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Synthesis of 2-Formylpyrroles from Pyridinium Iodide Salts

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02178 Read Online

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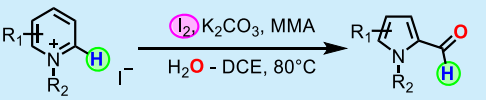
ABSTRACT: The first I_2-mediated synthesis of 2-formylpyrroles from pyridinium salts is reported. This protocol enables the synthesis of diversely substituted 2-formylpyrroles in good yields under operationally simple conditions. The detailed mechanistic studies reveal that the reaction proceeds via a novel H_2O-triggered ring opening of the pyridinium salt and a subsequent intramolecularly nucleophilic addition sequence.



- 35 Examples, up to 86% yield
- Operationally simple conditions
- Readily available substrates

2-Formylpyrrole-derived alkaloids are one of the most important classes of structural motifs found in numerous pharmaceutical molecules,[1] natural products,[2] and functional materials.[3] In addition, they also represent privileged building blocks and have been widely used as intermediates in the construction of porphyrins,[4] anion receptors in biomedical analysis,[5] unnatural base pairs,[6] and oligopyrrole-based metallocomplexes.[7]

Given its broad applicability, many synthetic methods toward 2-formylpyrroles have been developed (Scheme 1). So far, numerous efficient methodologies have been developed for the synthesis of 2-formylpyrroles. The conventional methods rely on the Vilsmeier−Haack formylation of the preformed parent pyrrole,[8] which is usually synthesized by Hantzsch,[9] Knorr,[10] Paal−Knorr,[11] Barton−Zard,[12] and Trofimov reactions.[13] A sustainable Maillard approach to 2-formylpyrroles from primary amines and sugar was described by Fujimaki, Zhao, Koo, and others.[14] Padwa and coworkers constructed the 6-phenyl-2-formylpyrrole from 2*H*-azirine by treating with Grubb's catalyst.[15] A highly substituted 2-formylpyrrole was successfully synthesized by Sato and Urabe by using a coupling reaction of acetylene and nitrile mediated by a titanium reagent.[16] A two-step synthesis from ketones and 4-formyloxazole was also described by Senanayake.[17] In 2017, Kumar's group reported a pseudo-[3 + 2] annulation between *N*-(4-methoxyphenyl)aldimines and glutaraldehyde for the direct synthesis of pyrrole-2,4-dialdehydes.[18] Very recently, Wu et al. prepared the 2-formylpyrroles bearing an ester group at the three-position from methyl ketones, arylamines, and acetoacetate esters with the assistance of molecular iodine.[19]

However, these methods suffer from several drawbacks, such as the use of a toxic reagent, the restricted availability of substrates, the requirement for specially designed starting molecules, tedious experimental operations, poor functional group compatibility, and harsh conditions. Therefore, the discovery of a more efficient and greener route to synthesize 2-formylpyrroles is still highly desirable.

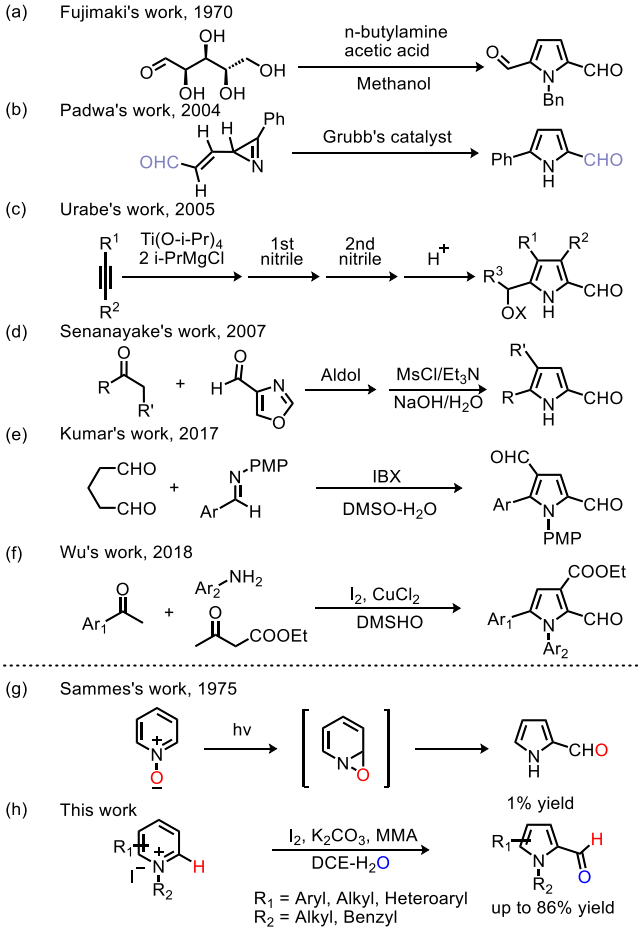
Pyridines are cheap and abundantly available and have served as versatile synthetic intermediates in organic chemistry.[20] 2-Formylpyrrole formation by the rearrangement of the pyridine *N*-oxides via photolysis[21] has been known. Unfortunately, the yield of this process is very low. We are interested in developing the synthetic method for 2-formylpyrrole from pyridinium salts. In the past several decades, molecular I_2 has been widely used in promoting the intramolecular cyclization to prepare many important heterocycles, such as furans, thiophenes, and pyrroles.[22] In view of the capability of iodine in promoting intramolecular cyclization and the ring-opening tendency of the pyridinium salts in the presence of an appropriate nucleophile,[23] we expected that the treatment of the pyridinium salt with a basic aqueous solution in the presence of I_2 would lead to a H_2O-triggered ring-opening reaction to form an acyclic intermediate, which subsequently undergoes an intramolecularly nucleophilic attack to give 2-formylpyrroles. To the best of our knowledge, this type of transformation has never been reported in the literature.

To evaluate the feasibility of the proposed protocol, a variety of I_2 sources, bases, solvents, and additives were extensively screened (Table S1). The optimal condition was determined to be the following: *N*-methyl-2-phenylpyridinium salts **A** (0.25 mmol) were treated with 0.64 equiv of I_2 in the presence of 4.0 equiv of K_2CO_3 and 1 equiv of methyl methacrylate (MMA) in a solvent mixture of DCE/H_2O (1:1) at 80 °C under air for 20 h. (See Table S1 for details.) The desired 2-

Received: July 1, 2020

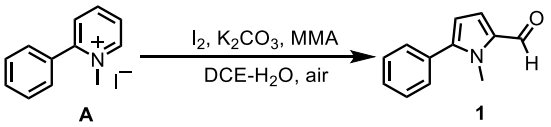
https://dx.doi.org/10.1021/acs.orglett.0c02178
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Represent Examples for 2-Formylpyrrole Synthesis



formylpyrrole could be obtained in 79% isolated yield, with 21% of pyridinium salt recovery, which was determined on the basis of the ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 1). It should be pointed out that the optimal amount of I_2 is 0.64 equiv, which seems insufficient to react with pyridinium salt (1.0 equiv), but the resulting I^- or the counterion I^- of the pyridinium salt would be oxidized by air to iodine. Notably, the replacement of I_2 with *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS) also produced the product in comparable yield (72 and 68% yield, respectively) (Table 1, entries 2 and 3). The reaction could still occur at room temperature and afforded the product in 56% yield (Table 1, entry 4). The controlled experiments showed that no product was formed in the absence of I_2 or K_2CO_3, revealing their important roles in the reaction (Table 1, entries 5 and 6). Of the examined bases, K_3PO_4 provided a similar result as K_2CO_3, and other bases, such as Na_2CO_3, Li_2CO_3, Cs_2CO_3, KOAc, NaOH, K^{t}OBu, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table S1), were all inferior in the reaction. The amount of K_2CO_3 also had an impact on the reactivity. The yield of **1** decreased to 55% when the amount of K_2CO_3 was decreased from 4 to 2 equiv (Table 1, entry 7). The removal of the additive MMA from the system impaired the reaction efficiency to some extent and generated **1** in 68% yield (Table 1, entry 8). The use of other olefins as the additives exhibited a lower efficiency than MMA (Table S1). Finally, various solvents, including 1,2 dichloroethane (DCE), CCl_4, acetone, PhCl, hexane, and tetrahydrofuran

Table 1. Optimization of Reaction Conditions[a]



entry	variation from standard conditions	yield (%)[b]
1	none	79
2	NBS instead of I_2	72
3	NCS instead of I_2	68
4	r.t.	56
5	w/o I_2	0
6	w/o K_2CO_3	0
7	2.0 equiv of K_2CO_3	55
8	w/o MMA	68
9	H_2O	54
10	DCE	0
11	DCE/H_2O 10:1	48
12	DCE/H_2O 4:1	56
13	DCE/H_2O 3:2	74
14	DCE/H_2O 2:3	70

[a]Reaction conditions: **A** (0.25 mmol), I_2 (0.64 equiv), K_2CO_3 (4 equiv), MMA (1 equiv), DCE/H_2O (1:1, 0.25 M), 80 °C, 20 h. [b]Isolate yields.

(THF), were screened as cosolvents, and DCE proved to be the best one (Table S1). Using H_2O alone as the solvent resulted in a 54% yield of **1**, and in the absence of H_2O, no product was formed (Table 1, entries 9 and 10). The variation of the ratio of DCE/H_2O from 1:1 decreased the yield to different extents (Table 1, entries 11−14).

With the optimal condition in hand, we next investigated the scope of the pyridinium salts (Scheme 2). Several features should be pointed out: (1) In the case of aryl-substituted pyridinium salts, a wide range of functional groups on the aryl rings were tolerated. The pyridinium salts bearing either the electron-withdrawing (*p*-F, *p*-Cl, *p*-CF_3, *p*-CN) or -donating (*p*-Me, *p*-MeO) substitutents on the 2-aryl group underwent the reaction very well to afford the corresponding 2-formylpyrrole derivatives **1**−**7** in 62−84% isolated yields. (2) Notably, *N*-methylpyridinium salts with heteroaryl groups such as furanyl, thiophenyl, and pyridinyl, could also be employed, giving products **9**−**11** in 50−78% yields. (3) In the case of alkyl-substituted pyridinium salts, the reaction outcome was dependent on the types of the alkyl groups. The pyridinium salts bearing an α-branched alkyl group at their two-position reacted very well to deliver the desired products **12**−**16** in 66−86% yields, whereas the linear alkyl-substituted substrate led to a very low yield of the product. On the contrary, the 2-cyclohexyl- and 2-cyclopropylpyridinium salts could be smoothly converted into the 5-cycloalkyl-2-formylpyrroles **17** and **18** in 69 and 28% yields, respectively. (4) It is worth mentioning that the reaction efficiency was greatly influenced by the substitution patterns of the pyridinium ring. For example, the 3-aryl-substituted pyridinium salts generally produced the corresponding products **19**−**23** in moderate yields (40−56%). The 2,3-disubstituted pyridinium salts were also viable substrates, furnishing the products **24**−**29** in 48−74% yield. (5) Introducing the functional groups such as MeO, CN, or NO_2 on the pyridinium ring resulted in a complicated mixture. For instance, 3-methoxy-1-methyl-2-phenylpyridinium iodide only afforded product **30** in a very low yield of 18%. (6) The alkyl group on the quaternary nitrogen also

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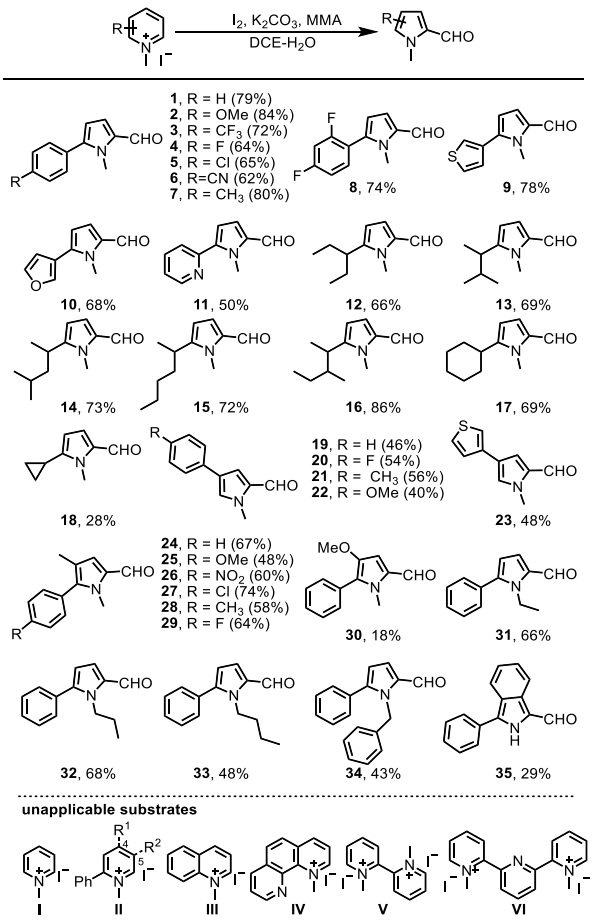
Scheme 2. Scope of Substrates[a,b]



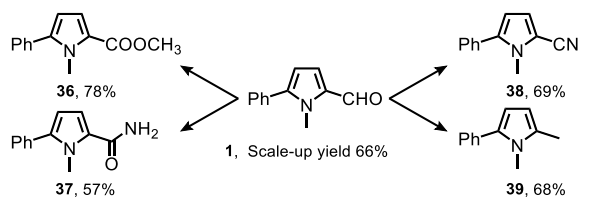
[a]All reactions were run under the conditions: **A** (0.25 mmol), I_2 (0.64 equiv), K_2CO_3 (4 equiv), MMA (1 equiv), DCE/H_2O (1:1, 0.25 M), 80 °C, 20 h. [b]Isolate yields.

influences the reaction reactivity. The reactivity gradually decreased with increasing alkyl chain length (**31**−**33**), and *N*-benzyl-2-phenylpyridinium iodide gave the product **34** in 43% yield. (7) *N*-methyl-isoquinolinium iodide afforded 3-phenyl-1-formylisoindole **35**, albeit in a relatively lower yield of 29%. (8) However, the *N*-methyl iodide salts of quinoline, 1,10-phenanthroline, 2,2′-bipyridine, terpyridine (**III**−**VI**), proved to be not effective substrates in this reaction.

The protocol was next demonstrated in a scale-up reaction. Thus the reaction of 10 mmol **A** under the standard conditions afforded the 2-formylpyrrole derivative **1** in 66% yield. The CHO could be easily transformed into the functionalities such as ester, amide, carbonitrile, and methyl groups (Scheme 3).

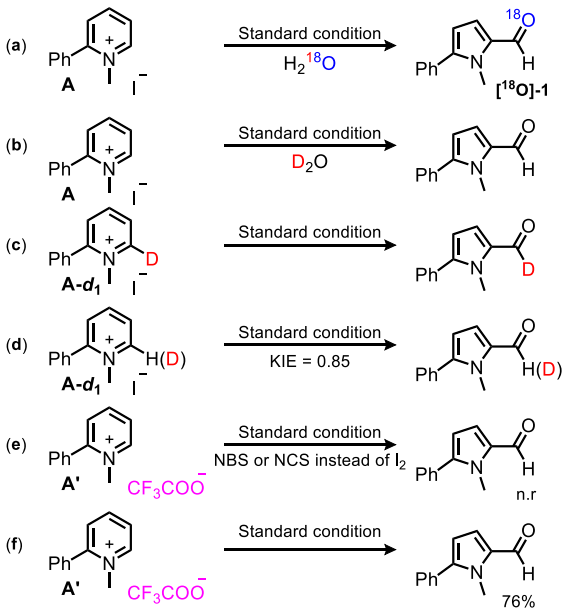
To shed light on the mechanistic pathway, a set of experiments was carried out. When the reaction was conducted in the presence of a stoichiometric amount of radical

Scheme 3. Scale-Up Synthesis of 1 and Its Applications



scavenger,2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), the 2-formylpyrrole was still obtained in 78% yield, without any loss of activity (Table S1, entry 45). This indicated that the free-radical pathway might be ruled out. Isotope labeling experiments by reacting **A** in $H_2{}^{18}O$−DCE solution led to the formation of [^{18}O]-**1** exclusively (Scheme 4a), and this result

Scheme 4. Studies on the Reaction Pathway



was unambiguously confirmed by mass spectrometry (Figure S2). This provided direct evidence of the fact that the O atom originates from the solvent H_2O. In addition, the model reaction conducted in D_2O afforded **1** without deuterium incorporation in CHO group (Scheme 4b). Meanwhile, **A**-d_1 completely delivered the product with deuterium incorporation into CHO; these results implied that the hydrogen in the −CHO group came from C_6−H instead of H_2O (Scheme 4c).

Furthermore, a competitive reaction of **A** and **A**-d_1 under the standard condition demonstrated a moderate inverse secondary kinetic isotope effect (SKIE) of 0.85. As the previously described experiments proved, the H in the CHO group of the product originated from the C_6−H bond of the 2-phenylpyridinium salts. Because both of the carbons to which the H atom attached are sp^2-hybridized and an inverse SKIE value was observed for the C_6−H bond, we assume that the C_6 goes through rehybridization from sp^2 to sp^3 and then to sp^2. Furthermore, the sp^2 to sp^3 rehybridization must occur during the rate-determining step, and thus an inverse secondary KIE was expected ($K_H/k_D \cong 0.85$) (Scheme 4d).[24]

As previously mentioned, when NBS or NCS was used as the additive instead of I_2, the reaction could also produce the desired products in comparable yields (Table 1, entries 2 and 3). This might be attributed to I_2 generated in situ via the oxidation of an iodide anion with NBS or NCS. To further confirm this assumption, we reacted the pyridinium salts **A**′ bearing CF_3COO^- as the counteranion with NBS or NCS and found that the substrates were totally recovered without any product **1** (Scheme 4e). Whereas **A**′ reacts in the presence of I_2, a 76% yield of product **1** was obtained (Scheme 4f). These results strongly suggest the vital role of I_2 in the process.

https://dx.doi.org/10.1021/acs.orglett.0c02178
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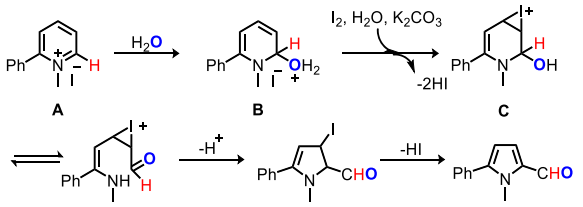
A plausible reaction pathway proposed on the basis of experimental observations is depicted in Scheme 5. The

Scheme 5. Plausible Reaction Pathway



reaction was initiated by nucleophilic attack on the C_6 position of the pyridinium salts **A** by H_2O to give species **B**. One molecule of HI was released with the assistance of a base, and in the presence of molecular iodine, a hemiaminal species **C** containing a three-membered iodonium ring was formed, which exists in equilibrium with the iodonium enamine aldehyde **D**. The intramolecular cyclization of **D** followed by the elimination of HI through intermediate **E** gives the final product *N*-methyl-5-phenyl-2-formylpyrrole. The role of MMA in the reaction remains unclear in this stage.

In conclusion, we have developed an efficient way to synthesize 2-formylpyrroles from cheap and readily available pyridinium salts. The reaction proceeds as an I_2-mediated, H_2O-triggered pyridinium ring-opening/intramolecular cyclization sequence. Further exploration of the construction of other types of heterocycles from pyridinium salts is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02178.

Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (nos. 21871187 and 21572137), the Collaborative Fund of Luzhou Municipal Government and Sichuan University (2018CDLZ-13), and the Key Program of Sichuan Science and Technology Project (2019YFG0146) for financial support. We also thank Chunchun Zhang from the Centre of Testing & Analysis, Sichuan University for NMR measurements.

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