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Synthesis of Pyrrole-2-carbaldehyde Derivatives by Oxidative Annulation and Direct $C_{sp}3$−H to C═O Oxidation

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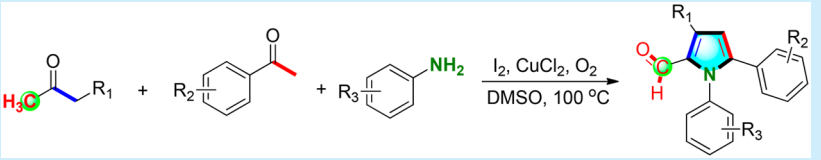
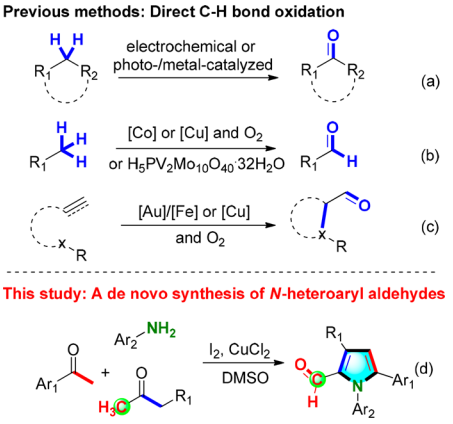
Supporting Information



ABSTRACT: An efficient and practical de novo synthesis of pyrrole-2-carbaldehyde skeletons featuring oxidative annulation and $C_{sp}3$−H to C═O oxidation is presented, exemplified by the preparation of pyrrole-2-carbaldehyde derivatives from aryl methyl ketones, arylamines, and acetoacetate esters. Preliminary mechanistic investigations indicate that the aldehyde oxygen atom originates from oxygen. Moreover, the developed scalable approach provides a distinct advantage over traditional oxidative functionalization of C−H moieties, avoiding the use of stoichiometric quantities of hazardous oxidants.

The aldehyde group is involved in numerous name reactions (e.g., Ugi, Prins, aldol, and Schmidt reactions),[1] with (hetero)aromatic aldehydes being versatile intermediates in the synthesis of pharmaceuticals, fragrances, fine chemicals, and natural products.[2] Due to the ubiquitous application of (hetero)aryl aldehydes, numerous classical (e.g., Vilsmeier−Haack, Gattermann and Gattermann−Koch, Reimer−Tiemann, and Duff reactions as well as the Rosenmund reduction)[3] and nonclassical (e.g.,C−C bond cleavage and photocatalytic formylation)[4] approaches are available for their synthesis. However, the social and environmental demands for greener, more atom-economical, and sustainable methods require the development of alternative protocols such as direct oxidation of C−H bonds to C═O bonds, which represents an ideal chemical synthesis as it does not involve the use of hazardous oxidants/harsh reaction conditions and has unsurprisingly attracted the increased attention of the scientific community.[5] Meanwhile, significant efforts have been directed toward the development of more efficient catalytic processes in this field, with considerable progress achieved during the past five years, as exemplified by a gracefully scalable electrochemical oxidation of nonactivated aliphatic methylene C−H bonds to ketone groups described by Baran and co-workers.[6] In parallel, photo- or metal-catalyzed aerobic oxidation of (hetero)benzylic C−H bonds to ketone C═O bonds has been described by Lei, Xiao, Shi, and others (Scheme 1a).[7] More importantly, efficient and highly selective catalytic oxidation of methyl C−H bonds to aldehyde C═O groups has also been developed (Scheme 1b).[8] Moreover, metal-catalyzed intramolecular dehydrogenative aminooxygenation or bioxygenation of alkenes and alkynes to synthsize heterocyclic aldehydes have been described by Chemler, Shi, Zhu, and Zhang (Scheme 1c).[9] Despite the fact that such reactions are beautifully developed, they feature single oxidation of C−H to the C═O bond. Direct de novo synthesis of heteroaromatic aldehydes relying on C−H bond oxidation has not yet been reported, mainly due to the difficulty of achieving high selectivity and preventing overoxidation to (hetero)benzoic acids.[10] Therefore, developing oxidation conditions for selective heteroaromatic aldehyde formation by fine-turning the reaction parameters, especially those of de novo synthesis, is an important synthetic task. Herein, we report a de novo synthesis of pyrrole-2-carbaldehyde derivatives from aryl methyl ketones, arylamines, and acetoacetate esters

Scheme 1. Oxidation of C−H Bond Functionalization To Synthesize Ketones and Aldehydes



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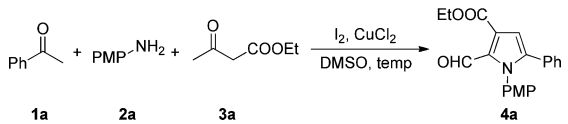
using selective C−H to C═O oxidation as a key step (Scheme 1d).

Considering previously reported methods and the appeal of a de novo synthesis, we investigated new reaction paradigms, aiming to develop more efficient selective oxidation to synthesize *N*-heteroaryl aldehydes. For this purpose, the oxidative condensation of acetophenone **1a**, 4-methoxyaniline **2a**, and ethyl acetoacetate **3a** was selected as a model reaction, affording ethyl 2-formyl-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate **4a** (a pyrrole-2-carbaldehyde derivative) in 32% yield in the presence of a copper salt and iodine (Table 1, entry 1). The structure of **4a** was unambiguously confirmed

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a** **4a**

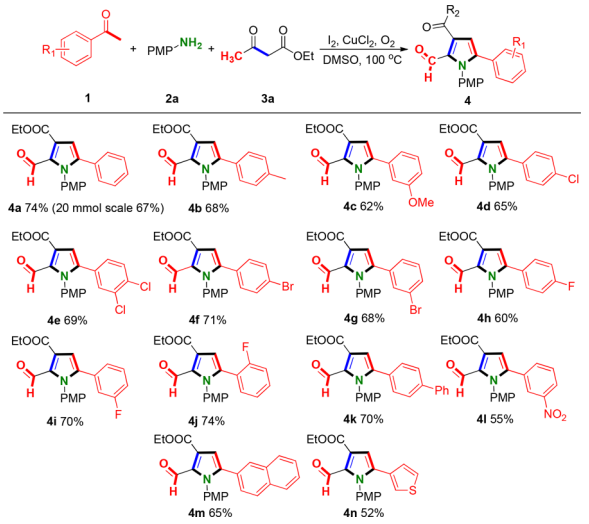
entry	$CuCl_2$ (equiv)	temp (°C)	I_2 (equiv)	yield[b] (%)
1[c]	0.2	100	1.6	32
2	0.2	100	1.6	50
3	0.1	100	1.6	28
4	0.5	100	1.6	62
5	1.0	100	1.6	53
6	0.5	90	1.6	58
7	0.5	110	1.6	55
8	0.5	100	1.0	54
9	0.5	100	2.0	61
10[d]	0.5	100	1.6	67
11[e]	**0.5**	**100**	**1.6**	**74**

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), $CuCl_2$, and I_2 heated in DMSO (4 mL) within 12 h. [b]Products were obtained in isolated yields. [c]CuCl was used instead of $CuCl_2$. [d]Under air. [e]O_2 balloon was used. PMP = 4-OMe-Ph.

by X-ray crystallography (for details, see the Supporting Information). Notably, pyrrole and its derivatives have found numerous applications in areas such as organocatalysis and natural product/biologically active substance synthesis.[11] After a number of trials, the use of 0.5 equiv $CuCl_2$ was found to be optimal (entries 2−5 of Table 1; for more details, see the Supporting Information), with the best yield (62%) obtained for a **1a**/**2a**/**3a** molar ratio of 1:1:1 (see the SI). Subsequently, we varied the amount of iodine and temperature, achieving the best results at 1.6 equiv of I_2 and 100 °C (Table 1, entries 6−10). Finally, screening of a series of amines and Brønsted/Lewis acids as additives under these conditions showed that none of them had a positive impact on the reaction yield (see the SI). Pleasantly, the desired product **4a** was obtained in 67% yield upon prolonged exposure of the reaction mixture to air (Table 1, entry 10). Moreover, the reaction yield was further increased when a O_2 balloon was used (Table 1, entry 11). After several experimental optimizations, the optimized conditions were determined as **1a** (1.0 mmol), **2a** (1.0 mmol), and **3a** (1.0 mmol) in the presence of I_2 (1.6 mmol), $CuCl_2$ (0.5 mmol), and O_2 in DMSO at 100 °C to afford the desired product in 74% yield (Table 1, entry 11).

With the optimized conditions in hand, we tested the substrate scope of this iodine/copper-mediated selective oxidation (Scheme 2), showing that the reaction could be readily extended to a variety of aryl-substituted methyl ketones **1**, with both electron-withdrawing and -donating substituents

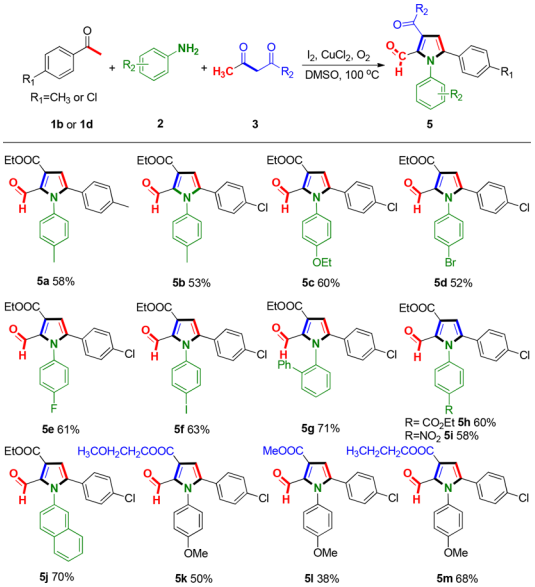
Scheme 2. Scope of Aryl Methyl Ketones



such as Me, OMe, Cl, Br, F, Ph, and NO_2 (Scheme 2, **4b**−**l**) being well tolerated. The results indicated that the electronic and steric properties of the aromatic ketone had little impact on the efficiency of this reaction. The gram-scale reaction could proceed very smoothly. Moreover, methyl ketone containing naphthalene moiety could also be employed to the pyrrole aldehyde scaffold without any difficulties (Scheme 2, **4m**). Notably, methyl ketones with heteroaryl groups such as thiophenyl could also be employed, affording the corresponding products in good yields (Scheme 2, **4n**, 52%).

Further, we investigated the scope of arylamines and acetoacetate esters, with the results displayed in Scheme 3

Scheme 3. Scope of Arylamine and Acetate Esters



indicating that anilines with electron-donating, electron-withdrawing, and halogen groups such as Me, OMe, I, Br, F, Ph, NO_2, and COOEt could be successfully utilized, furnishing the desired products in moderate to good yields (Scheme 3, **5a**−**h**). Importantly, halo-substituted products could be used for further transformations. Furthermore, the phenyl ring could be replaced by a naphthalene moiety (Scheme 3, **5j**). In

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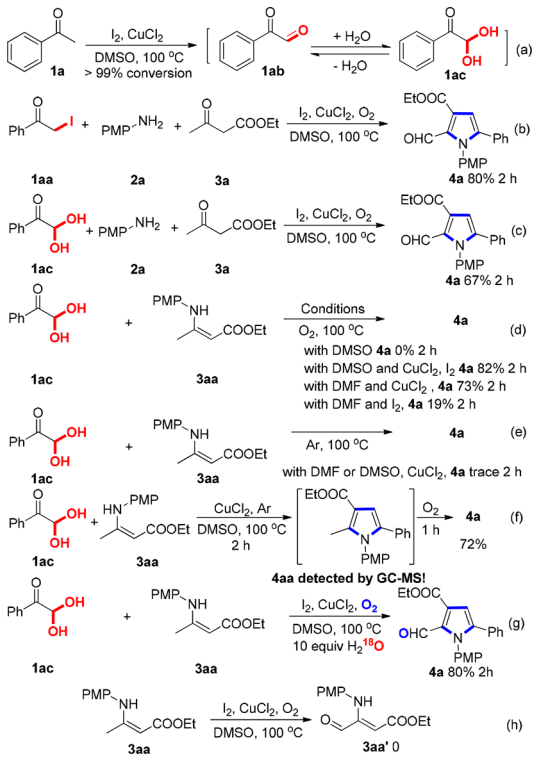
addition, a number of acetoacetate esters **3** were suitable for this reaction, smoothly reacting with **1d** and **2a** to afford the desired products in moderate to good yields (Scheme 3, **5k–m**).

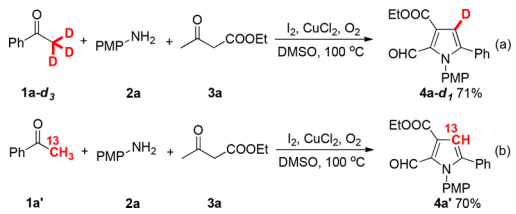
To gain insight into the reaction mechanism, the following experiments were performed. Acetophenone (**1a**, 1.0 mmol) was heated under standard conditions to give phenylglyoxal **1ab** and the corresponding hydrated species **1ac** in quantitative yield (Scheme 4a). Moreover, α-iodoketone **1aa** and hydrated species **1ac** were reacted with **2a** and **3a** under standard conditions (Schemes 4b,c), giving the desired product **4a** in 80% and 67% yields, respectively, and confirming that **1aa** and **1ac** were key intermediates. Subsequently, preformed enaminone **3aa** was reacted with **1ac** under different conditions (Scheme 4d), and the results indicated that **3aa** is a key intermediate and implied that the oxygen atom of aldehyde group does not originate from DMSO. The experiments also highlighted the crucial role of $CuCl_2$ which is more efficient in promoting the reaction than iodine. Next, the product **4a** was obtained in trace when using argon protection. Moreover, **3aa** was reacted with **1ac** under argon for 2 h, affording **4a** in 72% yield after subsequent exposure of the reaction to oxygen (Scheme 4e,f). Meanwhile, the reaction of **3aa** and **1ac** was investigated in the presence of $H_2{}^{18}O$ (10 equiv); however, no ^{18}O-labeled product (^{18}O-**4a**) was detected (Scheme 4g). The above results indicated that oxygen atom of aldehyde group of **4a** was derived from oxygen. Finally, enaminone **3aa** was reacted under standard conditions and no product **3aa′** was yielded. The results further implied that the aldehyde group was formed from the intermediate **4aa**.

To develop a better understanding of the reaction mechanism, we performed D-labeling (Scheme 5a) and ^{13}C-labeling (Scheme 5b) experiments under optimized conditions,

Scheme 4. Control Experiments



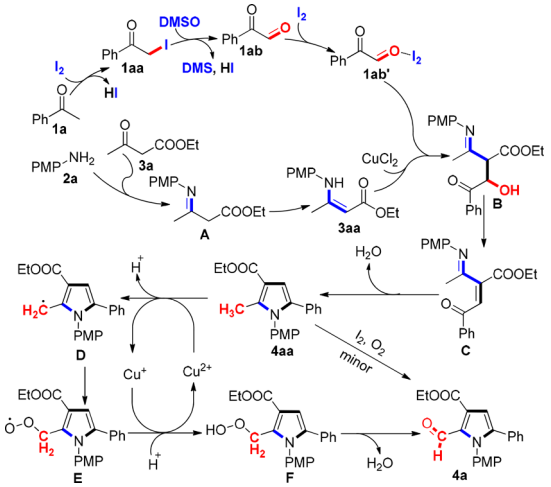
Scheme 5. Labeling Experiments



using acetophenone-β,β,β-d_3 and acetophenone-β-^{13}C as substrates, respectively, with the corresponding products **4a-d_1** and **4a′** obtained in 71 and 70% yields. The obtained results indicated that methyl ketones provide two carbons for the construction of the pyrrole ring.

Based on the above findings and previously reported results,[12] we propose a plausible reaction mechanism for the representative reaction of **1a**, **2a**, and **3a** (Scheme 6). In this mechanism, **1a** is converted to phenylglyoxal **1ab**, releasing HI and dimethyl sulfide (DMS) via sequential iodination/Kornblum oxidation. Concomitantly, the condensation of **3a** with **2a** affords intermediate **A**, which undergoes tautomerization to give **3aa**. Subsequently, **1ab** is activated by Lewis acidic I_2 or copper salt and reacts with **3aa** via in situ cross-trapping to yield intermediate **B**, which undergoes dehydration/cyclization/oxidative aromatization to produce intermediate **4aa**. In the next step, **4aa** is directly oxidized by Cu^{II} to afford radical **D** and generate Cu^{I} and H^+. Intermediate **D** easily reacts with molecular oxygen to form **E**, a peroxy radical, which is reduced by Cu^{I} and protonated to generate intermediate **F**. Finally, **F** eliminates H_2O to produce the desired **4a**. Alternatively, a small amount of intermediate **4aa** maybe undergo a rapid oxidation reaction with iodine and oxygen to form product **4a**.

Scheme 6. Proposed Mechanism



In summary, we have developed an unprecedented de novo synthesis of pyrrole-2-carbaldehyde derivatives based on I_2/$CuCl_2$-mediated oxidative cross-coupling/annulation/C–H oxidation, exemplified by the formation of 2-formylpyrrole derivatives under mild conditions. The above transformation tolerates a wide range of aryl methyl ketones, arylamines, and acetoacetate esters, affording polysubstituted pyrroles bearing an aldehyde group. Further research on this synthetic strategy and its applications is currently underway in our laboratory and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03821.

Experimental procedures, product characterizations, crystallographic data, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1560777 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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