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# Two-step One-Pot Multicomponent Reaction Improved by TBAF for the Preparation of 2-Amino-3, 5-dicyano-4-aryl-6-phenylsulfanylpyridines

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**Abstract:**
To further explore TBAF's catalytic properties, a study investigated its role in the synthesis of 2-amino-3, 5-dicyano-4-aryl-6-sulfanyl-pyridines under mild conditions. Two-step One-Pot Multi-component reaction (MCR) synthesis of pyridines derivatives using TBAF as the catalyst was conducted across different organic solvents. The formation of 1a was observed in polar solvents like methanol, acetonitrile, dimethylformamide (DMF), and ethanol, with ethanol yielding the highest yield (91%). Notably, the absence of TBAF led to no product formation even after extended reaction times.

**Keywords:** Pyridines, TBAF, multi-component reaction (MCR), antimicrobial, antioxidant, and anticancer drugs.

## Introduction:

Fluoride ions are very strong hydrogen bond acceptors, so their salts tend to become hydrated, limiting their solubility in organic solvents. TBAF solves this problem as a source of fluoride ions, but TBAF samples are almost always hydrated, and the nature of the fluoride is unclear, since not only fluoride but also heavy fluoride (HF2-) and hydroxide (OH-) are formed. Many applications tolerate heterogeneous or poorly defined fluoride sources. As a fluoride source in organic solvents, TBAF is used to remove silyl ether protecting groups. It is also used as a phase transfer catalyst and soft base. As a deprotecting agent, TBAF in DMSO converts O- silylated enolates to carbonyls [1].

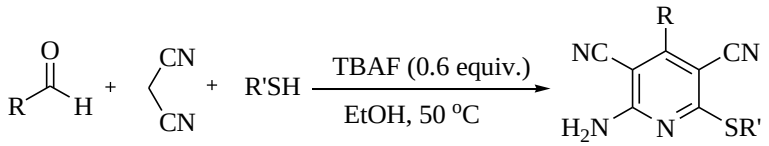
Tetrabutylammonium fluoride (TBAF) is a widely used soluble organic fluoride salt. TBAF is a quaternary salt that is used as a source of fluorine. The fluorine anion is typically used for deprotection of silyl ether groups or as a mild base. The good solubility of TBAF in organic solvents makes it a useful alternative to poorly soluble inorganic bases. Reactions involving TBAF are typically carried out at temperatures below 100 C due to its low thermal stability. It is used as a base [2], [3], [4], phase transfer catalyst [5], [6], [7], and fluorine source. After dissolution, the fluoride in TBAF can be considered as free fluoride with little interaction with ammonium cations. Since TBAF should not absorb light with wavelengths above 240 nm, it is useful to use visible spectroscopy to monitor. One fluorine sensor approach is based on molecules containing conjugated tricoordinate boron atoms. Fluoride binds to the vacant p-orbital of boron, which changes the conjugation within the molecule and generally alters the optical properties. These changes can be correlated with the presence of fluoride anions. In some cases, the color change is noticeable even without the use of instrumentation, which makes it useful for field testing under environmental conditions. Our interest in measuring fluoride binding to boron arose from the recent synthesis of the conjugated polymer poly (9-borafluorene) (P9BF). P9BF exhibits strong yellow fluorescence, which changes to blue upon reaction with fluoride. In a series of control experiments measuring the absorbance and fluorescence of the commercially available TBAF solution (TBAF-com1), absorbance at 295 and 370 nm, and fluorescence at 435 nm were observed. This was surprising since TBAF is optically transparent at these wavelengths and should not fluoresce. It should be noted that many commercially available TBAF samples are yellow or brown in colour. No comments on this subject were identified in the literature [8-16].

Recent patents have also highlighted the potential of derivatives such as 2-thio-3,5-dicyano-4-aryl-6-aminopyrimidines as selective adenosine receptor ligands for cancer treatment, along with 3,5-dicyanopyridine derivatives exhibiting excellent efficacy in opening the maxi-K channel. Given these observations, the development of 3,5-dicyanopyridine derivatives as potential antitumor agents appears highly promising. Building on our ongoing interest in pyridine derivatives with anticancer properties, we have designed and synthesized a novel series of 4-aryl or -heteroaryl-2,6-dibenzylamino-3,5-dicyanopyridines to evaluate their anticancer potential [17-19].

In summary, the introduction of 3,5-dihydropyridines provides a foundational understanding of these important heterocyclic compounds, emphasizing their synthetic accessibility, biological activities, and potential applications in medicinal chemistry and beyond. Hence, the synthesis of these 3, 5-dihydropyridines has emerged as a vibrant area of investigation in recent years. Traditionally, the synthesis of 3,5-dihydropyridines has involved multistep methodologies, yielding the desired compounds with an overall efficiency ranging between 25-45%. However, a breakthrough was achieved by Evodkimov et al., who pioneered a novel one-pot multi-component reaction (MCR) for synthesizing compounds. This innovative approach utilized either $Et_3N$ or DABCO as catalysts, resulting in a moderate yield of 35-43% of the target compound [20-27].

**Results and Discussion:**

Moreover, this novel MCR method applies to aliphatic aldehydes, yielding satisfactory to moderate yields (Table 1, entries 14-15). Notably, when t-butanal was employed, predominantly the dihydropyridine precursor was formed as the major product (Table 1, entry 15). To obtain the desired pyridine product, the reaction temperature was increased to 80°C in a polar solvent to expedite the oxidation process. Surprisingly, employing a more polar solvent like DMSO at 100 °C led to the successful isolation of only the pyridine product (2d) in 76% yield (Table 1, entry 15). Intriguingly, NMR studies indicated that the obtained pyridine lacked the t-butyl substituent at the 4 position (1H and 13C NMR and mass in SI).




**2 : 3 : 1** **1(a-k), 2(a-d)**

**Table 1**. Synthesis of 2-amino-3,5-dicyano-4-aryl-6-arylsulfanylpyridines via the modified two-step one-pot synthetic approach.

| Entry | R | R' | product | t (h) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Ph | 4-Br-Ph | **1a** | 4.6 | 86 |
| 2 | 4-MeO-Ph | 4-Br-Ph | **1b** | 5.1 | 86 |
| 3 | 3,4-MeO-Ph | 4-Br-Ph | **1c** | 5.1 | 87 |
| 4 | Ph | 4-$NH_2$-Ph | **1d** | 4.1 | 87 |
| 5 | 4-MeO-Ph | 4-$NH_2$-Ph | **1e** | 4.6 | 88 |
| 6 | 3,4-MeO-Ph | 4-$NH_2$-Ph | **1f** | 5.1 | 89 |
| 7 | 5-benzo[1,3]dioxole | 4-$NH_2$-Ph | **1g** | 5.1 | 88 |
| 8 | Ph | 2-napthalene | **1h** | 5.6 | 89 |
| 9 | 4-MeO-Ph | 2-napthalene | **1i** | 5.1 | 86 |
| 10 | 3,4-MeO-Ph | 2-napthalene | **1g** | 6.1 | 92 |
| 11 | 5-benzo[1,3]dioxole | 2-napthalene | **1k** | 6.1 | 88 |
| 12 | Ph | 2-$NH_2$-Ph | **2a** | 4.1 | 91 |
| 13 | 3,4-MeO-Ph | 2-$NH_2$-Ph | **2b** | 4.6 | 92 |
| 14 | Cyclohexanol | Ph | **2c** | 5 | 68 |
| 15[b] | *t*-butanal | Ph | **2d** | 7 | 76(21) |

[a]: Isolated yield after column chromatography (based on R'SH). [b]:parenthesis yield for dihydropyridine.

To confirm our hypothesis and find out the workable solvent media, we have conducted the MCR synthesis of 1m-1w using 0.6 equivalent of TBAF as the catalyst in a wide range of conventional organic solvents at their respective reflux temperature for 4-7 h. Although the reaction temperatures (>81 °C) have little effect on the overall yields of 1m-1w plus 2c-d' (~71-92 %), we in general obtained higher percentage of 1v at higher reaction temperatures. From preliminary screen of different solvents and catalyst (TBAF) loading we found that 0.5 equivalent of TBAF was sufficient to give 1v and 2b in good yield in ethanol at reflux temperature (entry 10 & 13 of Table 1). Interestingly, the same reaction conditions (>80°C, 5-6 h) work similarly well for a wide variety of other derivative 3,5-dicyanopyridines 1m-1w (entries 1-11, Table 1), giving respectable yields of 80-92%, which is comparable with most of the literature results. Thus, TBAF indeed works as a new and effective catalyst for making 3, 5-dicyanopyridines via a multi-component reaction.

**Conclusion:**

In Summary, I have demonstrated that tetrabutylammonium fluoride works well as a new and effective catalyst to assist the modified tw step one-pot MCR synthesis of the privileged medicinal scaffolds, 2-amino-3,5-dicyano-6-sulfanyl pyridines

based on mixtures of aldehyde/malononitrile/thiol (in 1:2:1 mole ratio) giving comparable or better yields (50-70%) than the previous reported methods. Of particular interest, this method enables the direct synthesis of highly sterically hindered, bioactive 4-(2,6-dihalophenyl)-3,5-dicyano-6-sulfanylpyridines (2a-c) with yields exceeding 85%, achieved simply at elevated temperatures (80-100 °C) without the necessity for an additional oxidation treatment step.

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