# TRIAZOLINES 30. NONREGIOSPECIFIC 1,3-CYCLOADDITION OF ARYL AZIDES TO VINYLPYRIDINES: A UNIQUE ROUTE TO PYRIDYL SUBSTITUTED AZIRIDINES (1)

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## Abstract

The 1,3-cycloaddition of phenyl azides to the olefinic double bond of 4-vinylpyridine, yields the 1-phenyl-2-pyridylaziridine as the main product with only smaller amounts of the 1-phenyl-5-pyridyl-1,2,3-triazoline, although the reaction constitutes a general approach to the synthesis of $\Delta^2$-1,2,3-triazolines. Experimental and theoretical evidence are provided to explain the results on the basis that the olefinic bond in 4-vinylpyridine is an electron-deficient bond and that azide addition is not regiospecific. In the bidirectional addition reaction, the $HOMO_{azide}$-$LUMO_{olefin}$ interaction predominates leading to a 1-phenyl-4-pyridyl-1,2,3-triazoline, which, unlike the 5-pyridyl compound, loses nitrogen under thermal conditions to yield the aziridine, and at room temperature, a mixture of the respective triazole and the aziridine.

## Introduction

There are two main approaches to the synthesis of $\Delta^2$-1,2,3-triazolines. These constitute the 1,3-cycloaddition reactions of organic azides to the olefinic carbon-carbon double bonds or of diazoalkanes to the carbon-nitrogen double bonds in Schiff bases (aldimines) (2). The azide-olefin additions are concerted, stereospecific, cis additions, with the terminal azido nitrogen binding to the more nucleophilic carbon of the olefin. Unsymmetrically substituted olefins also exhibit a marked orientational specificity, the direction of addition being controlled by electronic rather than steric factors. Thus unsymmetrical olefins give only one triazoline isomer, as in the case of phenyl azide-styrene adducts, which are exclusively, 1,5-diaryl-triazolines. The same rules for orientational specificity apply to electron rich olefins (eg. enamines) and olefins bearing electron withdrawing groups (eg. methyl acrylate); as a rule, the electron releasing groups appear at the 5-position of the triazoline ring and electron withdrawing substituents at the 4-position,

although azide addition to electron deficient olefinic bonds is not always regiospecific (2). In most instances where two isomers are possible, one isomer usually predominates, often to the exclusion of the other (3).

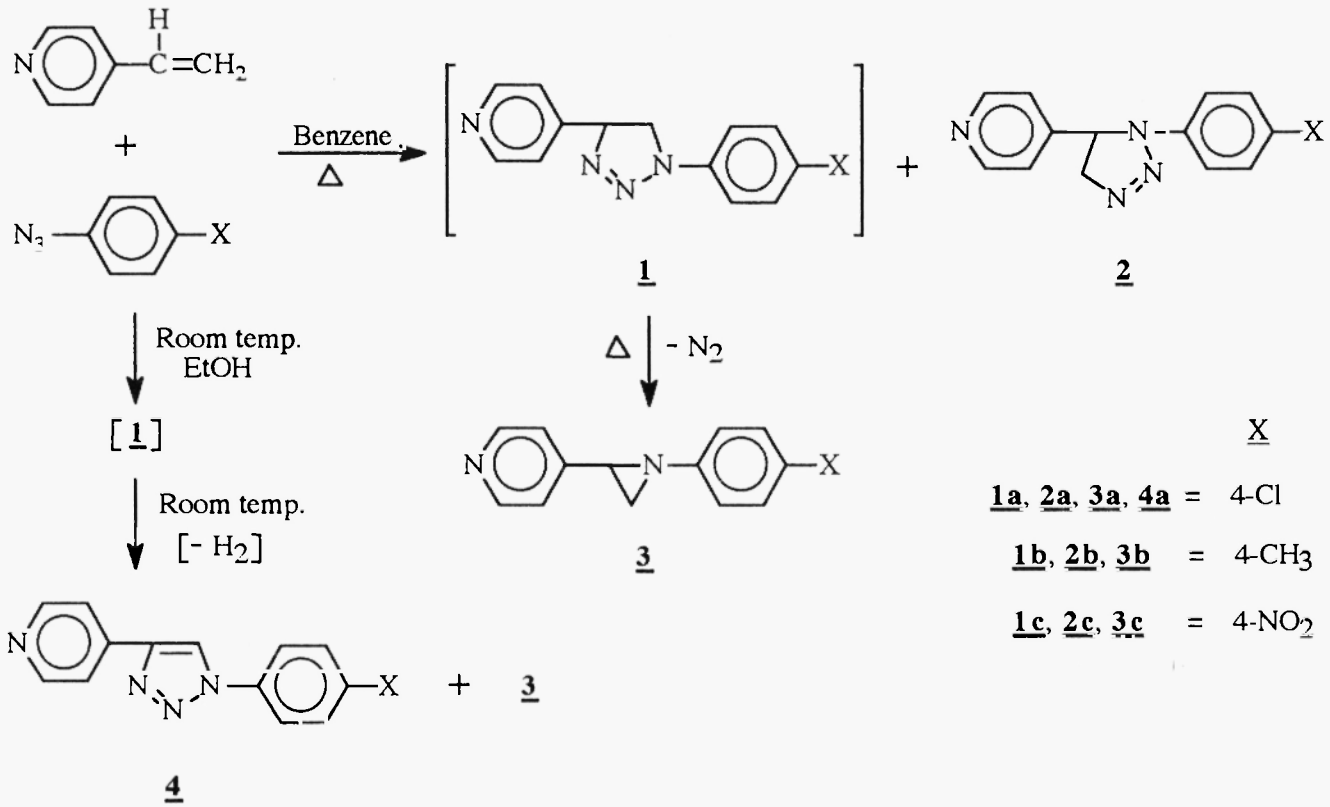
## Results and Discussion

This paper reports the preliminary results of the first-time investigation of the 1,3-cycloaddition of 4-chlorophenyl azide to 4-vinylpyridine. Reaction of equivalent amounts of the vinylpyridine and the azide in refluxing benzene, yielded a product that was found to consist exclusively of a mixture of 1-(4-chlorophenyl)-5-(4-pyridyl)-1,2,3-triazoline (**2a**) and 1-(4-chlorophenyl)-2-(4-pyridyl)aziridine (**3a**). Quantitative HPLC analysis showed the aziridine **3a** to be the predominant component, comprising almost 80% of the reaction product. Repeated fractional crystallization of the product mixture yielded pure samples of both triazoline **2a** and aziridine **3a**. The identity of **2a** and **3a** was established by comparison of their m.p.s, NMR ($CDCl_3$ with TMS as internal standard) and MS with authentic samples; **2a** was prepared by the cycloaddition reaction of diazomethane to 4-[(4-chlorophenyl)iminomethyl]pyridine (4) and **3a** was obtained by photolysis of **2a** (5). Triazoline **2a**, melted at 151-152°C with decomposition and brisk evolution of $N_2$ (4); $^1$H NMR, δ, ppm 4.3 (q, 5-CH), 4.9 (m, 4-$CH_2$), 8.5 (d, 2,6-Pyr H), 7.3 (d, 3,5-Pyr H), 7.0 (d, 2,6-Ph H), 7.3 (d, 3,5-Ph H); MS, m/z ($M^+$, %) 229 ($C_5H_4N$-C($CH_2$)-N-$C_6H_4Cl$, 71), 215 ($C_5H_4N$-C-N-$C_6H_4Cl$, 54), 138 (CH-N-$C_6H_4Cl$, 61), 125 (N-$C_6H_4Cl$, 35), 111 ($C_6H_4Cl$, 100). Aziridine **3a**, m.p. 105-106°C, with no decomposition; $^1$H NMR, δ, ppm 3.0 (q, 2-CH), 2.4 (dd, 3-$CH_2$), 2.5 (dd, 3-$CH_2$), 8.6 (d, 2,6-Pyr H), 7.5 (d, 3,5-Pyr H), 7.0 (d, 2,6-Ph H), 7.3 (d, 3,5-Ph H); MS, m/z ($M^+$, %) 229 [$(M-1)^+$, 100], 138 (CH-N-$C_6H_4Cl$, 43), 125 (N-$C_6H_4Cl$, 57), 111 ($C_6H_4Cl$, 47). The peak at m/z 215 for triazoline **2a** helps to distinguish it from aziridine **3a**, which does not give rise to this fragment in the electron-impact MS.

Our initial objective was to explore the use of the 4-vinylpyridine-aryl azide addition as a safer procedure for the scaled-up synthesis of the biologically active (6) 1-aryl-5-pyridyl-1,2,3-triazolines; although our usual method of triazoline synthesis by the addition of diazomethane to aldimines gives excellent yields (4,6), use of large amounts of the toxic, explosive diazomethane gas is hazardous for scaled-up synthesis. However, azide addition to 4-vinylpyridine does not appear to be regiospecific; two isomeric triazolines seem to be formed from a bidirectional addition reaction, with the 1-aryl-5-(4-pyridyl)-1,2,3-triazoline **2a** formed only in minor amounts.

The olefinic bond in 4-vinylpyridine is apparently an electron deficient bond, since pyridine, quinoline and similar heterocyclic ring systems where the nitrogen is incorporated onto the six-membered ring are considered electron withdrawing or π-deficient as opposed to pyrroles, etc. which are π-excessive

(7,8). Thus orientational rules dictate the formation of triazoline **1a** bearing the electron withdrawing 4-pyridyl group in the 4-position as the major (if not the exclusive) product (2,3). However, no **1a** could be isolated from the reaction mixture and it was argued that at the temperature of refluxing benzene, **1a** undergoes *in situ* thermolysis to yield the aziridine **3a**. This is supported by the fact that triazolines bearing an electron withdrawing substituent in the 4-position, upon thermolysis, are known to undergo ring cleavage with nitrogen expulsion to give aziridines (2) (see Scheme), while those with electron withdrawing groups in the 5-position lead exclusively to ketimines (2,5). However, the possibility of aziridine formation by interaction of vinylpyridine with nitrene that may result from azide thermolysis, cannot be completely ruled out. Obviously, olefin-azide addition is not the reaction of choice for the preparation of 1-aryl-5-pyridyl-1,2,3-triazolines (2), as opposed to the diazomethane-imine reaction, where the 1,5-substituted triazolines are formed exclusively in high yields (4,6).




SCHEME

With a view to isolate the 4-(4-pyridyl)triazoline **1a**, 4-vinylpyridine was allowed to react with 4-chlorophenyl azide at room temperature in the dark. Column chromatographic separation of the reaction mixture, after about two months, yielded two products; the major one was identified by elemental analysis, NMR and MS to be a 4-(4-pyridyl) substituted triazole **4a** and the other product to be an aziridine **3a**. The triazole **4a** (M.p., 210-212°, with no decomposition and gas evolution) is distinctly different from the 1-aryl-5-(4-pyridyl)triazole (M.p., 124.5-125.5°) (9) obtained by oxidation of the corresponding 5-pyridyl substituted triazoline. $^1$H NMR, δ, ppm, 8.3 (s, 5-CH), 7.6 (d, 2,6-Ph H), 7.8 (d, 3,5-Ph H), 8.7 (d, 2,6-Pyr H) 7.8 (d, 3,5-Pyr H); $^{13}$C NMR ($CDCl_3$), δ, ppm 150.6 (2,6-Pyr C), 146.1 (4-Pyr C), 137.3 (1-Ph C), 135.2 (4-triazole ring C), 135.0 (4-Ph C), 130.1 (3,5-Pyr C), 121.8 (3,5-Ph C), 120.0 (2,6-Ph C), 119.0 (5-triazole ring C); MS by FAB (fast atom bombardment) yielded an intense base peak at $M^{+1}$ 257.

No 5-(4-pyridyl)triazoline **2a** was observed in the reaction mixture at room temperature. This experiment thus provides further support that the 4-(4-pyridyl)triazoline **1a** is formed exclusively at room temperature as expected; however, unlike **2a**, **1a** appears to be very unstable and undergoes major dehydrogenation to the stable aromatic triazole, while also yielding aziridine **3a** by loss of nitrogen. Under reflux conditions in benzene, the triazoline **1a** undergoes complete *in situ* thermolysis to yield only the aziridine.

The formation of the triazoline intermediate **1a** is also explained by the frontier molecular orbital (FMO) treatment of 1,3-cycloadditions. The FMO approach permits a rational interpretation of the effect of substituents on reactivity and regioselectivity (2). Reactions fall into three types, depending on whether the dominant interaction is between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile, or the dipole LUMO and the dipolarophile HOMO, or whether both interactions are of comparable significance. In the case of azide addition to electron rich olefins, the dominant interaction will be $HOMO_{olefin}$-$LUMO_{azide}$, whereas $HOMO_{azide}$-$LUMO_{olefin}$ interaction will govern additions to electron poor olefins. While HOMO energy is increased by electron donating groups, LUMO energy is decreased by electron withdrawing substituents.

Experimental evidence consistent with the FMO theory was obtained by reacting 4-vinylpyridine with 4-methyl- and 4-nitrophenyl azides in refluxing benzene. Analysis of the reaction mixture by NMR spectroscopy indicated that in each case, the aziridines **3b** and **3c** predominated with minor amounts of the 1-aryl-5-(4-pyridyl)triazolines **2b** and **2c**. Such analysis is reliable and made possible by each compound's characteristic chemical shifts and splitting patterns; the $>CH_2$ and >CH- protons of the aziridines usually appear upfield in the 2.5 to 3.1 ppm region, while the same protons in the triazolines appear much more downfield in the 4.3-4.9 ppm range. Column chromatographic separation and purification of the products from these two reactions as well as from that of 4-chlorophenyl azide with 4-vinylpyridine, gave percent

yields of **3a**, 49, **2a**, 10; **3b**, 53, **2b**, 21; and **3c**, 22, **2c**, 12. The triazolines **2a-2c** were identified from their previously reported m.p.'s and $^1$H NMR (4) and the aziridines, from their elemental analysis and $^1$H NMR. The results clearly indicate that the HOMO energy of the azide is increased by the electron releasing $CH_3$- group and decreased by the electron withdrawing $NO_2$ group, which are in agreement with the FMO theory that azide addition to 4-vinylpyridine is a $HOMO_{azide}$ -$LUMO_{olefin}$ interaction.

Aziridine **3b**, m.p., 123-125°C; $^1$H NMR, δ, ppm, 2.3 (s, $CH_3$), 3.0 (dd, 2-CH), 2.4 (dd, 3-$CH_2$), 2.5 (dd, 3-$CH_2$), 8.6 (dd, 2,6-Pyr H), 7.3 (dd, 3,5-Pyr H), 7.1 ( dt, 2,6-Ph H), 6.9 (dt, 3,5-Ph H); triazoline **2b**, m.p. 156-158°C (d) [lit. 157-158°C (d) (4)]; $^1$H NMR, δ ppm 2.3 (s, $CH_3$), 4.2 (m, 5-CH), 4.8 (m, 4-$CH_2$).

Aziridine **3c**, m.p. 142-143°C; $^1$H NMR, δ, ppm 3.2 (dd, 2-CH), 2.5 (dd, 3-$CH_2$), 2.6 (dd, 3-$CH_2$), 8.6 (dd, 2,6-Pyr H), 7.3 (dd, 3,5-Pyr H), 7.1 (dt, 2,6-Ph H), 8.2 (dt, 3,5-Ph H); triazoline **2c**, m.p. 151-152°C (d) [lit. 151-152°C (d) (9)]; $^1$H NMR, δ, ppm 4.5 (m, 5-CH), 5.0 (m, 4-$CH_2$).

## Conclusion

In terms of the FMO model, the 1,3-cycloaddition of phenyl azides to 4-vinylpyridine appears to be predominantly, but not exclusively, a $HOMO_{azide}$-$LUMO_{olefin}$ interaction as evidenced from the preferential formation of the 4-(4-pyridyl)triazolines **1** which decompose *in situ* under heat to give rise to the aziridines **3** and at room temperature to give triazoles **4** and aziridines **3**. Thus azide addition to 4-vinylpyridine provides a unique route to the synthesis of 2-(4-pyridyl) substituted aziridines.

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