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Nucleophilic Aromatic Substitution, General Corrected Mechanism And Versatile Synthetic Tool

Mieczyslaw Makosza*

Institute of Organic Chemistry, Polish Academy of Sciences, Poland

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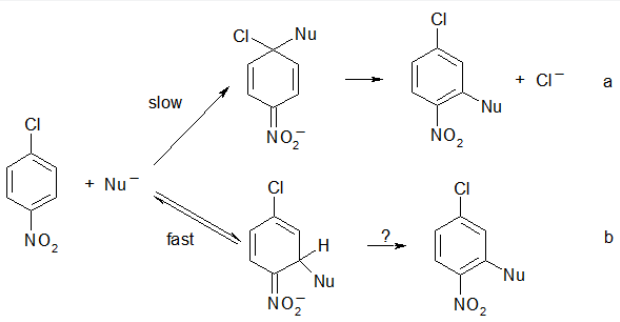
***Corresponding author:** Mieczyslaw Makosza, Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa, Poland, Email: icho-s@icho.edu.pl

Mini Reveiw

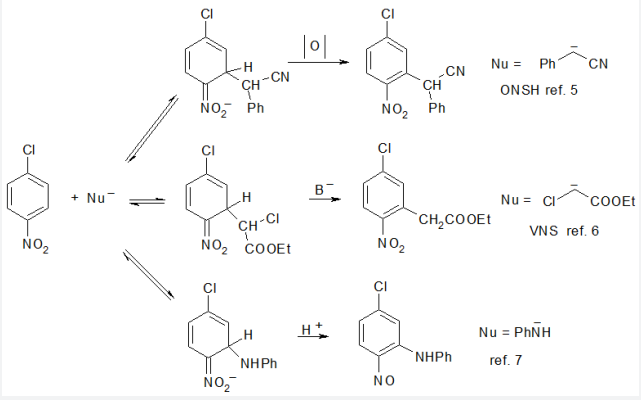
Nucleophilic aromatic substitution in electron-deficient arenas, particularly nitroarenes is an efficient tool in synthesis and manufacturing of pharmaceuticals [1-3]. It is therefore of crucial importance to know how exactly these reactions proceed. For many years it was considered that these reactions are limited to substitution of halogens or other nucleofugal groups X and proceed via addition of nucleophile at positions occupied by X to form intermediate σ^X adducts. Fast departure of X– from these adducts leads to products of S_NAr. This addition-elimination mechanism formulated by Bunnet [4] where as a rule the addition is the slow, rate limiting step was subject of thorough studies and refinements and is presented in many reviews, monographs and text-books [5-7] (Scheme 1a).



Scheme 1: Addition at positions occupied by halogens is a slow and as a rule irreversible process, whereas addition at positions occupied by hydrogen fast and reversible.

About 30 years ago it become evident that nucleophile can add to nitroarenes, including halonitroarenes, also at positions occupied by hydrogen to form σ^H adducts and that this addition mode proceeds faster than the addition at positions occupied by halogen – the first step of the classical S_NAr. Since spontaneous departure of hydride anions from the initially formed σ^H adducts does not proceed, they usually dissociate so substitution of halogens via slower formation of σ^X adducts can proceed (Scheme 1b).

Nevertheless σ^H adducts of some nucleophiles under proper conditions can be converted into products of nucleophilic substitution of hydrogen, S_NArH on several ways: oxidation by external oxidants, (oxidative nucleophilic substitution of hydrogen, ONSH) [8, 9], elimination of HL when nucleophile contain a nucleofugal group L, vicarious nucleophilic substitution (VNS), and conversion into substituted nitrosoarenes [10, 11]. These reactions are exemplified in Scheme 2.



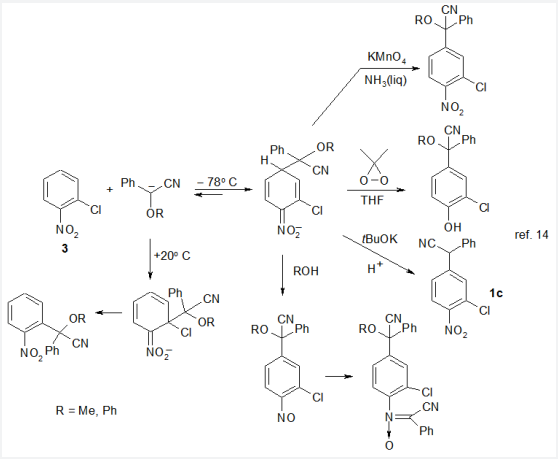
Scheme 2: Three main variants of SNArH in p-chloronitrobenzene proceeds faster than then SNAr of chlorine, so mechanism of this reaction should be corrected.

These results lead to the conclusion that commonly accepted mechanism of S_NAr reaction should be corrected. Indeed on the basis of additional experimental mechanistic studies and ab initio calculations general mechanistic picture of reactions between nucleophile and nitroarenes, that embrace S_NAr and S_NArH reactions was formulated [12, 13].

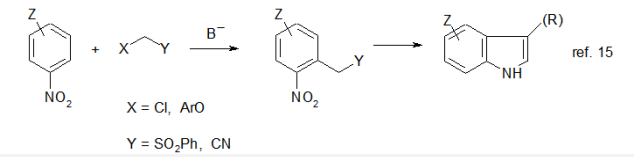
Thus, since classical S_NAr of halogens and S_NArH of hydrogen can proceed in the same molecule of a halo nitrobenzene they can be considered as complementary processes. Moreover it is possible that the same reactants (nitroarenes and nucleophile) can react in two or even more different ways depending on the structure and conditions. For instance, carbanion of α-phenoxy- and α-methoxyphenylacetonitriles can react with o-chloronitrobenzene in five different ways to give five products with high yields and selectivities sic!!! [14]. Scheme 3.

Conclusion

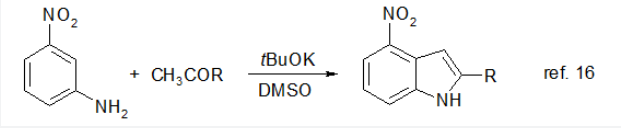
It is therefore evident that the corrected general mechanism of nucleophilic aromatic opens wide avenue Avenue in organic synthesis particularly valuable for pharmaceutical chemistry. Very useful classical S_NAr of halogens is well known, so it is not necessary to present here examples illustrating its value. On the other hand S_NArH variant of nucleophilic aromatic substitution is much less known hence its versatility and great practical value, as well as some specific features are illustrated by examples presented in Schemes 3-7.



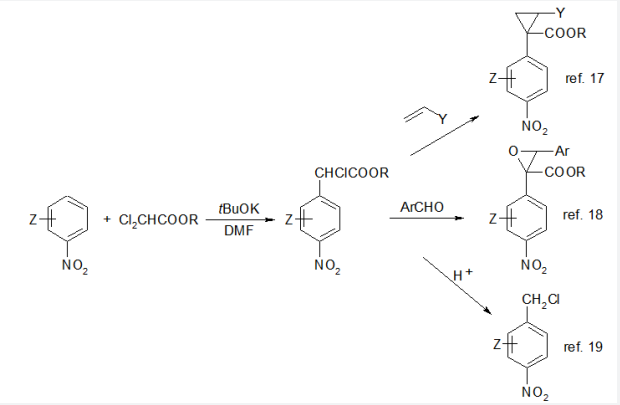
Scheme 3: Carbanions of α-alkoxyphenylacetonitriles can react with o-chloronitrobenzenes in five different ways with high selectivity!!!



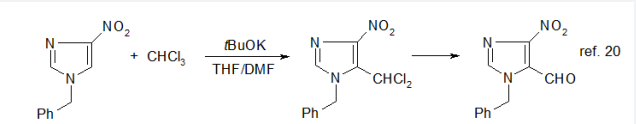
Scheme 4: VNS reaction is versatile tool for synthesis of indoles.



Scheme 5: ONSH is m-nitroanilines by enolate anions open the simplest way of synthesis of 4- or 6-nitroindoles.



Scheme 6: VNS with carbanions of alkyl dichloroacetates can be used for introduction of a variety of functionalized substituents into nitroarenes.



Scheme 7: Nucleophilic formylation of nitroarenes and nitroheteroarenes via VNS with haloforms is a process of high practical value.

It should be stressed that all the presented reactions proceed without using of transition metal catalysts, so are well suited for synthesis of pharmaceuticals. I certainly hope that this text will help chemists practicing organic synthesis to find simple and efficient solutions of their problems.

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