs} = E^{o} + \frac{2.303RT}{F} \log \frac{[NCIN]}{[INA]}$$

The purity of NCIN was confirmed by elemental analysis (C 45.96 %, H 3.11 %, N 17.49 % and Cl 22.83 %). The IR spectra of NCIN showed the presence of secondary amide (1660 cm^{-1}), a carbonyl group (1500 cm^{-1}) and a N-Cl bond (1270 cm^{-1}).

The ^1H NMR signals for the pyridine ring protons have the same chemical shifts in both isonicotinamide and N-chloroisonicotinamide, while the peak corresponding to NH_2 signal is slightly shifted to a larger value, the integration of the peak was half. This indicates that only one proton of the NH_2 group is substituted by the chlorine atom. ^1H NMR δ: 9 (due to C_2-H and C_6-H), 8.2 (due to C_3-H and C_5-H), 4.4 (broad singlet due to CO-NH proton coupled with C_3-H and C_5-H).



N-Chloroisonicotinamide (NCIN)

Antimicrobial activity: The antibacterial activity was carried out by disc diffusion technique[19]. The test microorganisms of gram positive *Staphylococcus aureus* and gram negative *Proteus vulgaris*, *Salmonella typhi*, *Klebsiella aerogenes* and fungus *Candida alebicans*, *Aspergillus niger* were obtained from National Chemical Laboratory (NCL), Pune and maintained by periodical sub culturing on nutrient agar and sabouraud dextrose medium for bacteria and fungi, respectively. The effect produced by the compound was compared with the effect produced by the positive control (reference:standard ciprofloxacin 5 µg/disc for bacteria and standard fluconazole 100 units/disc for fungi). All the observations are given in Table-1.

TABLE-1
ANTIMICROBIAL ACTIVITY OF N-CHLOROISONICOTINAMIDE

Name of the microorganisms	Zone of the inhibition (mm) sample-NCIN				Standard
	50	100	200	250	
Staphylococcus aureus (NCM 2079)	10	13	15	18	32
Klebsiella aerogenes (NCM 2098)	10	10	10	12	30
Proteus vulgaris (NCM 2027)	–	–	10	12	32
Salmonella typhi (NCM 2023)	10	10	10	14	30
Candida alebicans (NCM 3102)	–	–	8	10	31
Aspergillus niger (NCM 105)	10	12	13	14	32

Preparation of disc: A known quantity of the compound NCIN was dissolved in water. The required quantity of the compound is loaded on the sterile discs using micropipette. Discs impregnated with known concentration of the compound are placed on Muller Hinton agar plate that has been inoculated uniformly over the entire plate with a culture of the bacterium and fungi to be tested. Dried discs are stored in sterile containers till use.

Preparation of inoculum: The microbial strains are inoculated in peptone water and sabouraued dextrose broth and incubated at 37 ºC and 25 ºC for 6-18 h for bacteria and fungi, respectively.

Disc diffusion method was performed to look for the antimicrobial activity of various extracts. The zone of inhibition of growth was measured by making use of Tripartigan rule (Hoechst) (NCCLS, 1993)[20].

A plot of E_{obs} against log [NCIN]/[INA] from the Nernst equation is made which yield a straight line with non-zero intercept and the potential from it has been calculated to be 1.05 V at 25 ºC. This value shows it is a fairly strong oxidizing agent. The value of formal redox potential of the NCIN/INA couple is comparable to the value of +1.14 V for chloramine-T, +1.16 V for bromamine-T and +1.02 V for N-chloronicotinamide. The oxidation of benzyl ethers using NCIN is in progress.

N-Chloroisonicotinamide is fairly stable and serves as an efficient reagent for oxidation, halogenation and polymer induced cyclization, peroxidation, side chain substitution similar to other known N-chloro compounds. The active oxidizing species in NCIN can be Cl_2, HOCl, H_2OCl^+. N-Chloroisonicotinamide can be used for preferential halogenation also, similar to that of N-chloronicotinamide.

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