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Advanced Synthesis & Catalysis

A Method to Access Symmetrical Tetrasubstituted Pyridines via Iodine and Ammonium Persulfate Mediated [2+2+1+1]-Cycloaddition Reaction

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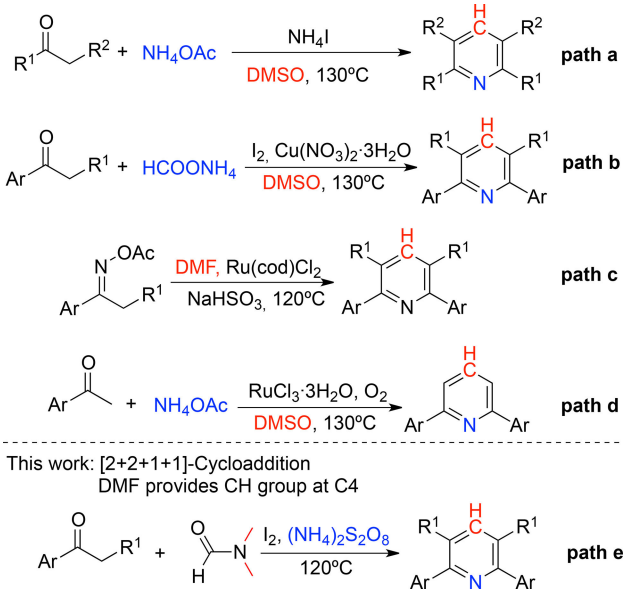
Abstract: A novel metal-free [2+2+1+1]-cycloaddition method for rapid and productive preparation of symmetrical 2,3,5,6-tetrasubstituted pyridines has been developed from α-substituted arones and N,N-dimethyl formamide (DMF) using iodine (I_2) and ammonium persulfate ($(NH_4)_2S_2O_8$) as mediators. In this process, both DMF and $(NH_4)_2S_2O_8$ play a dual role for the formation of pyridines. DMF acts as the reaction medium and the C4 source (the methyl group of DMF), while $(NH_4)_2S_2O_8$ serves as the oxidant and nitrogen resource. Notably, this transformation exhibited a broad substrate scope towards a wide variety of different arones to give the corresponding tetrasubstituted pyridines in moderate to excellent yields.

Keywords: Symmetrical tetrasubstituted pyridines; [2+2+1]-cycloaddition; α-substituted arones; alkynes; N,N-dimethyl formamide (DMF)

Pyridines constitute privileged structures in natural products,[1] functional materials,[2] pharmaceuticals and agrochemicals,[3] as well as in biological[4] and synthetic chemistry.[5] Starting with the seminal synthesis by the greatest chemist William Ramsay, synthetic approach to this class of compounds has received widespread attention for more than 130 years,[6] and a wide range of synthetic methods has became available.[7] Among the numerous synthetic routes to pyridines, condensation of amines and carbonyl compounds, and transition-metal-catalyzed cross cyclization reactions are considered to be the main available routes.[8]

Recently, Yuan et al. developed a facile NH_4I-promoted method to synthesize symmetrical 2,3,5,6-tetrasubstituted pyridines from α-substituted ketones and NH_4OAc using DMSO as the source of methylene units (Scheme 1, path a).[9] This method was the first report for capturing in situ-generated methylene intermediates from DMSO. Based on this result, Wu et al. reported an improved approach to access the symmetrical 2,3,5,6-tetrasubstituted pyridines by using iodine and $Cu(NO_3)_2{\cdot}3H_2O$ as the alternative promoters (Scheme 1, path b).[10] Similar to DMSO, DMF



Scheme 1. Different procedures for pyridine synthesis employing DMF and DMSO as the sources of carbon.

is also a popular, cheap and low-toxic polar solvent, and has been widely used in organic synthesis as a reaction medium and a promising reactant for the formation of –CHO,[11] $–N(CH_3)_2$,[12] –CN,[13] and –H.[14] Lately, Guan et al. and Deng et al. diclosed two novel methods for synthesis of pyridines using DMF as CH group (C4 or C6) source (Scheme 1, path c and d).[15] To the best of our knowledge, employing DMF as a source of one carbon synthon to provide CH group for cyclization reaction has rarely been reported.[16]

Herein, we report another example using DMF as C4 source to access symmetrical 2,3,5,6-tetrasubstituted pyridines. This approach is the first example of iodine and ammonium persulfate-mediated [2+2+1+1]-cycloaddition reaction for pyridines synthesis from α-substituted arones involving the capture of in situ generated ammonia and methylene group (Scheme 1, path e).

Initial screening was performed to find the optimum reaction conditions for preparation of **2a** by varying different parameters (Table 1). The product **2a** was obtained with 81% yield when propiophenone (**1a**, 0.25 mmol) was reacted with $(NH_4)_2S_2O_8$ (0.5 mmol) and DMF (2 mL) in the presence of I_2 (0.25 mmol) at 120 °C for 8 h (entry 1). After screening the reaction time (entried 1–3), we found that the reaction was completed in 10 h and afforded the desired product **2a** with 86% yield (entry 2). Unfortunately, this desired reaction did not occur in the absence of $(NH_4)_2S_2O_8$ or I_2 (entries 4–5). Furthermore, increasing the amount of $(NH_4)_2S_2O_8$ did not enhance the yield of the product (entry 6), however decreasing it to 1.0 equivalent reduced the yield considerably (entry 7). Likewise, increasing the loading of I_2 to 1.5 equivalent did not show any beneficial effect (entry 8), and decreasing I_2 to 0.5 equivalent greatly reduced the product yield (entry 9). The structure of compound **2** was unambiguously confirmed by ^{1}H-NMR, ^{13}C-NMR, HR-MS and X-ray crystallography (Figure 1).[17]

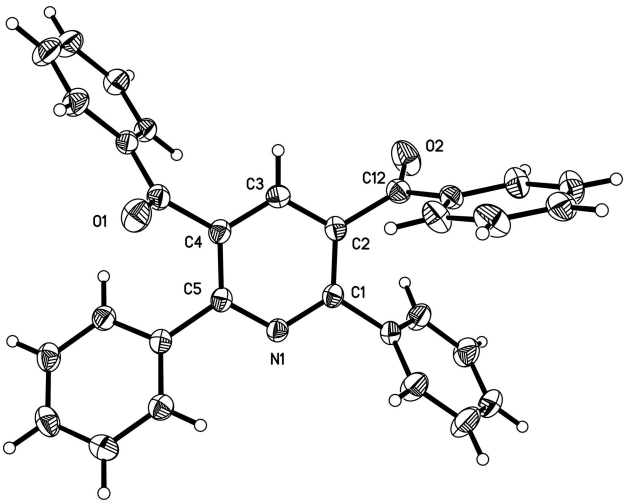
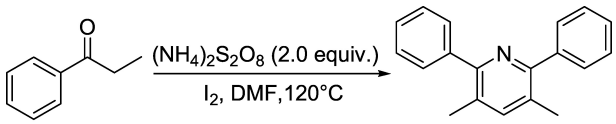


Figure 1. X-Ray structure of 2,6-diphenyl-3,5-dibenzoylpyridine **2l**.

Table 1. Optimization-synthesis of symmetrical 3,5-dimethyl-2,6-diphenylpyridine[a].



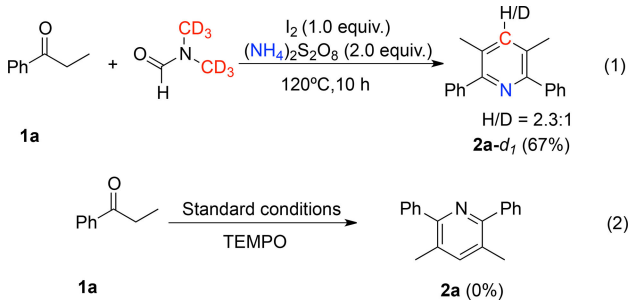
Entry	I_2 (equiv.)	Time(h)	Yield%[b]
1	1.0	8	81
2	1.0	10	86
3	1.0	12	86
4[c]	1.0	10	–
5	–	10	–
6[d]	1.0	10	86
7[e]	1.0	10	57
8	1.5	10	86
9	0.5	10	69

[a] Unless otherwise specified, all the reactions were carried out on **1a** 0.25 mmol, DMF 2.0 mL, $(NH_4)_2S_2O_8$ 2.0 equivalent.
[b] GC yield.
[c] Without $(NH_4)_2S_2O_8$
[d] $(NH_4)_2S_2O_8$ 3.0 equivalent.
[e] $(NH_4)_2S_2O_8$ 1.0 equivalent.

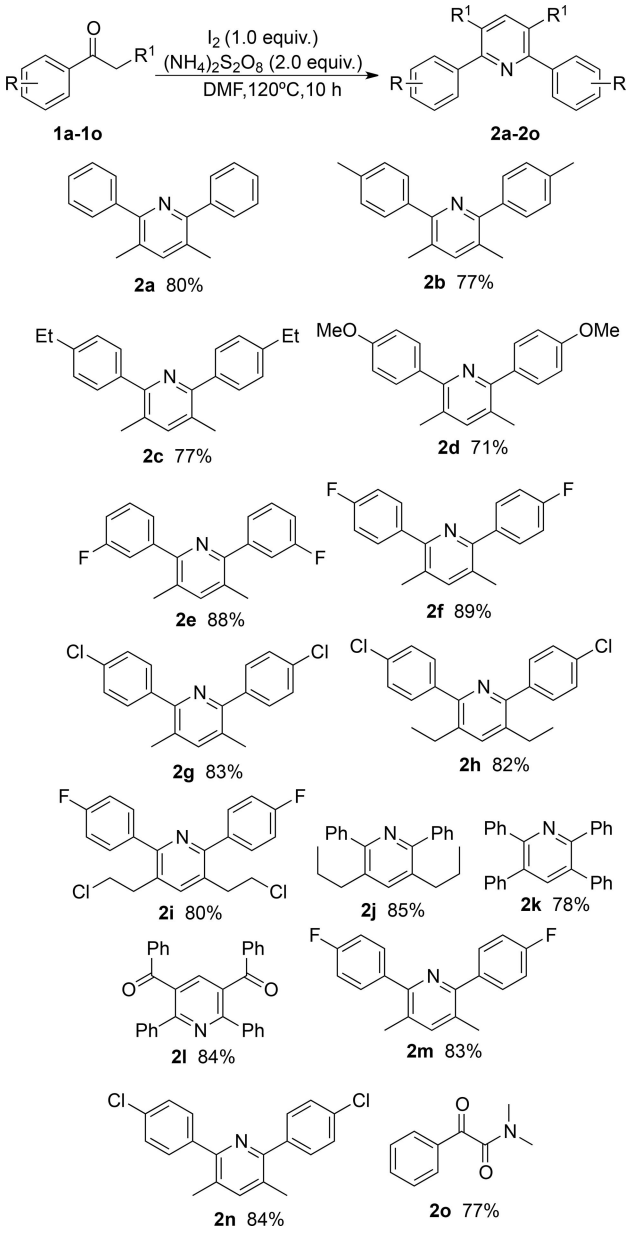
Based on the optimized conditions identified for the [2+2+1+1]-cycloaddition reaction, we explored the scope of α-substituted arones, the results are summarized in Scheme 2. In general, a range of electron-neutral (**1a**), electron-rich (**1b**–**1d**) and electron-deficient (**1e**–**1g**) propiophenones reacted with ammonium persulfate and DMF with high yields (71-–89%) under the stipulated conditions. However, it is worth mentioning that propiophenones with strong electron-donating groups (–OCH_3) show lower reactivity than those with electron-withdrawing groups (–Cl and –F). The scope of β-substituted arones, such as 1-(4-chlorophenyl)butan-1-one (**1h**), 4-chloro-1-(4-fluorophenyl)butan-1-one (**1i**) and 1-phenylpentan-1-one (**1j**) were also investigated, The results showed that all reactions exclusively produced the corresponding 2,3,5,6-tetrasubstituted pyridines **2h**–**2i** with excellent isolated yields. Meanwhile, we also performed the conversion employing 1,2-diphenylethanone (**1k**) and 1,3-diphenylpropane-1,3-dione (**1l**) as the partners of propiophenone under the optimized conditions. The results indicated that **1k** and **1l** were fully converted, and afforded the corresponding products with 78% and 84% isolated yield, respectively. To

further extend the adaptability of this transformation, 1-(4-fluorophenyl)propan-2-one and 1-(4-chlorophenyl)propan-2-one were employed as the partners of α-substituted arones under the standard conditions. We are pleased to find that these two reactions proceed smoothly, and provide 2,6-bis(4-fluorophenyl)-3,5-dimethylpyridine (**2m**) and 2,6-bis(4-chlorophenyl)-3,5-dimethylpyridine (**2n**) with high regioselectivity. However, the acetophenone fails to go through this conversion under the stipulated conditions, and affords N, N-dimethyl-2-oxo-2-phenylacetamide as the main product (**2o**).

To gain a deeper insight into the mechanism for the formation of product **2**, several parallel experiments were conducted (Scheme 3). First, to determine the C4 source, a deuterium labelled experiment was carried out using N,N-dimethyl-d_6-formamide (DMF-d_6) as the solvent. It is found that this transformation become slightly slower, but affords 4-deuterated pyridine **2a**–d_1 as the only product (Scheme 2, eq1). This finding evidences that the C4 carbon unit of the pyridine ring derives from the methyl group rather than the aldehyde group of DMF. However, this conversion is completely inhibited when the radical scavenger TEMPO is used (Scheme 2, eq2), which suggested that a radical pathway may involve in the mechanism.

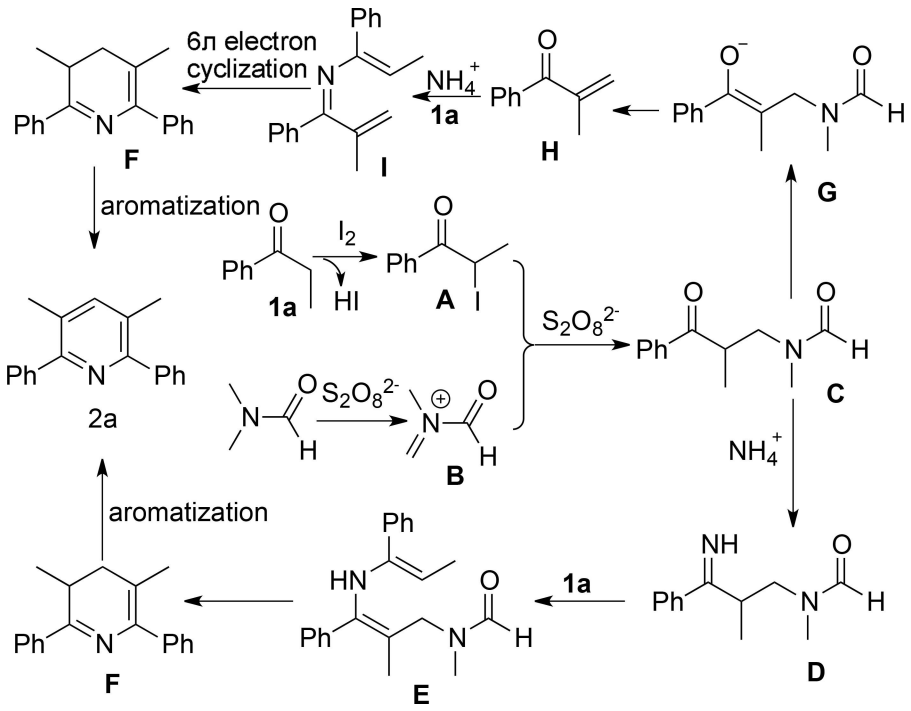


Scheme 3. Investigation of the reaction mechanism.



Scheme 2. Synthesis of symmetrical 2,3,5,6-tetrasubstituted pyridines (**2a**–**2n**) from α-substituted arones, $(NH_4)_2S_2O_8$ and DMF (All reactions were carried out on **1a**–**1o** 1.0 mmol scale, DMF 2.0 mL).

On the basis of the aforementioned results and the previous literatures, a tentative mechanism for the reaction is proposed in Scheme 4 and exemplified by the formation of **2a.** The process is commenced with the formation of two key intermediates, α-iodo propiophenone **A** and iminium **B**.[18] **A** is produced from iodination propiophenone (**1a**) with iodine,[19] and **B** is generated from the oxidation of persulfate to DMF via a radical mechanism.[20] The interaction of **A** and **B** leads to the formation of **C** in the presence of persulfate, which is then attacked by the ammonium cation to form imine intermediate **D**.[10] The condensation of **D** with propiophenone (**1a**) gives intermediate **E**.[15a] The subsequent nucleophilic substitution of **E** by NH_4HSO_4 which is generated in-situ from the ammonium persulfate and intramolecular cyclization forms dihydropyridine intermediate **F**, this process is known in the literature.[15a] Next, **F** undergoes the process of aromatization giving the final pyridine product **2a.**[21,10, 15] Alternatively, the resulting enolate intermediate **G** generated from **C** undergoes a C–N bond cleavage to afford the unsaturated ketone intermediate **H**.[19] Subsequently, the condensation of ammonium cation with **H** and **1a** leads to intermediate **I**. Finally, **I** experience the sequential 6π electro-



Scheme 4. Proposed mechanism for the cycloaddition reaction.

cyclization and aromatization reactions to provide the expected pyridine **2a**.

In summary, a convenient and efficient [2+2+1+1]-cycloaddition method has been developed for the preparation of symmetrical 2,3,5,6-tetrasubstituted pyridines via iodine and ammonium persulfate mediated cyclization of α-substituted arones with DMF. In this reaction system, both DMF and $(NH_4)_2S_2O_8$ play an important dual role, DMF is used not only as an effective reaction medium, but also as the source of C4 via the methyl group, while $(NH_4)_2S_2O_8$ serves as an oxidant and nitrogen source for the formation of pyridines. This reaction complements related transition-metal catalyses and broadens the synthetic possibilities of metal-free methodology to employ DMF (the methyl group) as the carbon source.

Experimental Section

General method.

All the reactions were carried out at 120 °C for 10 h in a round-bottom flask equipped with magnetic stir bar. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. Melting points were measured on a melting point apparatus equipped with a thermometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in solutions of $CDCl_3$ using tetramethylsilane as the internal standard, δ values are given in ppm and coupling constants (J) in Hz. HR-MS were obtained on a Q-TOF micro spectrometer.

Typical procedure: 3,5-dimethyl-2,6-diphenylpyridine (2a)

A mixture of ethyl propiophenone (**1a**) (134 mg, 1.0 mmol), $(NH_4)_2S_2O_8$ (228 mg, 2.0 mmol), iodine (254 mg, 1.0 mmol) and DMF (2.0 mL) was added successively in a round-bottom flask, and the resulting soln. stirred for 10 h at 120 °C. The mixture was purified by column chromatography on silica gel to afford product **2a** with hexanes/ethyl acetate as the eluent.

Acknowledgements

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UPDATES

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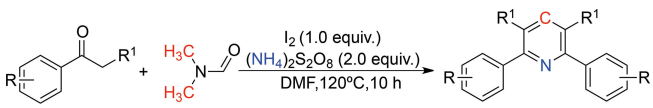

R = H, F, Cl, Me, Et, OMe; R^1 = alkyl,Ph, benzoyl
[2+2+1+1]heteroannulation
facile access to diverse symmetrical tetrasubstituted pyridines
readily available starting material
DMF provides CH group at C4
14 examples up to 89% yield