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Vicarious Nucleophilic Substitution of Hydrogen in Azulenes

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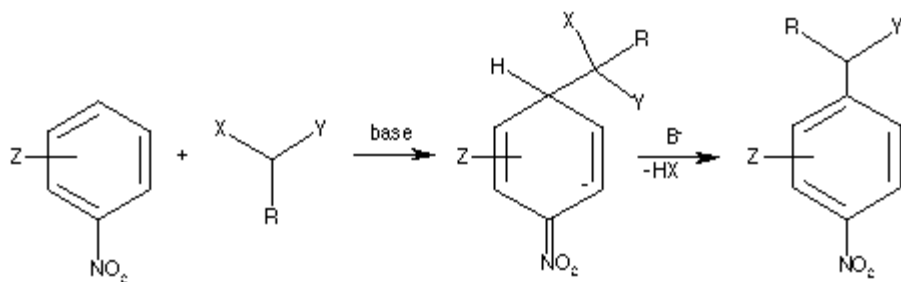
Abstract: Recent results of vicarious nucleophilic substitution of hydrogen in azulenes are reviewed.

Keywords: Nucleophilic substitution, azulenes.

Introduction

Azulene ring system can be considered as a combination of the aromatic cyclopentadienyl anion and cycloheptatrienyl (tropylium) cation, hence it exhibits a high chemical reactivity towards electrophilic and nucleophilic agents respectively. Nucleophilic agents add readily to seven-membered ring of azulene. Oxidation of these adducts results in oxidative nucleophilic substitution of hydrogen (ONSH).

Electrophilic aromatic rings, e.g. nitroarenes, react with nucleophiles containing leaving groups to give products of vicarious nucleophilic substitution, VNS reaction.

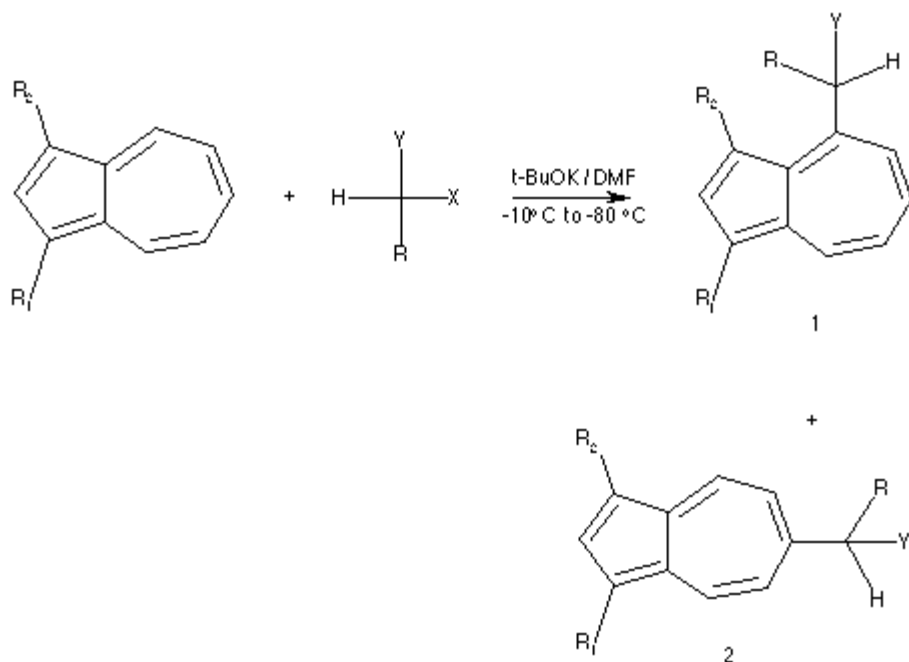


VNS with Carbanions

We have found that the VNS reaction with carbanions proceeds with azulene and its derivatives.

Azulene reacts with carbanions bearing a leaving group according to the VNS scheme. Two isomeric products can be formed, arising from the substitution of the hydrogen at C-4 or C-6. Carbanions of chloromethanesulfonamides and p-chlorophenoxyacetonitrile react with azulene giving products of VNS in positions 4- and 6- which are related to the positions *ortho*- and *para*- in nitrobenzene.

Introduction into the five-membered ring of azulene of the electronwithdrawing groups such as -Cl, -COOEt, -CN, -PhCO etc. increases activity of the azulenes in the VNS reaction.



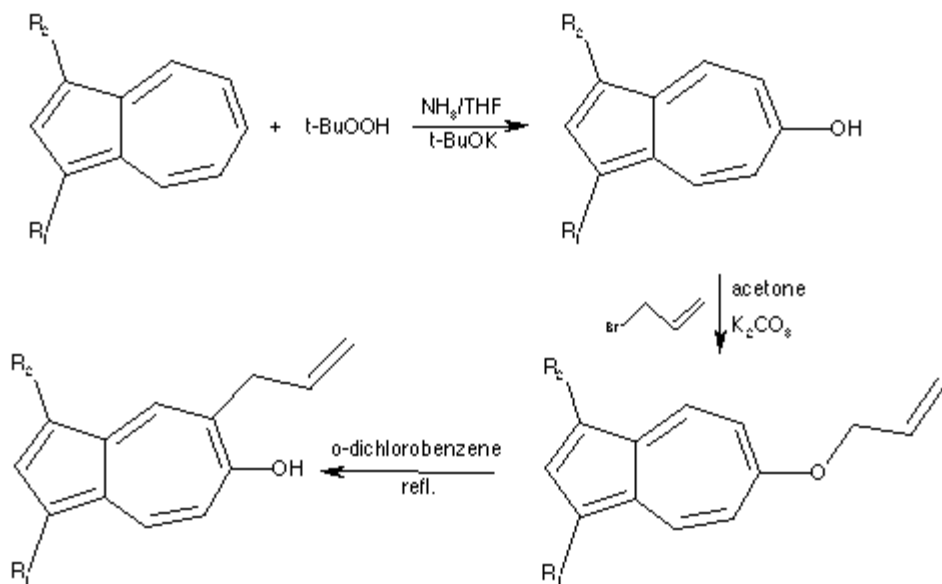
R ₁	R ₂	R	X	Y	Yields (%)	
					1	2
H	H	H	Cl	SO ₂ NMe ₂	18	22
H	H	Pr	Cl	SO ₂ N	-	19
H	H	H	4-ClC ₆ H ₄ O	CN	21	39
CN	H	H	Cl	SO ₂ NMe ₂	35	35*
COOEt	COOEt	H	Cl	SO ₂ NMe ₂	-	82
PhCO	H	H	Cl	SO ₂ NMe ₂	15	40

*10% of isomer 8- was also obtained.

Hydroxylation

Treatment of the azulene derivatives containing electronwithdrawing groups in five-membered ring with *tert*-butylhydroperoxide in the presence of an excess of potassium *tert*-butoxide in liquid ammonia / THF results in the VNS hydroxylation. The reaction proceeds selectively in position 6-. *t*-Butylhydroperoxide anion, being a weak nucleophile, does not enter the VNS reaction with the unsubstituted azulene.

6-Hydroxyazulenes behave as phenols, e.g. when treated with allyl bromide and K₂CO₃ they form readily allyl ethers which undergo the Claisen rearrangement.

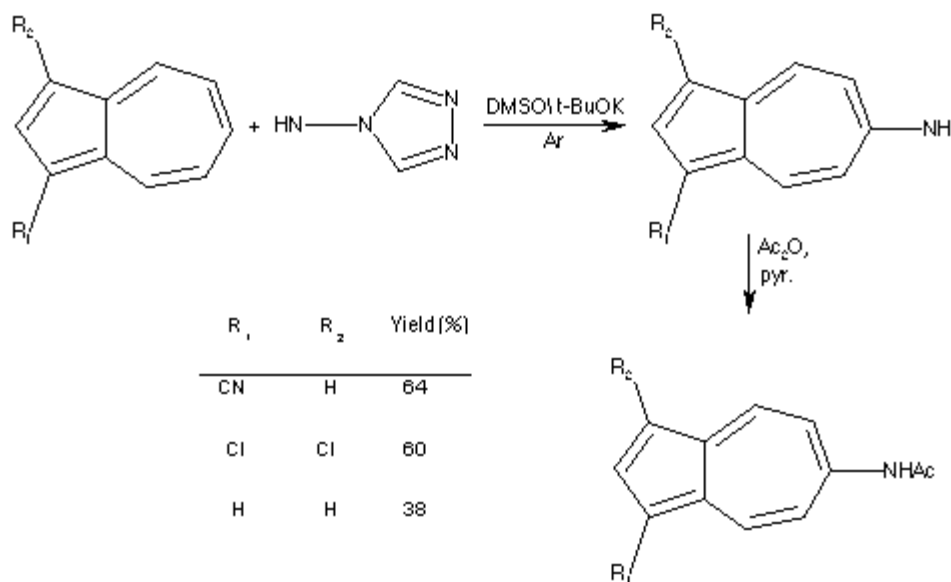


$R_1, R_2 = \text{COOEt}$ 43% $R_1, R_2 = \text{COOEt}$ 82% Cl 28% Cl 70%

Amination

It is possible to obtain aminoderivatives of azulenes in the VNS reaction with 4-amino-1,2,4-triazole as aminating agent. The reaction should be carried out in the oxygen free atmosphere. In the presence of oxygen oxidative nucleophilic substitution of hydrogen competes with VNS. Similarly to the VNS hydroxylation only 6-aminoazulenes are formed. Because of the low stability they were isolated and purified in the form of N-acetyl derivatives.

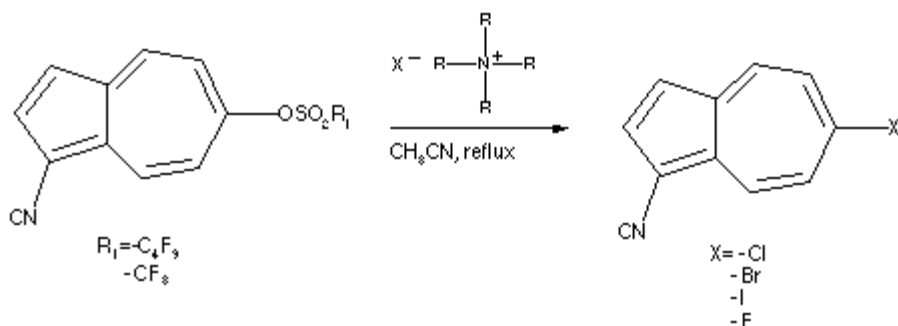
Attempts of amination of azulenes with sulfenamides failed. No amination products were obtained in these cases.



S_NAr reactions in azulenes

6-Hydroxyazulenes open an easy route to obtain 6-haloazulenes. First step is an activation of hydroxyl group with nonafluorobutanesulfonyl or trifluoromethanesulfonyl substituent. Obtained derivative react with tetraalkylammonium halides in the S_NAr reaction resulting in formation of 6-haloazulenes with very good yields. Chloro-, bromo- and iodoazulenes can be prepared. The process is carried out in CH_3CN under reflux for several hours.

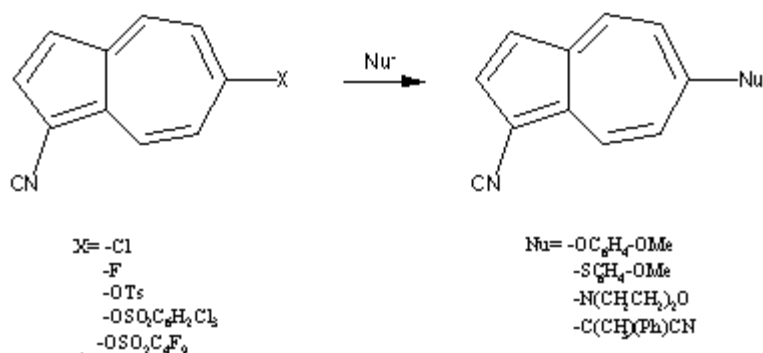
It is also possible to obtain fluorine derivative in the similar way. However due to the large basicity of the fluorine anion trifluoromethanesulfonyloxy group cannot be used in this case. Reaction with tetraethylammonium fluoride results in the recovering of the starting hydroxyazulene. Nonfluorobutanesulfonyloxy group is not that sensitive to the fluorine anion and it is possible to substitute it in the S_NAr reaction with the fluorine atom although some amount of 6-hydroxyazulene is also produced.



Tetraalkylammonium salt	t (h)	...1-cyanoazulene	Yield (%)
$\text{Et}_3\text{BzN}^+ \text{Cl}^-$	4	6-chloro-	96
$\text{Bu}_4\text{N}^+ \text{Br}^-$	36	6-bromo-	94
$\text{Bu}_4\text{N}^+ \text{I}^-$	48	6-iodo-	91
$\text{Et}_4\text{N}^+ \text{F}^-$	0.25*	6-fluoro-	60

* THF was used as a solvent

Halogen atom can be substituted in S_NAr reaction with many substituents. New C-C, C-O, C-N and C-S bonds can be formed. It is also possible to exchange other groups, e.g. 2,4,5-tribenzenosulfonyloxy, nonfluorobutanesulfonyloxy and tosyloxy (excluding carbanions). Some examples are listed below. Yields are good or very good.

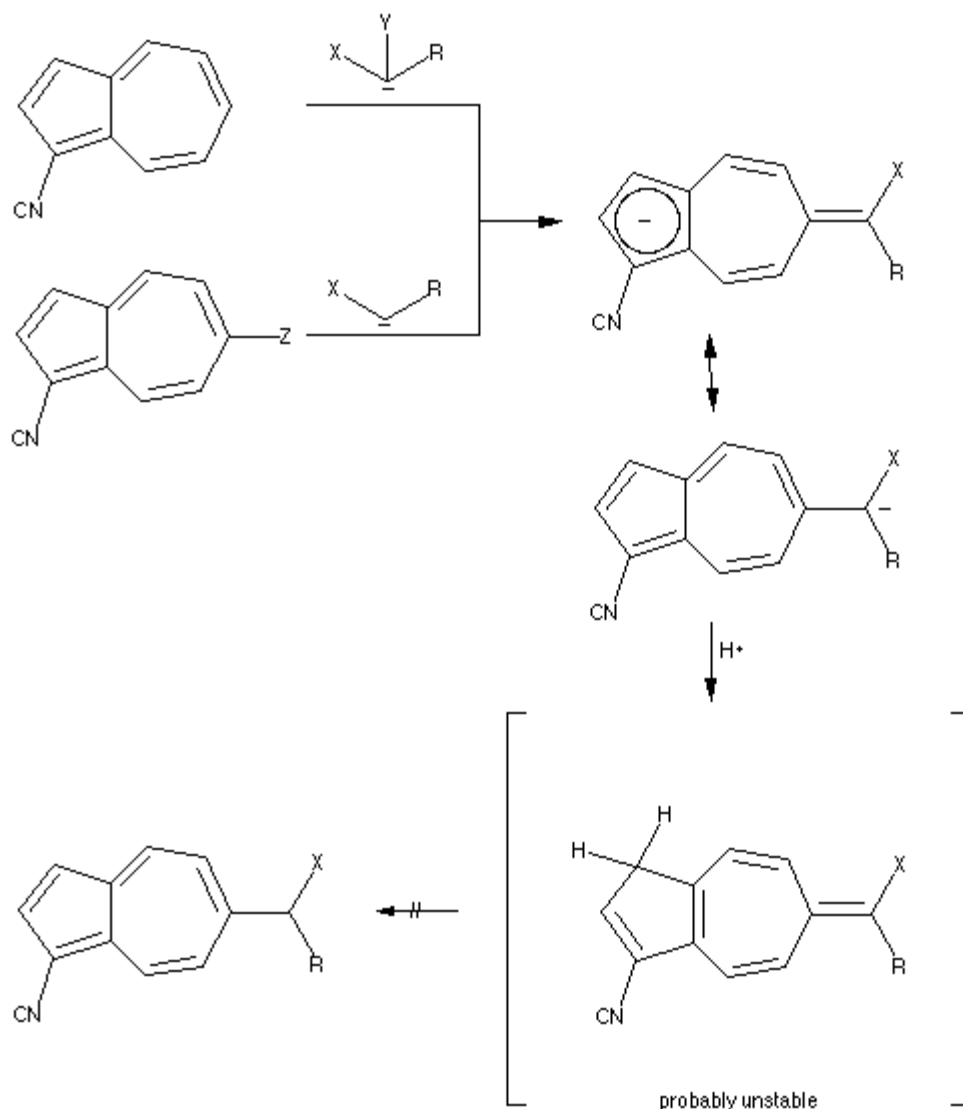


Limitations of the VNS and S_NAr reactions

Although there are many examples of the VNS and S_NAr reactions of azulenes with a variety of carbanions, sometimes it is impossible to obtain an expected product.

Azulenes activated in the five-membered ring with the electronwithdrawing group (e.g. 1-cyanoazulene) in the VNS reaction with tertiary carbanions or in the S_NAr with secondary carbanions form unstable products that cannot be isolated.

It can be explained on the ground that the supposed anionic products of these reactions possess a highly stabilized charge in the five-membered ring. From the other hand a carbon atom bearing negative charge in the side chain is sterically hindered thus protonating of such a product will preferably take place in the five-membered ring. As a result an unstable product with many conjugated unsaturated bonds that is not able to rearrange is formed.

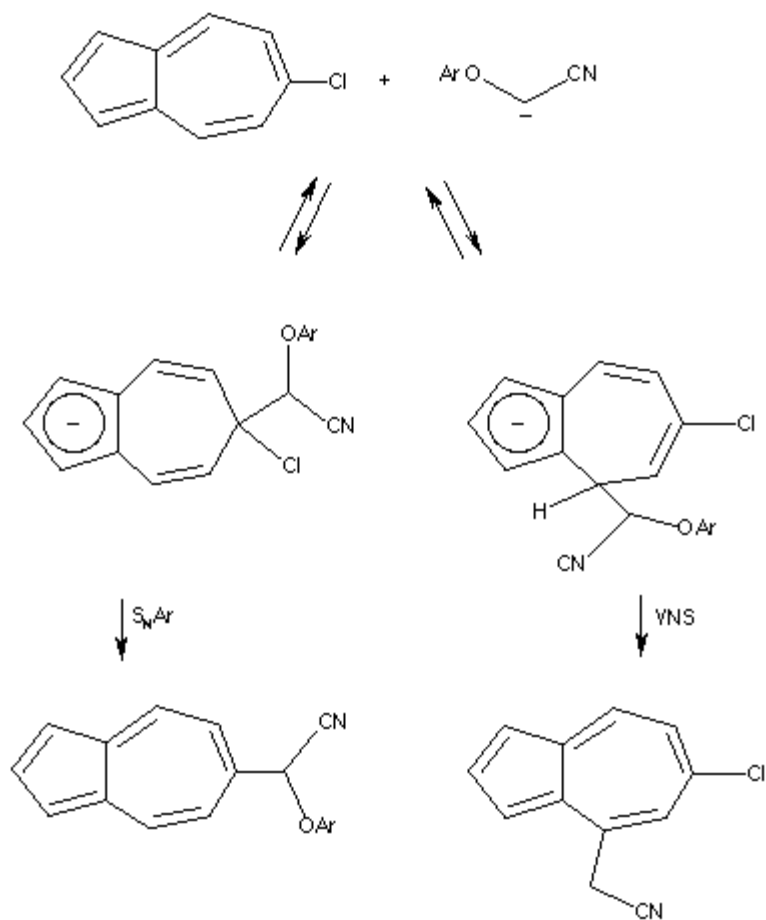


Mechanism

To check whether the VNS reaction in azulenes proceeds *via* the addition-[beta]-elimination mechanism the influence of base on competing processes VNS and S_NAr was examined. 6-Chloroazulene was chosen as the model compound for these studies.

p-Chlorophenoxyacetonitrile under the standard reaction conditions (excess of the base) forms only the VNS product. On the other hand when a base free solution of its carbanion was slowly added to a solution of 6-chloroazulene both of these reactions S_NAr and VNS proceeded.

Thus the general scheme of the VNS reaction - nucleophilic addition followed by base induced [beta]-elimination - appears to be valid for the azulene system.



References

1. Mieczyslaw Makosza, Renata Kuciak, Krzysztof Wojciechowski, *Liebigs Ann. Chem.* **1994**, 615.

Comments

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