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A REMARKABLE S_Ni-S_N2-S_Ni-FRAGMENTATION-S_Ni-REACTION SEQUENCE OF N-(2-CHLOROETHYL)p-NITROBENZENESULPHONAMIDE IN AQUEOUS ALKALI

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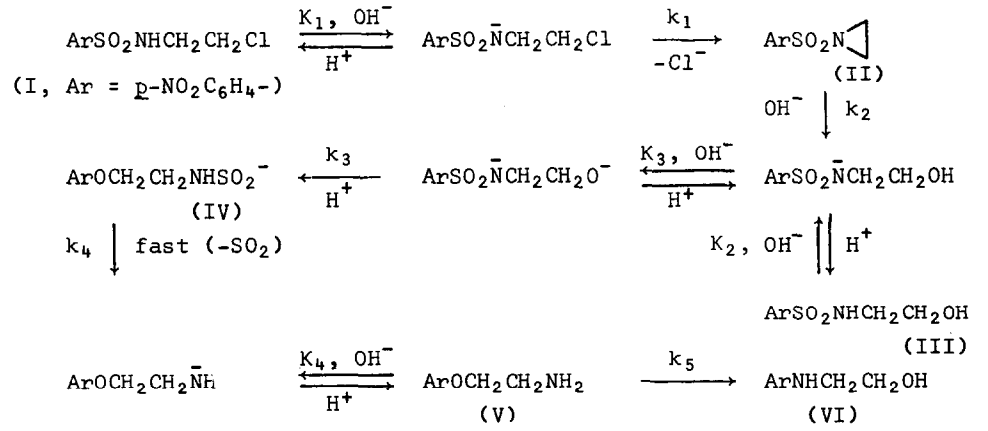
During an investigation of reactions of a variety of N-substituted p-nitrobenzenesulphonamides it was discovered that at 60°C in sodium hydroxide (0.5M) containing 20% acetone the N-(2-chloroethyl)-derivative (I) undergoes dehalogenative hydrolysis with concomitant desulphonation to give N-(2-hydroxyethyl)p-nitroaniline (VI) in 95% yield:

$$p\text{-}NO_2C_6H_4SO_2NHCH_2CH_2Cl \xrightarrow[-SO_2,\ -Cl^-]{OH^-} p\text{-}NO_2C_6H_4NHCH_2CH_2OH$$

The following mechanism is proposed for this reaction which has now been studied by isolation of intermediates, TLC investigation of the reaction sequence and by kinetic analysis:



where constants K and k are equilibrium constants for deprotonation, and first (k_1, k_3, k_4 and k_5) or second (k_2) order rate constants respectively. For aqueous hydroxide (0.1 - 0.5M):

$k_1 < k_2[OH^-] > k_5 > k_3K_3[OH^-]$; $K_1[OH^-]$ and $K_2[OH^-] > 100$; $K_3[OH^-]$ and $K_4[OH^-] < 100$. However, in dilute base (0.01 - 0.005M) $k_1 > k_2[OH^-]$.

Formation of N-(2-hydroxyethyl)- from N-(2-chloroethyl)-p-nitrobenzenesulphonamide is by neighbouring group participation (rather than direct substitution). The conjugate base of the sulphonamide undergoes rapid S_Ni displacement of chloride ion to form N-(p-nitrophenylsulphonyl) aziridine (II) which by subsequent base catalysed ring opening (S_N2-reaction with OH^-) gives N-(2-hydroxyethyl)p-nitrobenzenesulphonamide (III). The S_Ni reaction has been followed by repetitive scan of the ultraviolet spectrum during reaction of the chlorosulphonamide at 50.2°. In both 0.01 and 0.005M aqueous NaOH the first order rate constant (determined from the time dependence of the decrease in absorbance at 320 nm) is independent of base concentration (k_1 = 0.0105 s^{-1}, $t_{\frac{1}{2}}$ = 66 s) and much greater than that for hydrolysis of n-chloroalkanes.

The intermediate aziridine (m.p. 137°) has been isolated, in 85% yield, from a methylene chloride layer which was shaken in contact with aqueous sodium hydroxide (200 ml, 1.0M) to which I (0.5g) was subsequently added at 18°. Under these conditions the aziridine, formed from the base-soluble sulphonamide, is immediately extracted and thereby protected from hydrolysis. The aziridine has also been isolated in 95% yield following reaction of I for 2 min at 56°C in sodium hydroxide (0.005M) containing acetone (20%). If the aziridine is allowed to remain in the base solution, III is eventually formed. Compound III (m.p. 125°) has been isolated in 90% yield from reaction of I in 0.5M base for 5 min at 56°. The ring opening has also been monitored by repetitive scan of the ultraviolet-visible spectrum during reaction II → III (5×10^{-5}M) in aqueous sodium hydroxide (0.1M) at 50.2°. By analysis of the time dependence of the increase in absorbance at 325 nm the rate constant, k_2 = 0.0153 ± 0.0002, mol^{-1} dm^3 s^{-1} has been determined.

The reaction was monitored at 325 nm since an isosbestic point develops at this wavelength during the subsequent conversion of III to VI in 0.1M base and the necessary determination of absorbance at infinite time is therefore unaffected by decomposition of III.

The surprising conversion of III to VI was previously noted by Kleb (I) for reaction in refluxing aqueous sodium hydroxide (1.5M). A mechanism which featured double Smiles' rearrangement (2-4) was proposed (III → IV → V → VI) although there was no direct evidence for the suggested intermediates IV or V. No attempt to determine either the base dependence or the relative rates of the consecutive Smiles' rearrangements (S_Ni reactions of hydroxy and amino functions, respectively, with the p-nitro-activated aryl ring) has been reported.

By repetitive scan of the spectrum (230 - 450 nm) during the conversion of III (λ_{max} = 265 nm) to VI (λ_{max} = 410 nm) in aqueous sodium hydroxide (0.1 - 1.0M) at 61°C, we have detected the formation and decay of an intermediate (λ_{max} ≈ 315 nm). The wavelength of absorption maximum is that expected (5) for a p-nitrophenyl alkyl ether such as V.

A high yield (> 95%) of VI has been obtained upon reaction of I, II or III for 24 hr at 61° in 0.5M sodium hydroxide containing 20% acetone.

A preliminary kinetic study has revealed that the rate of formation of V from III is proportional to the base concentration ($t_{\frac{1}{2}}$ = ca 11,300 and 1,900 s at 61° in 0.1 and 0.5M aqueous hydroxide, respectively). This is to be expected of a reaction in which neighbouring alkoxide ion, rather than the unionized alcohol, is the nucleophile for the first Smiles' rearrangement. In contrast, the rate of the second Smiles' rearrangement (V → VI) is largely independent of base concentration ($t_{\frac{1}{2}}$ = ca 690 s at 61°).

Kinetic study is complicated by the comparable rates of these consecutive reactions under the pseudo first order conditions employed. Our investigation has been extended to include related compounds which undergo double Smiles' rearrangement, and rate constants which reveal the interesting effects of C- and N-substituents on both the rate and mechanism of the rearrangement steps will be reported in due course.

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