Isonitriles from Alkyl Halides and Onium Dicyanoargentates

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Due to Ugi's convenient and general synthesis of isonitriles from monosubstituted formamides,[1,2] isonitriles have assumed increasing importance as intermediates in organic synthesis [3–5] and as ligands in inorganic complexes.[6]

Prior to Ugi's method, aromatic isonitriles were made from primary amines and chloroform in the presence of potassium hydroxide — the carbylamine reaction — or more generally from organic halides and heavy metal cyanides.[7]

In the latter heterogeneous reaction, both cyanides and isonitriles are formed, depending upon temperature, solvent, organic halide, and especially heavy metal employed. The exact mechanisms in these heterogeneous reactions are complex and mostly unknown. By far, the best yields of isonitriles are obtained using silver cyanide [8–11] where reaction intermediates as $(AgCN)_2 \cdot RX$ and $AgCN \cdot RX$ have been suggested.[12]

We now wish to report a novel synthesis of isonitriles from alkyl halides and onium dicyanoargentates in homogeneous reactions in dipolar aprotic solvents. The solubilities of these salts in dipolar aprotic solvents are high, and furthermore it is known that salts of large onium cations are extensively dissociated in these solvents.[13] In the experiments, tetraphenylarsonium dicyanoargentate was employed, and also the less expensive triphenyl methylphosphonium dicyanoargentate.

It is known from an X-ray study [14] that the dicyanoargentate ion is linear, and from more recent IR [15] and Raman [16] spectra of $KAg(CN)_2$ it has been concluded that the cyanide groups are bonded through the carbon atom to the metal.

Of the possible mechanisms of this reaction one may consider the case of a soft-soft catalysis [17] through a transition state involving an increased coordination number of the silver atom, creating a partly or complete carbonium ion of the alkyl halide, or even a multicenter transition state where the new bond has developed prior to a complete bond-breaking. The reaction mechanism and the generality of this reaction will be further explored.

Experimental. Tetraphenylarsonium dicyanoargentate. To 5 g purified and dried tetraphenylarsonium chloride (m.p. 255°) was added twice the equivalent amount of freshly prepared silver cyanide in 100 ml absolute ethanol. After reflux with stirring for 30 min, the precipitate was filtered off and the process repeated with 1 g silver cyanide. After cooling and filtering, the volume was reduced in vacuum to 20 ml and the product precipitated with ether. Recrystallized twice from chloroform-ethyl acetate mixture and dried in vacuum, the compound, 6.4 g, had m.p. 169 – 170°C. IR_{CN} at 2139 cm^{-1}. The salt is very soluble in acetone, chloroform, acetonitrile, ethanol, and nitrobenzene, but only slightly soluble in water. The compound was found not to be hygroscopic. (Found: C 56.92; H 3.69; N 5.16; Ag 19.9. Calc. for $C_{26}H_{20}N_2AsAg$: C 57.49; H 3.71; N 5.16; Ag 21.0.)

Triphenyl methylphosphonium dicyanoargentate. This salt was made similarly from the corresponding iodide, m.p. 127°C. No odour of any isonitrile or cyanide could be detected during its synthesis and purification.

Benzhydryl isonitrile. In 25 ml acetonitrile, dried with P_2O_5 and finally with CaH_2, was dissolved 1.0 g benzhydryl bromide and 2.2 g tetraphenylarsonium dicyanoargentate. The clear solution was refluxed with stirring for 30 min. The solvent was then removed in vacuum and the product extracted from the residue with low-boiling petroleum ether (40 – 60°C) and crystallized twice from this solvent. Yield 0.77 g, 88 %, m.p. 47°C (35 – 36°C [2]). IR_{NC} 2135 cm^{-1}. (Found: C 86.84; H 5.91; N 7.14. Calc. for $C_{14}H_{11}N$: C 86.92; H 5.73; N 7.24.)

To 1.0 g of benzhydryl isocyanide in 20 ml acetone in an open baker was added 2 ml conc. hydrochloric acid in 10 ml water. The clear solution was gently heated with stirring for 30 min to evaporate the acetone. Upon cooling, a white crystalline product precipitated, 0.90 g (85 %), m.p. 135° (benzene). IR and analysis showed the compound to be 2-hydroxy-2-methyl propanoic acid benzhydrylamide formed by the Passerini reaction.[18,19] (Found: C 75.76; H 6.80; Calc. for $C_{17}H_{19}NO_2$: C 75.81; H 7.11.) This compound was made in 100 % yield by mild alkaline hydrolysis in water-acetone mixture of the corresponding 2-acetoxy compound, m.p. 173 – 174°C, formed by the Passerini reaction from benzhydryl isocyanide, acetic acid, and acetone.

Methyl isonitrile. To 14.1 g (0.1 mole) methyl iodide in 100 ml purified nitrobenzene was added 33 g (0.11 mole) triphenyl methylphosphonium dicyanoargentate. The odour of an isonitrile was detected after few minutes. The clear reaction mixture was refluxed at 80°C for 30 min whereupon the low-boiling product was distilled off. Yield, 3.6 g. NMR in CCl_4 showed a contamination of approximately 10 % of unreacted methyl iodide and no signal due to methyl cyanide. The total yield of methyl isonitrile is thus more than 80 %. No trace of methyl cyanide could be detected by IR using a gas cell.

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Proton Chemical Shifts in Some Benzhydryl Compounds

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Many authors have recently given attention to the NMR shifts of different kinds of protons for the identification of organic compounds. Quite some effort has been devoted to collecting and compiling the proton shift values for compounds with selected functional groups (Ref. 1 and references therein).

Generally it is now accepted that the Shoolery rule on the additivity of substituent effects on proton shifts is quite successful for methyl and methylene protons, while for compounds of the general type XYZC—H, *i.e.*, methine protons, Shoolery's rule is rather unreliable.[2]

Attempts have been made to correlate proton chemical shifts and charge densities in different series of compounds.[3] Beside electron density changes around the proton due to the electronegativity of substituents, other factors, as magnetic anisotropy [4] and electrostatic field effects,[5] are important. For numerous substituted aliphatic hydrocarbons a linear relationship could be established between Taft's $\sum\sigma^*$ values and chemical shift, using the anisotropy correlations ($\Delta\sigma$) due to Reddy and Goldstein,[6] except for highly polar substituents like CN, COR, NO_2, and COOH.[7,8] By correcting the chemical shifts for lone pair dipole moment in substituents this relationship has been improved.[9] The importance of the combined effect of the electric dipole moment and the anisotropic magnetic susceptibility of substituents has been particularly stressed by Zürcher.[10]

Recently a good correlation between proton chemical shifts and proton charge densities has been obtained,[11] but limited to substituents of the same row of the periodic system, suggesting that proton chemical shifts and charge densities have a different sensitivity to valence electron configuration.

To try to shed further light on the effect of polyatomic, highly polar substituents, the proton chemical shifts of some benzhydryl compounds have been determined. In a recent compilation of proton chemical