Industrial Chemistry – Synthesis

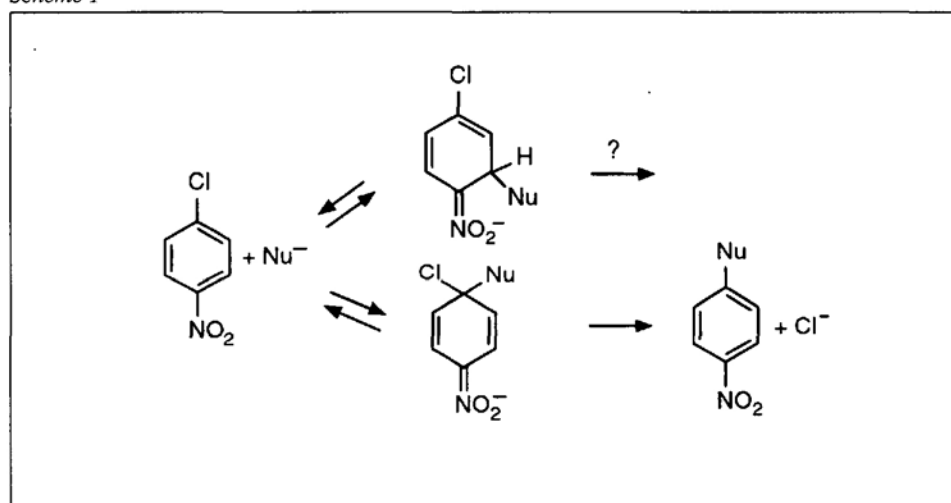# Vicarious Nucleophilic Substitution of Hydrogen

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Nucleophilic aromatic substitution is a process of great practical importance for chemical industry, and substantial interest in synthetic and mechanistic organic chemistry. The reaction can proceed along many mechanistic pathways – the most practically important is the replacement of halogen or other leaving groups in electrophilic arenes, mostly nitroarenes, proceedings *via* addition – elimination mechanism. According to the 'common knowledge' nucleophilic aromatic substitution is limited to the replacement of halogen (or other leaving groups), possibility of nucleophilic replacement of hydrogen was for long time totally neglected and even presently it is underestimated [1][2].

On the other hand there is no doubt that nucleophiles add to nitroaromatic rings faster in positions occupied with hydrogen than in that occupied with halogens or other substituents [2][3]. This is exemplified with the reaction of nucleophiles with *p*-chloronitrobenzene (*Scheme 1*). Since there is no general way for further transformation of the initially formed σ^H adducts and the addition is a reversible process the secondary process of S_NAr of the halogen takes place, whereas initial formation of the σ^H adducts is usually overlooked, even in thorough mechanistic investigations of the S_NAr reaction [1].
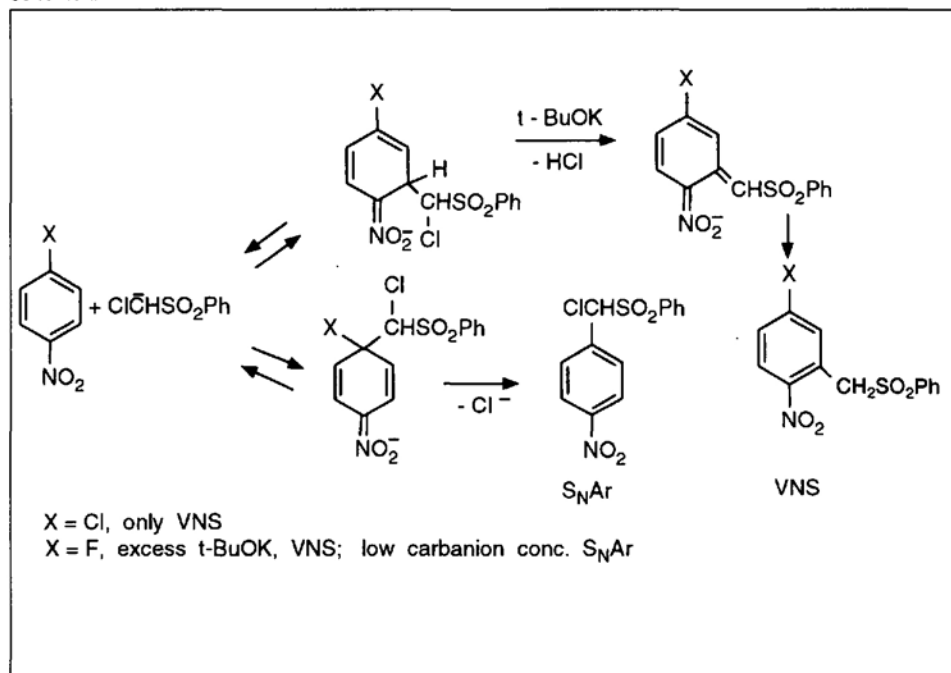
Searching for a possibility to exploite rapid formation of the σ^H adducts we have hypothesized that the σ^H adduct produced via addition of nucleophiles containing leaving groups X can be readily converted to the products *via* base induced β-elimination of HX.

The most representative examples of such nucleophiles are α-halocarbanions generated *via* deprotonation of α-chloroalkanesulfones, α-chloronitriles, esters,

Scheme 1
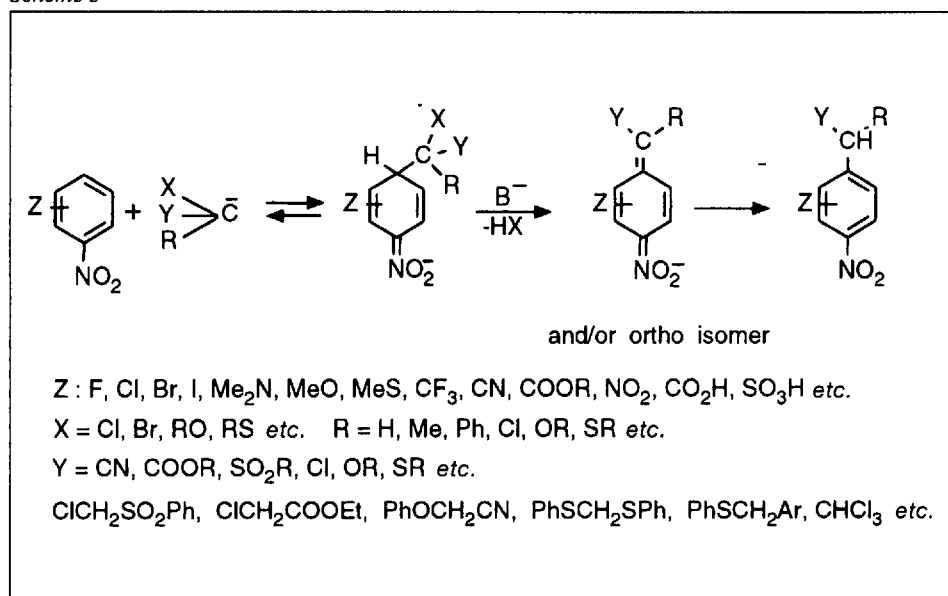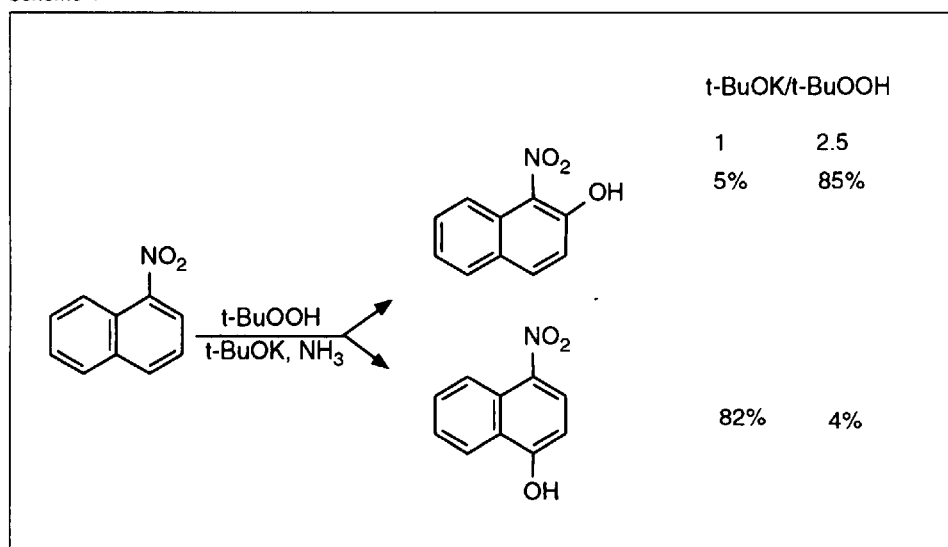

Scheme 2

X = Cl, only VNS
X = F, excess t-BuOK, VNS; low carbanion conc. S_NAr

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Scheme 3

and/or ortho isomer

Z : F, Cl, Br, I, Me₂N, MeO, MeS, CF₃, CN, COOR, NO₂, CO₂H, SO₃H *etc.*

X = Cl, Br, RO, RS *etc.*   R = H, Me, Ph, Cl, OR, SR *etc.*

Y = CN, COOR, SO₂R, Cl, OR, SR *etc.*

ClCH₂SO₂Ph, ClCH₂COOEt, PhOCH₂CN, PhSCH₂SPh, PhSCH₂Ar, CHCl₃ *etc.*

Scheme 4

almost without limitation, although it is desirable that they provide some stabilization of the carbanions.

The general scheme of VNS is applicable not only to the reaction of α-halocarbanions or similar carbon nucleophiles. Some other nucleophilic agents possessing leaving groups at the nucleophilic centers react in similar way. The most interesting and practically important in this respect is direct hydroxylation of nitroarenes in the VNS reaction with anions of *tert*-butyl or cumyl hydroperoxides. For example, treatment of 1-nitronaphthalene with cumyl hydroperoxide and *t*-BuOK in liquid ammonia results in formation of 1-nitro-2-naphthole or 1-nitro-4-naphthole in high yield (*Scheme 4*) [8]. The process is of general character concerning the nitroarenes and proceeds *via* typical addition β-elimination mechanism as it was shown *via* effect of base on the competition between VNS of hydrogen and S$_N$Ar of halogen in 4-chloronitrobenzene.

The direct amination of nitroarenes with hydroxylamine in basic medium which is known for many years proceeds apparently *via* the VNS mechanism. Much more general is the VNS amination with aminotriazoles [9] or sulfenamides [10]. Because of availability and facile regeneration of the sulfenamides, the latter process can be of substantial practical use and industrial interest.

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[3] M. Mąkosza, *Polish J. Chem.* **1992**, *66*, 3.
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haloforms *etc.* Indeed, such carbanions replace readily H-atoms in nitroarenes with the carbanion moiety. For this reaction the term vicarious nucleophilic substitution (VNS) was proposed [4][5].

The main characteristic feature of this reaction and its relation with typical S$_N$Ar process are shown on *Scheme 2* [6]. The results of these simple experiments lead to a few conclusions: *1*) Rate of the addition of carbanions to nitroaromatic rings in position occupied with substituents Z decrease in order Z = H > F > Cl. *2*) The fast addition of carbanions giving σ^H adducts is a reversible process. *3*) Rate of the conversion of σ^H adducts of α-halocarbanions to the products depends on the base concentration, and when it is sufficiently high it exceeds even the rate of the σ^F adducts formation. Thus the VNS reaction under properly choosen conditions

proceeds much faster than eventually competing S$_N$Ar of halogen, even florine.

The VNS reaction is of general character in respect to the nitroarenes and carbanions (*Scheme 3*). There is practically no limitation concerning substituents Z in the nitroaromatic rings which can be carbo and heterocyclic [7], only such substituents as *e.g.* OH or SH, which in strongly basic conditions are deprotonated and the negative charge in the resulting anions is conjugated with the ring inhibite the reaction. Since in the VNS reaction the products are formed as nitrobenzylic carbanions, it proceeds as selective monosubstitution. For the carbanions C̄XYR to enter VNS it is necessary that at least one substituent X is able to be eliminated as HX from the intermediate σ^H adducts. It can be Cl, Br, RO, RS *etc.* Other substituents Y and R at the carbanionic center can vary