Preparation of Substituted Pyridines via a Coupling of β-Enamine Carbonyls with Rongalite-Application for Synthesis of Terpyridines

Yung-Yuan Lee and Shiuh-Tzung Liu

Department of Chemistry, National Taiwan University, Taipei 10617, Taiwan
* Correspondence: stliu@ntu.edu.tw; Tel.: +886-23366-1661

Abstract: A Hantzsch-type strategy for the synthesis of 2,3,5,6-tetrasubstituted pyridines via an oxidative coupling of β-enamine carbonyl compounds with rongalite was developed. This method employs rongalite as a C1 unit for the assembly of a pyridine ring at C-4 position, offering a facile method for the preparation of substituted pyridine derivatives with a broad functional group tolerance. In particular, this method allows us to prepare terpyridine derivatives, which are important ligands or structural fragments for catalysts and 3D metal–organic frameworks.

Keywords: pyridine; rongalite; condensation; terpyridine

1. Introduction

Pyridine derivatives are one of the most important heterocyclic compounds that are found in natural products and used in pharmaceuticals and chemical reagents for organic synthesis [1–6]. Numerous synthetic approaches leading to various pyridines have been revealed [7–18]. Among them, the most popular method is the Hantzsch approach [15,16]. It is a two-step reaction involving a multicomponent condensation of two equivalent of 1,3-dicarbonyl compounds, an aldehyde and ammonia, followed by the oxidation of formerly formed 1,4-dihydropyridines (Scheme 1a).

- Classical method
- N-methylpyrrolidone as C-4 source
- DMSO as C-4 source

Scheme 1. Preparation of pyridine via Hantzsch approaches. (a) Classical method, (b) N-methylpyrrolidone as C-4 source, (c) DMSO as C-4 source.

In recent years, the focus on this Hantzsch approach has moved toward finding new C-4 sources of pyridine instead of aldehydes. A copper-catalyzed oxidative [2 + 2 + 1 + 1] cycloaddition gives the pyridine product, in which the C-4 carbon comes from the C-N bond cleavage of N-methylpyrrolidone (Scheme 1b) [17]. The reaction of 1,3-diketones
with ammonium acetate in the presence of trifluoroacetic acid in DMSO as the solvent produces the 2,3,5,6-tetrasubstituted pyridines in good yields (Scheme 1c) [18]. In this reaction, DMSO plays the role of solvent, carbon source, and oxidant. In other words, cleavage of the C-S bond in DMSO provides the C-4 unit of the pyridine.

Rongalite [NaHOCH$_2$SO$_2$·(H$_2$O)$_2$] is a useful and cheap chemical that has been used in the preparation of sulfones and sulfinates, the reduction of diselenides, and the dehalogenation of phenacyl chlorides [19]. The use of rongalite for providing a C1 unit in synthetic methodology has also been reported in the preparation of 2,4,5-trisubstituted furans [20], C3-sulfenylated chromones [21], 3-hydroxy-3-hydroxymethylxindoles [22] and others [23]. This is due to the generation of HCHO from the decomposition of rongalite itself. Inspired by the above-mentioned works, we envisaged utilizing rongalite as the C1 source for the construction of pyridine rings via the Hantzsch approach.

Terpyridines are a class of important molecules for the fields of coordination and material chemistry and have been used in the construction of polymeric coordination complexes—typically, metal-organic frameworks (MOF) [24–27]. Due to the highly conjugated nature of the terpyridine moiety, the resulting metal complexes frequently exhibit properties of photoluminescence [28] or electrical conductivity [29], which are important for the application of material chemistry and catalysis. For the synthesis of terpyridines, using the cross coupling of 2,6-dibromopyridines with 2-pyridinyl organometallic reagents via Stille or Negishi reactions is the most frequently employed method [30]. The other useful approach is the condensation of 2-acetylpyridine with dimethyl acetal in DMF, followed by sequential condensations with 2-acetylpyridine and ammonium acetate [31]. However, these approaches are limited by the presence of other functionality in the molecules.

2. Materials and Methods

2.1. Materials and Instrumentation

All the reactions were carried out in a sealed reaction tube under oxygen atmosphere and performed without any special precautions. Chemicals were purchased from the suppliers and used without further purification. Flash chromatography was performed using silica gel 230–400 mesh with an elution of ethyl acetate/hexane. All the compounds were characterized by $^1$H, $^{13}$C{($^1$H)} NMR and MS analyses. Nuclear magnetic resonance spectra were recorded in CDCl$_3$ on either a Bruker AM-300 or AVANCE 400 spectrometer. Chemical shifts are given in parts per million relative to Me$_4$Si. HRMS spectra were determined on a Bruker micrOTOF-QII spectrometer with electrospray ionization. β-Enamine carbonyl compounds were prepared according to the procedure reported [32,33].

2.2. General Procedure for Preparation of Pyridines and Terpyridines

In a pre-dried 10 mL glass sealed tube, 1 (0.56 mmol) and rongalite (0.56 mmol) in DMF (3.0 mL) were heated in an oil bath at 120 °C for 1 h. The reaction mixture was washed with water. After the removal of solvents, the residue was chromatographed on silica gel. The desired product was obtained upon concentration chromatographed on silica gel. For terpyridines, the procedure is similar to that for pyridine, except for the use of pyridinyl-substituted β-enamine carbonyl compound as the substrate.

2.3. Spectroscopic Characterization

Dimethyl 2,6-diphenlypyridine-3,5-dicarboxylate (3a). White solid (90.6 mg, 95%).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 8.53 (s, 1H); 7.62 (m, 4H); 7.43 (m, 6H); 3.73 (s, 6H). $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 167.68, 159.76, 140.51, 139.10, 129.31, 128.93, 128.09, 124.26, 52.42. HRMS (ESI) m/z: [M+H]$^+$ calc. for C$_{21}$H$_{18}$NO$_4$: 348.1230, found 348.1241. These spectral data are consistent with the reported data [34].

Dimethyl [2,2′:6′,2′′-terpyridine]-3′,5′-dicarboxylate (9a). Brown solid (76.9 mg, 78%).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 8.62 (m, 2H); 8.28 (d, $J$ = 5.0 Hz, 2H); 8.22 (s, 1H); 7.84 (td, $J$ = 7.8, 1.6 Hz, 2H); 7.33 (ddd, $J$ = 7.8 Hz, 4.8 Hz, 0.8 Hz, 2H); 3.81 (s, 6H). $^{13}$C-NMR
Dimethyl [2,2′:6′,2′′-terpyridine]-3′,5′-dicarboxylate (9a). Brown solid (76.9 mg, 78%).

3. Results and Discussion

3.1. Optimization of the Reaction

Initially, we examined the reaction of methyl 3-oxo-3-phenylpropanoate (2 eq.) and ammonium acetate (1 eq.) with rongalite in DMF at 120 °C but with a complicated mixture. Therefore, methyl 3-amino-3-phenylacrylate (1a), a β-enamine carbonyl compound, was subjected to this investigation [24] (Scheme 2). Table 1 summarizes the search of optimization conditions. By running the reaction in various solvents, it was found that the reaction in DMF solution gave the desired compound 3a in a 55% yield, appearing to be the best choice (entries 1–7). After significant screening efforts, we found that the reaction running at 120 °C gave the highest production (Table 1, entry 10). Finally, running the reaction under oxygen atmosphere provided a quantitative yield even within 1 h (entry 13). When rongalite was replaced by formaldehyde for the reaction under the optimized conditions, no desired product was obtained.

![Scheme 2. Reaction leading to the desired pyridine product.](image)

Table 1. Optimization of cyclization reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ratio of 1a:2</th>
<th>Temp</th>
<th>Yield of 3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>1.0:1.0</td>
<td>65 °C</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>1.0:1.0</td>
<td>65 °C</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>1.0:1.0</td>
<td>75 °C</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>1.0:1.0</td>
<td>80 °C</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>1.0:1.0</td>
<td>100 °C</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>100 °C</td>
<td>55%</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>1.0:1.0</td>
<td>100 °C</td>
<td>53%</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>1.0:2.0</td>
<td>100 °C</td>
<td>42%</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>110 °C</td>
<td>80%</td>
</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>120 °C</td>
<td>88%</td>
</tr>
<tr>
<td>11</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>130 °C</td>
<td>45%</td>
</tr>
<tr>
<td>12</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>120 °C</td>
<td>99%</td>
</tr>
<tr>
<td>13</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>120 °C</td>
<td>98%</td>
</tr>
<tr>
<td>14</td>
<td>DMF</td>
<td>1.0:1.0</td>
<td>120 °C</td>
<td>ND</td>
</tr>
</tbody>
</table>

1 Reaction conditions: 1a (0.18 mmol) and 2 in solvent (1.0 mL) under N₂ overnight. 2 NMR yields; ND = no desired product. 3 Under oxygen atmosphere. 4 1 h. 5 Use formaldehyde solution instead of rongalite.

3.2. Reaction Scope

With the optimized conditions, we investigated the scope and limitations for 1. The results obtained are summarized in Table 2. Various substituted 3-amino-phenylacrylates were reacted smoothly with rongalite to produce the corresponding pyridine derivatives in excellent yields (entries 1–6), except the iodo-substituted one (entry 7). Presumably, the aryl iodide moiety reacted with rongalite to give other side products, which was observed on a TLC analysis during the reaction. 3-Aminoacrylates with a heterocyclic ring as a substituent, such as furan-2-yl and thiophen-2-yl, were also suitable for this reaction to deliver the
pyridines with heterocyclic rings as the substituents at 2,6 positions (entries 9–10). Methyl 3-aminobut-2-enoate, a methyl substituted acrylate, can also be used as a substrate for the preparation of 2,6-dimethylpyridine derivative 3h in an 88% yield (entry 8).

Table 2. Reaction scope 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituent</th>
<th>Yield 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1 = C6H5</td>
<td>3a (95%)</td>
</tr>
<tr>
<td>2</td>
<td>R1 = p-MeC6H4</td>
<td>3b (93%)</td>
</tr>
<tr>
<td>3</td>
<td>R1 = p-MeOC6H4</td>
<td>3c (95%)</td>
</tr>
<tr>
<td>4</td>
<td>R1 = p-Me2NC6H4</td>
<td>3d (84%)</td>
</tr>
<tr>
<td>5</td>
<td>R1 = p-BrC6H4</td>
<td>3e (92%)</td>
</tr>
<tr>
<td>6</td>
<td>R1 = p-ClC6H4</td>
<td>3f (96%)</td>
</tr>
<tr>
<td>7</td>
<td>R1 = p-I C6H4</td>
<td>3g (72%)</td>
</tr>
<tr>
<td>8</td>
<td>R1 = CH3</td>
<td>3h (88%)</td>
</tr>
<tr>
<td>9</td>
<td>R1 = furan-2-yl</td>
<td>3i (83%)</td>
</tr>
<tr>
<td>10</td>
<td>R1 = thiophen-2-yl</td>
<td>3j (87%)</td>
</tr>
</tbody>
</table>

1 Reaction conditions: 1 (0.56 mmol); rongalite (0.56 mmol) in DMF (3.0 mL) at 120 °C for 1h. 2 Isolated yield.

We then contemplated the scope of the reaction with various β-enamine carbonyl compounds (Scheme 3). To our delight, 4-aminopent-3-en-2-one, 3-amino-3-phenylacrylamide, and 3-substituted 3-aminoacrylonitriles are suitable substrates for the preparation of the corresponding pyridine derivatives. The reaction of 4-aminopent-3-en-2-one with rongalite under the optimized conditions described above gave 4 in a 96% yield, whereas the substrate of 3-amino-3-phenylacrylamide 1c provided the corresponding 3,5-pyridinedicarboxamide 5 in an excellent yield. This reaction is also tolerated with a cyano functionality in the molecule. Thus, the reaction of 3-aminoacrylonitriles 1d with rongalite rendered 3,5-pyridinedicarbonitriles 6 in good yields.

Scheme 3. Pyridine products with various functionality.

In addition, we also examined the cross coupling of two different β-enamine carbonyl compounds with rongalite to yield unsymmetric substituted pyridines (Scheme 4). The employment of 1e to react with various β-enamine carbonyl compounds was investigated
for this cross coupling. In general, it shows a poor selectivity in these coupling reactions. In the reaction of 1e with 1a, three expected products were obtained (Scheme 4a), as was the reaction of 1e with 1b (Scheme 4b). Substrate 1e reacted with 1c provided two products: 7c (78%) and 5 (19%), showing a slight selectivity in this reaction (Scheme 4c). Evidently, the rate of the cross-coupling reaction of 1e toward 1c is faster than that of the self-coupling of 1c or 1e itself.

**Scheme 4.** Cross coupling study (yields are based on NMR determination). (a) Reaction of 1e with 1a, (b) reaction of 1e with 1b, (c) reaction of 1e with 1c.

Further attempts via the reaction of β-enamine carbonyl compound 1 with β-keto carbonyls for the cross-coupling reaction were investigated. The reaction of 1e with 2 equivalent of methyl acetoacetate gave the unsymmetrical substituted pyridine 7b in a 93% yield, as expected (Scheme 5a). However, similar reactions of 1a and 1c with acetoacetate majorly provided the unsymmetrical substituted pyridines 7a and 7c, respectively, but still with minor self-coupling products (Scheme 5b,c).

**Scheme 5.** Cross coupling of β-enamine carbonyls with β-keto carbonyls. (a) Reaction of 1e with acetoacetate, (b) reaction of 1a with acetoacetate, (c) reaction of 1c with acetoacetate.
3.3. Synthetic Application—Preparation of Terpyridine

Terpyridine molecules have been used in the construction of polymeric coordination complexes—typically, metal–organic frameworks (MOF) [28–31]. Due to the highly conjugated nature of the terpyridine moiety, the resulting metal complexes frequently exhibit properties of photoluminescence [32] or electrical conductivity [33], which are important for the application of material chemistry and catalysis.

With the successful preparation of 3i and 3j, we envisioned that the use of pyridinyl-substituted β-enamine carbonyl compounds (8) as the substrate should provide the corresponding terpyridine product (9). Table 3 summarizes the outcome of the reactions. Indeed, the reactions smoothly proceeded to give the corresponding terpyridines, but the reaction period varied depending on the substituents. For R” being an ester, carbonyl or nitrile functionality, the corresponding terpyridines were obtained in good yields (entries 1–4). However, with an amido group in 8, the desired terpyridine was not obtained. Nevertheless, the functionalities presented in 9a–9d could be potentially converted into others, which make these molecules useful for further applications.

Table 3. Preparation of terpyridines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents of R”</th>
<th>Time</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–COOMe</td>
<td>1 h</td>
<td>9a (78%)</td>
</tr>
<tr>
<td>2</td>
<td>–COCH₃</td>
<td>20 h</td>
<td>9b (68%)</td>
</tr>
<tr>
<td>3</td>
<td>–CN</td>
<td>12 h</td>
<td>9c (71%)</td>
</tr>
<tr>
<td>4</td>
<td>–COPh</td>
<td>24 h</td>
<td>9d (94%)</td>
</tr>
<tr>
<td>5</td>
<td>–CONMe₂</td>
<td>24 h</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Reaction conditions: 8 (0.56 mmol); rongalite (0.56 mmol) in DMF (3.0 mL) at 120 °C under O₂ atmosphere.

Finally, to further demonstrate the practicality and efficiency of the developed method, a gram-scale reaction was performed. Under the optimal conditions, the reaction of 3-amino-3-phenylacrylonitrile (1.153 g, 8 mmol) with rongalite (1.233 g, 8 mmol) in DMF (40 mL) provided 2,6-diphenylpyridine-3,5-dicarbonitrile (6b) in a 93% yield (1.046 g).

As for the reaction pathway, it is believed to be similar to that proposed for Hantzsch ester synthesis (Scheme 6). The decomposition of rongalite yields a molecule of formaldehyde, which undergoes condensation with β-enamine carbonyl compounds to produce intermediate I. Another molecule of I proceeds the Michael addition, with I followed by the cyclization accompanied by the elimination of ammonia to give the dihydropyridine II. The oxidation of II readily provides the desired pyridine derivative.

Scheme 6. Reaction pathway leading to pyridines.
4. Conclusions

In summary, we have shown the synthetic utilization of rongalite as a C1 unit source for the preparation of 2,3,5,6-tetrasubstituted pyridines. This method offers a simple and facile manipulation for the desired products. In addition, this approach is tolerated with various functionality, which allows us to prepare functionalized terpyridines. These obtained compounds are expected to act as valuable starting materials for synthetic uses. Typically, compounds 4–6 with functional groups at 3,5-positions can be further modified, leading to the desired pharmaceuticals. The functionalized terpyridines prepared in this work will also be valuable for the construction of metal–organic frameworks. Currently, the preparation of MOF with 9 in our group is under investigation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions3030029/s1, Table S1: spectral data of all compounds; Figure S1: 1H- and 13C-NMR spectra of 3a; Figure S2: 1H- and 13C-NMR spectra of 3b; Figure S3: 1H- and 13C-NMR spectra of 3c; Figure S4: 1H- and 13C-NMR spectra of 3d; Figure S5: 1H- and 13C-NMR spectra of 3e; Figure S6: 1H- and 13C-NMR spectra of 3f; Figure S7: 1H- and 13C-NMR spectra of 3g; Figure S8: 1H- and 13C-NMR spectra of 3h; Figure S9: 1H- and 13C-NMR spectra of 3i; Figure S10: 1H and 13C NMR spectra of 3j; Figure S11: 1H and 13C NMR spectra of 4; Figure S12: 1H- and 13C-NMR spectra of 5; Figure S13: 1H- and 13C-NMR spectra of 6a; Figure S14: 1H- and 13C-NMR spectra of 6b; Figure S15: 1H- and 13C-NMR spectra of 7a; Figure S16: 1H- and 13C-NMR spectra of 7b; Figure S17: 1H- and 13C-NMR spectra of 7c; Figure S18: 1H- and 13C-NMR spectra of 9a; Figure S19: 1H- and 13C-NMR spectra of 9b; Figure S20: 1H- and 13C-NMR spectra of 9c; Figure S21: 1H- and 13C-NMR spectra of 9d.

Author Contributions: Conceptualization, S.-T.L.; methodology, investigation, and data collection, Y.-Y.L.; writing—original draft preparation, S.-T.L.; data checking and editing, Y.-Y.L. and S.-T.L.; supervision, S.-T.L. funding acquisition, S.-T.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Science and Technology, Taiwan (MOST109-2113-M-002-010-MY2).

Data Availability Statement: The data reported in this article can be obtained from the authors upon reasonable request.

Acknowledgments: We thank the Instrumentation Center (NTU), Ministry of Science and Technology, Taiwan, for the assistance in X-ray crystallography. The mass spectrometry technical research services from the NTU Consortia of Key Technologies for mass measurement is acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

References
9. Vchislo, N.V. α,β-Unsaturated Aldehydes as C-Building Blocks in the Synthesis of Pyridines, 1,4-Dihydropyridines and 1,2-Dihydropyridines. Asian J. Org. Chem. 2019, 8, 1207–1226. [CrossRef]
15. Hantzsch, A. Condensationsprodukte aus Aldehydammoniak und ketonartigen Verbindungen. Chem. Ber. 1881, 14, 1637–1638. [CrossRef]
18. Xue, L.; Cheng, G.; Zhu, R.; Cui, X. Acid-promoted oxidative methylation of 1, 3-dicarbonyl compounds with DMSO: Application to the three-component synthesis of Hantzsch-type pyridines. RSC Adv. 2017, 7, 44009. [CrossRef]