Synthesis of 2-Pyridone from 2-Thiopyridines via Nucleophilic Aromatic Substitution Reaction

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Abstract
2-Thiopyridine has been used for the synthesis of 2-pyridones. Aromatic nucleophilic substitution reaction has been utilized for the transformation of 2-thiopyridine into 2-pyridones. Reusability of the released dithiol into generation of 2-thiopyridine explores reactivity of thiol as a template in synthesis of pyridine core. The present method explores making 2-pyridone derivatives utilizing 2-thiopyridines whereas thiol act as a template for pyridine synthesis.

Keywords: 2-Thiopyridine, 2-Pyridone, S₂Ar, DMSO, NaOH

Introduction
The 2-pyridone tautomer of 2-hydroxypyridine is one of the important moiety in many biologically active compounds (1). Although 2-pyridones are not documented as vast natural sources but those which are isolated shows potent cytotoxicity (2). Natural as well as unnatural 2-pyridones possesses a wide range of biological activities such as antitumor (3), antifungal (4), antibacterial (5), anti-inflammatory (6), antiviral (7) and antithrombotic (8) properties. Majority of the 2-pyridones are synthetic molecules and are found in pharmaceutical products some of which are as Topotecan and Irinotecan. Derivatives of 2-pyridones have also been investigated for their important applications in dyes, sensors, pigments and advanced materials, carriers of singlet oxygen and as catalysts (9). It has received considerable attention due to its promising features as a key scaffold and in privileged building blocks (10). Among various 2-pyridone molecules some marketed cyano-tethered drugs such as Milrinone (11) and Olprinone (12) are well-known to use in patients for the treatment with heart related problems. Similarly, Ricinine (13) another types of cyano-tethered 2-pyridones that serves as a biomarker and INDOPY-1 (14) in dolopyridones structure a potential inhibitor of human immunodeficiency virus. Recently, 3-cyano-pyridone of type (A) has been reported as antibacterial and antitubercular activities (15). The explored applications of 2-pyridones currently attracted attentions of synthetic and medicinal chemists for their further developments and can be found from recently published reviews and articles (16).

To quick access derivatives of 2-pyridones generally and most preferably synthetic strategy adopted are nucleophilic aromatic substitution reactions (S₂Ar). This potential method

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SaAr has become an ideal synthetic tool to obtain 2-pyridone heterocycles from starting 2-substituted pyridines (17).

The major class of transformations takes place displacement of halogens/amino groups by nucleophiles at position C-2 of the pyridine moiety (18). These reactions are versatile for the functionalization in pyridines but requires drastic reaction conditions, often leads to mixtures and low yields of product. The other class includes additions of nucleophiles to pyridine N-oxides in combination with a reagent to activate and dehydrate the pyridine N-oxide (19) (Scheme 1). Herein, to the best of our knowledge work in this manuscript is novel and explores nucleophilic aromatic displacement reaction of labile thiol in synthesis of 2-pyridones.

**Scheme 1**: Nucleophilic aromatic substitution strategies for the functionalization of pyridines to 2-Pyrodones

To the previously reported experiments (20) it was observed that synthesizing 2-thiopyridine (1) was not achievable in strong Bronsted base and was also reported in the literature (21). From this previous experimental studies we found that formation of thiol moiety at C-2 of pyridine was easily in situ replaced by alkoxy group just after the formation of thiopyridine. That’s why thiopyridine was never obtained in presence of concentrated Bronsted base and always final product was ended-up with alkoxy pyridine. Basically, the idea emerged from this model.
experiment that thiopyridine could be transformed to 2-pyridones. Direct synthesis of 2-Pyridones similar to structure 2 had been reported using reactions of aldehydes and malononitrile in presence of base and water but yields obtained were very low in amount and excess amount of malononitrile and aldehydes were sacrificed (22).

The important features of this method is that after the formation of 2-pyridones it forms by-product dimer of thiophenol. This dimer can be reduced to thiophenol (23) and can be reused again for the synthesis of thiopyridines and will follow a cyclic process. To our surprise it is interesting to note that here thiol act as a template for the synthesis of pyridine, which can be transformed to another important privileged molecules 2-thiopyridones. We are continuing our research in the same direction to explore transformation of one molecule to another using thiol as a template.

![Scheme 2: Synthesis of 2-pyridone from 2-thiopyridine](image)

**Experimental Methods**

All the reagents were used without further purification and were procured from commercial sources. The reactions were performed under the normal atmosphere condition. The progress of the reaction and purity of the compound were monitored using thin layer chromatography (TLC) carried out on the silica gel with UV light and iodine as visualizing agent. A Shimadzu FT-IR-B400 spectrophotometer was used for recording the IR spectra. $^1$H NMR and $^{13}$C NMR spectra were recorded using the Bruker advance-III 400 MHz spectrometers in DMSO-$d_6$ using TMS as an internal reference. The chemical shift ($\delta$ scale) was reported in parts per million (ppm). Elemental analysis was carried out using a Euro Vector EA3000 CHNS-O analyser at NFDD Saurashtra University, Rajkot, Gujarat.

**General procedure for the synthesis of compound 2 (GP1)**

A mixture of 2-thiopyridine (1.0 mmol), NaOH (1.0 mmol) and DMSO + H$_2$O (8:2; 5.0 mL) mixture was heated at 60 °C at appropriate time for complete the reaction and was monitored on TLC using CHCl$_3$: MeOH; 9:1. After completion of the reaction, reaction mass was cooled to room temperature. Added 5.0 mL water and the reaction mass was filtered. The clear filtrate was adjusted with 1N HCl to form the precipitates at acidic condition. The precipitate was filtered and washed with fresh water 10 mL twice and air dried. The obtained solid was pure enough for further characterization.

**The spectroscopic data for 6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (2a).** This compound was obtained according to above general procedure GP1; IR (potassium bromide): 3460, 3311, 3110, 2218, 1675, 1635, 1540, 1486, 1440, 1266, 1043, 874, 718, 649 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ = 11.90 (s, 1H, NH), 7.81 (brs, 2H, NH$_2$), 7.56-7.52 (m, 3H, ArH), 7.50-7.47 (m, 2H, ArH); Anal. Calcd. for C$_{12}$H$_8$N$_3$O: C, 66.10; H, 3.41; N, 23.72. Found: C, 66.03; H, 3.38; N, 23.66.
Results and Discussion

In our initial study of thiopyridine 2-amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (1.0 mmol) was stirred at room temperature for 24h in distilled water to react with it but no any trace for 2a was observed (Table 1, entry 1). Same reaction combinations were heated to reflux but no any changes were observed (Table 1, entry 2). This was attributed as substrate was insoluble in water. In another attempt DMSO (5.0 mL) as a solvent was taken and added water (1.0 equiv.) with the same starting substrate and heated at 100 °C but this time also no any changes were observed (Table 1, entry 3). Next, NaOH (1.0 eqv.) was added to water and stirred at reflux temperature for 24h but only trace amount for 2a was observed because of solubility problem of thiopyridine in water (Table1, entry 4).

In another experiment NaOH was added to DMSO alone and was heated at 100 °C, surprisingly 62% yield was obtained in 3h (Table 1, entry 5). Progress of the reaction can be easily monitored on TLC (CHCl₃: MeOH; 9:1) and also can be traced by smelling like thiophenol of the reaction mass. As the reaction proceeds towards 2a, smell become stronger. To this same reaction model solvent mixture of DMSO and water was taken into 8:2 ratio along with NaOH and was heated again at 100 °C, yield was increased to 88% and also reduces the reaction time (Table 1, entry 6). This may be due to the solubilizing factor of the starting substrate and NaOH in the solvent mixture.

To check the effect of temperature on yield, the same reaction combinations was heated at 60 °C instead of 100 °C, yield obtained was 97% in 2h (Table 1, entry 7). Looking towards mild reaction conditions the reaction was performed at room temperature, after 15h long reaction time only 58% yield was observed (Table 1, entry 8). Next, impact of solvent combinations of DMSO and water (Table 1, entries 9-10) was also checked but were not significant compare to the DMSO and water ratio 8:2. Similarly, other Bronsted bases such as KOH, LiOH, Mg(OH)₂ and Ga(OH)₃ were screened but results were not encouraging other than KOH (Table 1, entries 11-14). Finally, the same reaction combinations was heated at 60 °C in presence of HCl as a Bronsted acid but yield was extremely low with long reaction time (Table1, entry 15). Alcoholic solvents such as methanol or ethanol were not included as they form the alkoxy-thiopyridines. Due to solubility problems of the starting substrates thiopyridines in solvent such as toluene and dichloromethane and the formation of dichlorocarbene with chloroform and NaOH these solvents were not suitable in this transformation.

Table 1: Optimization of reaction conditions

![Reaction conditions](image)

- Put conditions on the left side of the image.
- Put 2a on the right side of the image.

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International Research Journal of Multidisciplinary Scope (IRJMS)
| Entry | Reagent (equiv.) | Solvent | Temp. (°C) | Time | Yield (\%) |
|-------|-----------------|---------|------------|------|------------|
| 1     | ---             | H₂O     | rt         | 24 h | nil        |
| 2     | ---             | H₂O     | reflux     | 24 h | nil        |
| 3     | H₂O             | DMSO    | 100        | 24 h | nil        |
| 4     | NaOH            | H₂O     | reflux     | 24 h | trace      |
| 5     | NaOH            | DMSO    | 100        | 3.0 h| 62         |
| 6     | NaOH            | DMSO-H₂O (8:2) | 100 | 1.5 h | 88         |
| 7     | NaOH            | DMSO-H₂O (8:2) | 60 | 2.0 h | 97         |
| 8     | NaOH            | DMSO-H₂O (8:2) | rt  | 15 h | 58         |
| 9     | NaOH            | DMSO-H₂O (1:1) | 60 | 5.0 h | 80         |
| 10    | NaOH            | DMSO-H₂O (9.5:5) | 60 | 3.0 h | 86         |
| 11    | KOH             | DMSO-H₂O (8:2) | 60 | 1.5 h | 92         |
| 12    | LiOH            | DMSO-H₂O (8:2) | 60 | 3.0 h | 83         |
| 13    | Mg(OH)₂         | DMSO-water (8:2) | 60 | 3.5 h | 70         |
| 14    | Ca(OH)₂         | DMSO-water (8:2) | 60 | 3 h  | 72         |
| 15    | HCl             | DMSO-water (8:2) | 60 | 10 h | 15         |

*Reaction of 2-amino-4-phenyl-6-(phenylthio)pyridine-3,5-dicarbonitrile (1.0 mmol) at different reaction conditions; Isolated yields.*

With the optimized conditions in hand we turned our attention to explore the scope and general applicability of this process by carrying out the synthesis of 2-pyridones using different thio-pyridines (Table 2). Thio-pyridine derivatives with varying electron donating/withdrawing functionality in the aromatic ring were tested and were found to be suitable in this reaction (Table 2, 2b-2k) in good yields. Highest yields were observed for N-protected isatin derivatives and in case of nitro derivative lower yield was observed among all the synthesized spirooxindole molecules. These synthesized molecules were confirmed from IR spectra and melting point reported in the literature. \(^1\)H NMR and \(^{13}\)C NMR spectra for one of the compound 4a are provided in Fig. 2 and Fig. 3 respectively. To check the feasibility of this developed process, a scale-up reaction was performed under the optimized reaction condition to obtain 4a by taking isatin (10 mmol), malononitrile (10 mmol) and 4-hydroxy coumarin (10 mmol) and the yield obtained was 97%.

Finally, a comparison was made between the present reaction process and many other earlier reported protocols for the synthesis of 4a as a model compound. The results summarized in Table 3 evident that the process developed by us is superior to most of the earlier reported methods in terms of operational simplicity, yields, reaction time, cost, easy availability, reusability and environmental compatibility.
Table 2: Substrates Scope$^a$

| Entry | R          | Product | Time (h) | Yield$^b$ (%) | Colour   | MP ($^\circ$C) |
|-------|------------|---------|----------|---------------|----------|----------------|
| 1     | C$_6$H$_5$ | 2a      | 2        | 97            | Yellow solid | > 300         |
| 2     | 4-CH$_3$-C$_6$H$_4$ | 2b | 2        | 92            | cream solid   | > 300         |
| 3     | 4-Br-C$_6$H$_4$   | 2c | 2        | 98            | brown solid   | > 300         |

1. NaOH (1.0 equiv.)
DMSO + H$_2$O / 60$^\circ$C
2. H$_3$O$^+$

$^a$R = alkyl/aryl
|   | Reaction | R1 | R2 | Yield | Color  | Melting Point |
|---|----------|----|----|-------|--------|---------------|
| 4 | 4-CH$_3$- | C$_6$H$_4$ | 2  | 95  | yellow | > 300 |
| 5 | 2,4-Cl-  | C$_6$H$_3$ | 2.5 | 98  | yellow | > 300 |
| 6 | 4-OCH$_3$- | C$_6$H$_4$ | 2  | 95  | yellow | > 300 |
| 7 | 3- OCH$_3$- | C$_6$H$_4$ | 2  | 92  | cream | 286-288 |
8  3,4-<br>\[\text{OCH}_3\]-\[\text{C}_6\text{H}_3\]<br>N-C\[\text{CN}\]
H\[\text{NH2}\]
\[\text{2h}\]
OCH\[\text{3}\]
\[\text{3}\]
98
yellow
solid
> 300

9  3-\[\text{C}_6\text{H}_5\text{O}\]-\[\text{C}_6\text{H}_4\]
\[\text{NC}\]-\[\text{Cn}\]
H\[\text{NH2}\]
\[\text{2i}\]
O
2.5
96
cream
solid
> 300

10  4-\text{OH}-\[\text{C}_6\text{H}_4\]
\[\text{NC}\]-\[\text{Cn}\]
H\[\text{NH2}\]
\[\text{2j}\]
\[\text{OH}\]
2
91
brown
solid
> 300

11  \[\text{C}_6\text{H}_{11}\]
\[\text{NC}\]-\[\text{Cn}\]
H\[\text{NH2}\]
\[\text{2k}\]
\[\text{2.5}\]
98
cream
solid
> 300
Conclusions
In summary, the present work describes a simple and facile method for the synthesis of highly functionalized 3-cyano-2-pyridone from simple starting substrate. This novel method explored the use of thiol template synthesis of 2-pyridone. The use of formed dithiol in cyclic reaction makes the process an economical. This new methodology can be useful strategy to explore synthesis of making different organic molecules.

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Disclosure
The authors report no conflicts of interest in this work. No violation of human rights and safety.

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