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# Synthesis of 2-Methyl-3-nitropyridines, 2-Styryl-3-nitropyridines and Their Reactions with S-Nucleophiles †

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**Abstract:** One of the most important and flexible tools for nitroarenes functionalization is nucleophilic aromatic substitution ($S_NAr$). This reaction generally requires number of conjugated electron-withdrawing groups and $S_NAr$ of non-activated nitro groups is rather uncommon. Most of these examples were obtained on polynitrobenzenes, but little is known about reactions of non-activated 3-nitropyridines. Here we report synthesis of several 2-methyl-3-nitropyridines and their reactions with various aromatic aldehydes, leading to corresponding 2-styrylpyridines under mild conditions. Both 2-methyl- and 2-styryl-3-nitropyridines readily react with thiolate-anions and give substitution products in good yields. Chemo- and regioselectivity is discussed, some of 2-styrylpyridines also showed remarkable fluorescent properties.

**Keywords:** nitro group; nitropyridines; nucleophilic substitution; fluorescence

## 1. Introduction

Nitroarenes and nitrohetarenes are valuable synthetic intermediates in organic synthesis due to variety of possible chemical transformations. Along with nitro group reductions that are used for synthesis of numerous dyes, reactions of nitroaromatic compounds with nucleophiles are widely used for functionalization of electron deficient arenes and hetarenes [1]. Nucleophilic aromatic substitution ($S_NAr$) is one of the most common and important mechanism for this type of reactions. It requires existing leaving group and thus is usually very selective. $S_NAr$ reactions also require one or more strong electron withdrawing groups which are conjugated to leaving group and activating it for substitution. In some cases strong EWG groups like $-NO_2$ or $-SO_2R$ can be substituted by nucleophiles without direct activation. This mode of $S_NAr$ is well documented for 1,3,5-trinitrobenzene and related bicyclic systems [2,3].

Heterocycles that are electron deficient by nature tend to react with nucleophiles more readily. Pyridine is the simplest example of such heterocycle and it is also common part of various pharmaceuticals, so it is important to explore different ways to introduce substituents into pyridine system. Nucleophilic substitution in position 2 and 4 is relatively well known due to activating nature of nitrogen atom in azines, but position 3 of pyridine is generally considered not reactive. We decided to synthesize 3-nitropyridines with simple carbon side chains like $-CH_3$ or -CH=CH-R and see if such compounds can be functionalized by means of nucleophilic aromatic substitution.

## 2. Results and Discussion

### *2.1. Synthesis of 2-Styryl-3-nitropyridines*

One of the most common way to synthesize unsymmetrical 1,2-diarylethenes is direct cross-coupling of halogen-substituted arene and terminal alkene, known as Heck reaction. This reaction is best performed with Br, I or TfO as leaving group, while chloroarenes generally give poor results. However, 2-chloropyridines are significantly more accessible than other 2-halopyridines because commercially available 2-hydroxypyridines can be easily chlorinated with various reagents like $SOCl_2$, $POCl_3$ or $PCl_5$, especially after introduction of nitro group into position 3 or 5. Previously we have successfully applied Sonogashira coupling to 2-chloro-3-nitropyridines [4], but attempted Heck coupling gave no desired product due to side reactions of activated 2-chloropyridines at elevated temperatures.

More reliable 3 step method was chosen, which utilizes high reactivity of 2-chloro-3-nitropyridines towards nucleophiles (Figure 1). 2-chloro-3-nitropyridines were converted to 2-methyl-3-nitropyridines by reaction with malonic ester anion, generated in situ from diethyl malonate and $K_2CO_3$ in anhydrous THF. Reaction proceeds smoothly and gives substituted malonic esters, that were without purification directly subjected to hydrolysis and decarboxylation in aqueous sulfuric acid. 2-methylpyridines (**1a,b**) were isolated in moderate to good yields and high purity. This procedure is based on literature [5], but optimizations were made to avoid inconvenient bases like sodium metal or NaH.

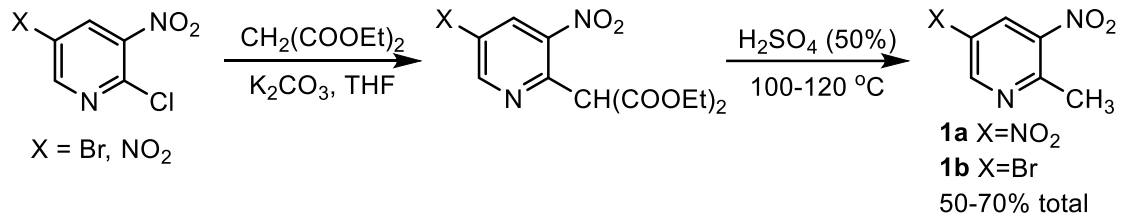



**Figure 1.** Two-step synthesis of 2-methyl-3-nitropyridines.

Methyl group in 2-methylpyridines is known to be relatively acidic, this property can be further increased by adding electron-withdrawing groups to aromatic ring. Positive charge on nitrogen, such as *n*-oxide moiety, also increases reactivity of adjacent methyl group. Both 2-methyl-3,5-dinitropyridine (**1a**) and 2-methyl-3-nitro-5-bromopyridine *n*-oxide (**1c**) reacted with various aromatic aldehydes upon heating in toluene with catalytic amounts of piperidine (Figure 2). This procedure is significantly milder than heating with molar equivalent of potassium tert-butoxide in tert-butanol required for 2-methylpyridines *n*-oxide containing no nitro groups [6]. It should also be noted that compound **1a** reacts several times faster than **1c**, indicating that 5-nitro group is more potent activating group for this reaction than *n*-oxide moiety.

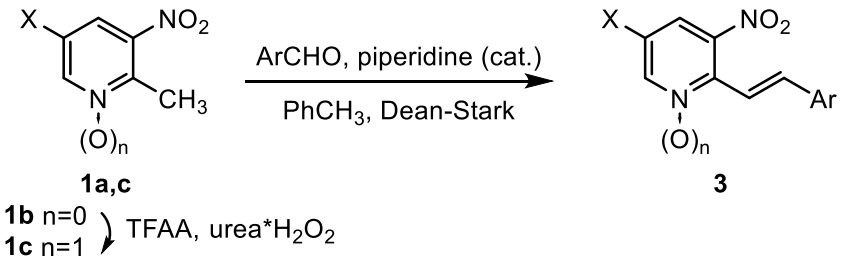
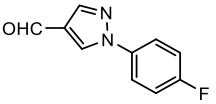



**Figure 2.** Condensation of 2-methyl-3-nitropyridines with aromatic aldehydes.

There was no noticeable difference in reaction time or product yield between aldehydes even with 4-dimethylaminobenzaldehyde, which is deactivated towards nucleophiles by strong electron-donating effect of dimethylamino group. Results are summarized in Table 1. High substrate tolerance

combined with mild conditions and easy accessibility of aromatic aldehydes makes this method valid alternative for Pd-based coupling reactions. It is also important that pure *trans*-alkene is produced.

**Table 1.** Condensation of 2-methyl-3-nitropyridines with aromatic aldehydes.

| Pyridine Substituents | Aldehyde | Product |
|---|---|---|
| **1a** X = $NO_2$, *n* = 0 | Ar = 4-Cl-Ph | **3a,** 85% |
| **1a** X = $NO_2$, *n* = 0 | Ar = 4-$(CH_3)_2$N-Ph | **3b**, 91% |
| **1a** X = $NO_2$, *n* = 0 |  | **3c**, 83% |
| **1c** X = Br, *n* = 1 | Ar = 4-$(CH_3)_2$N-Ph | **3d**, 78% |

*2.2. Reactions of 2-Methyl- and 2-Styryl-3-nitropyridines with S-Nucleophiles*

In our previous work [7] we have shown that 5-substituted 3-nitropyridines readily react with various anionic O,*n*,S-nucleophiles, so thiolate anions were chosen as model nucleophiles to test reactivity of 2-methylpyridines **1a**,**c** and 2-styrylpyridines **3a**–**d** in $S_NAr$ reactions (Figure 3).

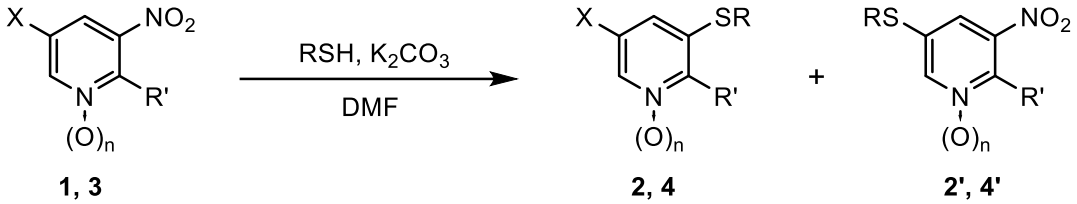



**Figure 3.** Reactions of 2-methyl- and 2-styryl-3-nitropyridines with S-nucleophiles.

More reactive 2-methyl-3,5-dinitropyridine **1a** reacted with BnSH to give monosubstituted product the same way as 3,5-dinitropyridine, but presence of 2-methyl group brings possibility of 2 different isomers. It was established by $^1$H NMR that reaction product is in fact a mixture of both isomers with 3-SBn isomer being predominant. This result matches known literature information about nucleophilic substitution in 2,4,6-trinitrotoluene and ortho-substitution can be attributed to steric effect of methyl group causing an "out-of-plane" effect [8]. Compound **1c** gave only 3-substituted products despite bromine atom being also viable leaving group in related nitroarenes [2].

All 2-styryl-3-nitropyridines reacted smoothly with various alkyl- and arylthiolates. β-vinyl substituents do not seem to influence either rate or yield of $S_NAr$ reaction even with strong electron donating group like $Me_2N$. All reactions were completed after 1 h at 50 °C. No Br/$NO_2$ competition was found in case of compound **3d**, but rather interesting results were obtained for 3-$NO_2$/5-$NO_2$ competition in compounds **3a,b,c**. Isomer ratio was calculated by $^1$H NMR of crude products and ortho-substituted compounds were found to be major products in all cases. The exact ratio depends on both electronic effects of styryl moiety and steric effects of thiolate anion. Ortho-selectivity is improved by electron-rich substituents on double bound and bulky aryl-thiolates. Yields and isomer ratios are summarized in Table 2.

**Table 2.** Nucleophilic substitution of nitro group by thiolate anions.

| Nitropyridine | Thiol | Product [1] | Isomer Ratio [2] |
|---|---|---|---|
| **1a** | BnSH | **2a/2a'**, 70% | 20:1 |
| **1c** | BnSH | **2b**, 96% | N/A |
| **1c** | 4-Cl-PhSH | **2c**, 95% | N/A |
| **3a** | BnSH | **4a/4a'**, 75% | 3:1 |
| **3a** | 4-Cl-PhSH | **4b**, 67% | N/A |
| **3a** | iBuSH | **4c/4c'**, 94% | 2:1 |
| **3b** | BnSH | **4d/4d'**, 88% | 10:1 |
| **3b** | 4-Cl-PhSH | **4e**, 83% | N/A |
| **3b** | iBuSH | **4f/4f'**, 84% | 5:1 |
| **3c** | BnSH | **4g/4g'**, 89% | 6:1 |
| **3c** | 4-Cl-PhSH | **4h**, 92% | N/A |
| **3d** | BnSH | **4i**, 67% | N/A |

[1] All yields correspond to total yield of isomers mixture. [2] "N/A" means that only one product could be detected.

### *2.3. Fluorescent Properties of 2-Styrylpyridines*

Some of the obtained 2-vinylpyridine derivatives appeared to have remarkable fluorescent properties. These properties differ greatly between compounds and some empirical patterns can be found.

All compounds bearing dimethylamino group (**3b**, **4d**, **4d'**, **4e**, **4f**, **4f'**, **4i**) have shown no visible fluorescence at all. Instead they have strong absorption of visible light resulting in deep purple coloration. This can be attributed to conjugation of electron-deficient nitropyridine ring with $N(CH_3)_2$ group.

Both compounds **3a** and **3c** with two nitro groups on pyridine ring are somewhat fluorescent but this can be observed only at high concentration and under intense UV-light. Substitution of nitro group with thiolate anions dramatically improves fluorescence of both compounds. It is interesting that only 3-substituted products (major ones) have strong fluorescence while isomeric 5-substituted products are only slightly different from their parent compounds. Nature of thiol does not have significant influence on either color or brightness. Derivatives of compound **3a** emit yellow light while derivatives of **3c** are orange. Fluorescence of some of these compounds can be seen on Figure 4. Quantitive measurements are being conducted at this moment.

**Figure 4.** Fluorescence of compounds **4a** (solution in $CHCl_3$), **4a** (solid), **4a'** and **4h** under 365 nm light. Difference in brightness between isomers **4a** and **4a'** can be seen.

## 3. Conclusions

Two 2-methyl-3-nitropyridines were synthesized according to improved literature procedure. Their reaction with various aromatic aldehydes yields 2-vinyl-3-nitropyridines in high yield as pure *trans*-isomer. Mild conditions and wide scope of readily available aromatic aldehydes make this reaction viable metal-free alternative for Heck reaction.

Reactions of 2-methyl- and 2-vinyl-3-nitropyridines with thiolate anions proceed smoothly by $S_NAr$ mechanism with substitution of nitro group. When two nitro groups at 3,5-position are present, variable amount of 5-substituted isomers are formed in some cases. Regioselectivity depends on both electronic effects of vinyl moiety and steric effects of thiol. Ratio of isomers were determined by $^1H$ NMR method.

Some of obtained 2-vinylpyridines were shown to be highly fluorescent. Empirical correlation between structure and fluorescent properties can be used for further development of novel fluorescent dyes.

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