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Microwave-assisted synthesis of 3-formyl substituted imidazo[1,2-*a*]pyridines

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ABSTRACT

An efficient, metal-free method for the synthesis of 3-formyl imidazo[1,2-*a*]pyridines is reported. The method utilises commercially available substrates and features a broad substrate scope. The intermediate enamine was isolated and a plausible reaction mechanism proposed.

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Introduction

The imidazo[1,2-*a*]pyridine scaffold is present in a number of biologically active compounds, including natural products [1]. Several drugs (e.g. zolpidem, alpidem, olprinone, zolimidine, rifaximin, minodronic acid) containing an imidazo[1,2-*a*]pyridine ring are available on the market. Imidazo[1,2-*a*]pyridine containing compounds show excited-state intramolecular proton transfer properties, which predispose them to applications in fluorescence sensors, laser dyes and molecular switches [2]. A number of excellent reviews on the synthesis and functionalization of compounds containing the imidazo[1,2-*a*]pyridine scaffold have been recently published (Scheme 1) [3–5].

Due to the presence of the formyl group, imidazo[1,2-*a*]pyridine 3-carbaldehydes are popular building blocks used for the incorporation of this heterocycle into diverse structures. Two general routes for the synthesis of imidazo[1,2-*a*]pyridine 3-carbaldehydes can be recognized. In the first approach (Scheme 1.1) the formyl group is appended to the imidazo[1,2-*a*]pyridine ring *via* a Vilsmeier-Haack reaction [6–8], Cu-catalyzed C3-formylation with DMSO and molecular oxygen [3], and aerobic iron(III)-catalyzed formylation using DMSO as a carbon source [9]. The second approach involves intramolecular closure of the imidazole ring in the imidazo[1,2-*a*]pyridine, with concurrent introduction of the formyl group (Scheme 1.2, 1.3). Within this route are silver-catalyzed aminooxygenation [10] and a number of copper-catalyzed transformations, such as the intramolecular dehydrogenative aminooxygenation of *N*-allyl-2-aminopyridines [11], the use of ethyl tertiary amines as a carbon source [12], the cyclization of aminopyridines and propiolaldehyde [13], and the annulation of 2-aminopyridines and bromomalonaldehyde [14,15]. Most of the above described procedures require long reaction times (10–24 h), heating at 100 °C or higher temperatures, the use of oxygen gas and metal catalysts, or pre-formation of the substrates. Only the latter approach (Scheme 1.3) combines advantages such as the use of commercially available substrates and no need for a metal catalyst. However, this method suffers from low yields and the formation of unidentified side-products [14–16].

Herein, we present a simple and efficient approach for the synthesis of diversely functionalized imidazo[1,2-*a*]pyridine 3-carbaldehydes (Scheme 2). The reaction does not require any additives and proceeds to completion within 10 to 20 min in EtOH/H_2O as the solvent. We have also isolated the side products and determined the factors promoting their formation. In addition, we have also isolated and characterized an intermediate, for the first time experimentally supporting one of the previously postulated mechanisms [17].

Results and discussion

In the original work of Hayakawa and co-workers [14,15] the reaction between 2-aminopyridine and bromomalonaldehyde was performed at reflux in acetonitrile or in MeCN/ethanol. The

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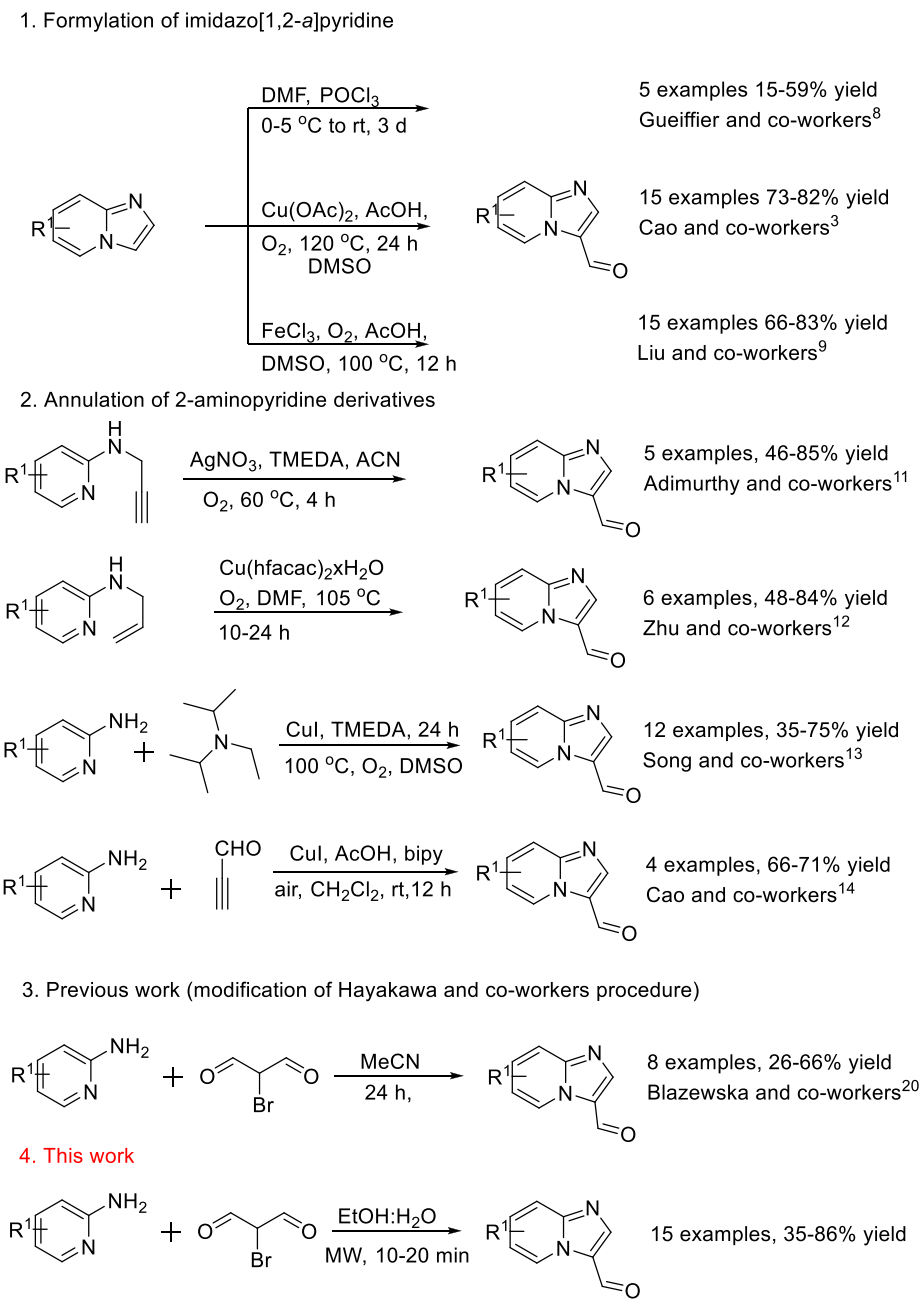
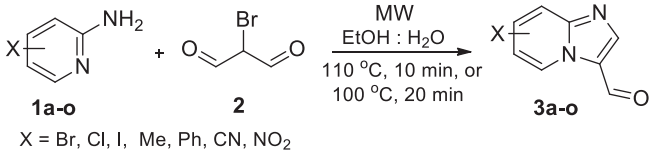


Scheme 1. Selected methods for the synthesis of imidazo[1,2-*a*]pyridine 3-carbaldehydes. Only compounds unsubstituted at the C-2 position are shown, as they directly correspond to the method reported herein.



Scheme 2. Optimised conditions for the synthesis of imidazo[1,2-*a*]pyridine 3-carbaldehydes.

products were isolated in moderate yields (28–52%). Our previous studies have shown that under such conditions substantial amounts of the side product imine **4** (formed through condensation of substrate **1** and product **3**; Fig. 1) and an insoluble tar are formed. The decomposition of bromomalonaldehyde was also observed under these conditions. Therefore, we have optimized

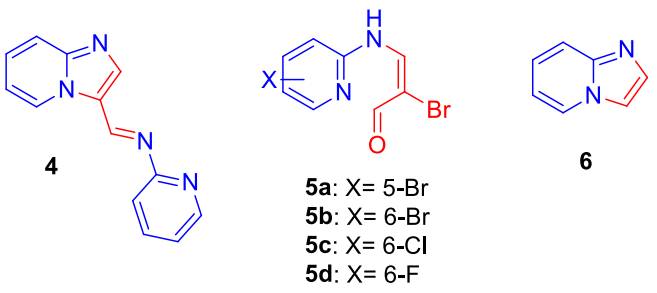


Figure 1. Structures of the side products formed during synthesis of imidazo[1,2-*a*]pyridine 3-carbaldehydes.

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the protocol, by adding bromomalonaldehyde portionwise (in total 4.5 eq, Table 1, entry 1) which led to reaction completion, giving higher yields compared with the original work (Scheme 1.3) [18,19].

In order to improve this protocol, we applied microwave (MW) irradiation for the synthesis of the title compounds. Although microwave-assisted synthesis was previously used for constructing diversely substituted imidazo[1,2-*a*]pyridines [17,20], such conditions were not optimal for the synthesis of imidazo[1,2-*a*] pyridine 3-carbaldehydes.

In the optimization studies 2-amino-5-bromopyridine **1a** was used as a model substrate. The reaction mixture was irradiated in a pressure vial with MW (initial 150 W power) at 100–110 °C for 5–20 min.

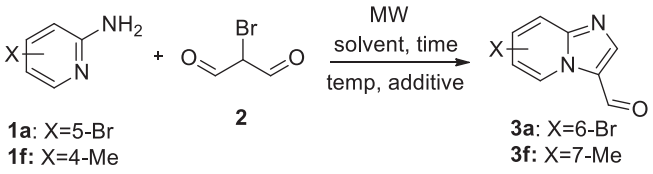
The use of MeCN (as in Hayakawa and co-workers procedure [14]), acetone or 1,4-dioxane as solvents at 100 °C led to mixtures of unidentified products (Table 1, entries 2–4). Running the reaction under solvent-free conditions led to decomposition (Entry 5). When ethanol:water (1/1, v/v) was used the desired product **3a** was obtained in 54% yield (Entries 6–7). Additional improvement was achieved by increasing the temperature from 100 °C to 110 °C (80% yield, entry 8). We also found that if none or a small amount of water (<10%, v/v) was used, the corresponding acetals may form (Entries 9, 11, and 12). Use of larger amounts of water (up to 33% v/v) circumvented the acetal formation (Entries 8, 10). On the other hand, when water was used as a reaction medium the yield dropped to 48%, and significant amounts of the intermediate product enamine **5a** was isolated (Fig. 1, Table 1, Entry 13).

We also examined the influence of both basic and acidic conditions on the reaction outcome. Carrying out the reaction in the presence of triethylamine or an inorganic base (Na_2CO_3), led to the formation of enamine **5a**, or recovery of the substrate (Entries 14–15). The addition of *p*-toluenesulfonic acid led to a decrease of the yield to 57% (Entry 16). We also found that the optimized conditions for 2-amino-5-bromopyridine were not suitable for the methylated analog **1f** (Entries 17–18). A lower temperature (100 °C), longer reaction time (20 min) and higher concentrations of substrate **1** were required for efficient transformation (Entries 19–20).

The regioselectivity of the reaction was proven by single crystal X-ray diffraction of aldehyde **3b** (Fig. 2).

Summarizing the optimization results, MW irradiation significantly reduced the time needed for reaction completion, from hours to minutes (Scheme 2). Consequently, the bromomalonaldehyde could be used in lower amounts (1.5 eq.), compared with standard heating, where its decomposition decreased the yield. We recommend to use EtOH/H_2O (1:1, v/v) as the solvent and two sets of conditions, which should be selected based on the type of substituents present in the 2-aminopyridines. For 2-aminopyridines substituted with halogens the reaction should be carried out at 110 °C for 10 min (Table 1, Entry 8); for methyl analogs a lower temperature (100 °C) and a longer time (20 min) is required

Table 1
Optimization studies.[a]



Entry	Solvent	Time [min]	T[b] [°C]	Additive	Yield (%)
1a/3a					
1	MeCN	4 h / reflux 24 h / rt		–	28
2	MeCN	5	100	–	n.d.[c]
3	acetone	5	100	–	n.d.[c]
4	1,4-dioxane	20	100	–	n.d.[c]
5	neat	20	100	–	n.d.[c]
6	EtOH:H_2O 1:1	10	100	–	54
7	EtOH:H_2O 1:1	20	100	–	54
8	**EtOH:H_2O 1:1**	**10**	**110**	**–**	**80**
9	EtOH:H_2O 2:0.1	5	100	–	n.d.
10	EtOH:1,4-dioxane:H_2O 1:1:1	10	110	–	63[d]
11	EtOH:1,4-dioxane:H_2O 1:2:0.1	5	110	–	n.d.
12	1,4-dioxane:ethanol 2:1	10	100	–	n.d.
13	H_2O	10	110	–	48
14	EtOH:H_2O 1:1	10	110	Et_3N	n.d.
15	EtOH:H_2O 1:1	10	110	Na_2CO_3	n.d.
16	EtOH:H_2O 1:1	10	110	*p*-TsOH	57
1f/3f					
17	EtOH:H_2O 1:1	10	110	–	42[e]
18	EtOH:H_2O 1:1	5	110	–	21
19	EtOH:H_2O 1:1	20	100	–	53[f]
20	**EtOH:H_2O 1:1 (1.2 M)**	**20**	**100**	**–**	**73**

[a] Reactions were carried out using **1** (0.3 or 0.6 M) and **2** (1.5 eq.) unless indicated otherwise; under standard heating conditions **2** was used in a higher amount (4.5 eq.) (Entry 1).
[b] Reactions were performed using microwave irradiation, except for entry 1.
[c] Not determined due to decomposition.
[d] The same yields were obtained using both isolation methods: column chromatography with or without prior extraction.
[e] Similar yields were obtained using 0.3 M or 0.6 M solutions of **1f**.
[f] Doubling the concentration to 2.4 M led to a lower yield (39%).

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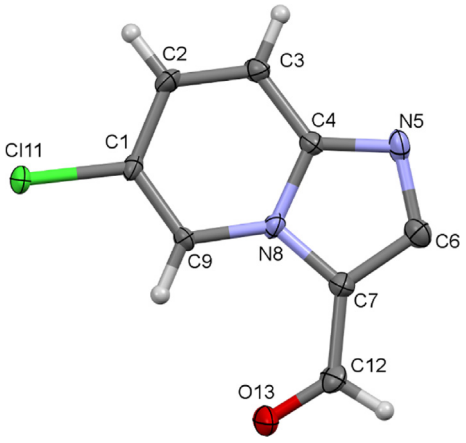

Figure 2. ORTEP plot of 3b at 50% ellipsoid probability.

(Entry 20). The side product imine **4**, formed under the standard heating conditions, and was not observed when microwave heating was applied.

With the optimized procedure in hand, we investigated the scope of the reaction, using various 2-aminopyridines **1** bearing electron-withdrawing and electron-donating groups. All substrates reacted with bromomalonaldehyde, in most cases affording the desired aldehydes **3** with significantly improved yields (48–86%), compared with the standard method (26–66%) [18] (Fig. 3, Table S1). As shown for two representative examples, the reaction can be also performed on a 10 times larger scale (1.2 *vs.* 12 mmol), with ~15% decrease in the yield (Fig. 3).

Lower yields (23–35%) were obtained for 6-methyl and 6-phenyl substituted 2-aminopyridines **1m** and **1n**. In the case of 6-bromo-2-aminopyridine only trace amounts of the product were detected, while the main product was enamine **5b**, or decarbonylation product **6** when more forcing conditions were applied (150 °C) (Fig. 1). The same outcome was observed for 6-chloro- and 6-fluoro-2-aminopyridines, leading to enamines **5c** and **5d**, instead of the desired aldehydes **3**. The enamine product **5a** could be also isolated from the reaction of 2-amino-5-bromopyridine. It precipitated from the reaction mixture within a few minutes, before microwave heating was applied.

In order to address the differences in the reactivity of 5- *vs.* 6-substituted 2-aminopyridines, we concentrated on the fact that for both derivatives we have isolated intermediate **5**. Presumably, the propensity of intermediate **5** towards closure of imidazole ring is responsible for the successful completion of the reaction. Such a predisposition could be affected by two factors: steric hindrance (for analogs with substituents on the C6 carbon, neighboring the pyridine nitrogen), and the electron-withdrawing character of the substituent near the pyridine nitrogen.

Firstly, the steric hindrance due to the substituent at C6 may hinder the approach of the pyridine nitrogen toward the electrophilic site [21,22]. On the other hand, the occurence of decarbonylation implies that while steric hindrance may prevent intramolecular closure of the imidazole ring, the repulsive interactions between the halogen and carbonyl may influence the stability of the products [23]. Secondly, the moderate propensity of the 6-methyl and 6-phenyl substituted 2-aminopyridines for cyclization into aldehydes **3**, compared with the complete lack of product formation for 6-halogen substituted 2-aminopyridines (halogens: F, Cl, Br), could be explained by the lower basicity/nucleophilicity of the endocyclic nitrogen in such 2-aminopyridines, leading to enamine **5** only [24]. When we studied the reaction using 5-nitro-2-aminopyridine **1c** the yield dropped to 54%. We concluded that the combination of steric hindrance and the electron-deficiency of aminopyridines prevents closure of the imidazole ring in **5**, terminating the reaction at the enamine stage. However, if only one of these factors is involved, the product forms, albeit with lower yields (Fig. 3, 3c, 3m, 3n).

Finally, we posed the question whether compound **5** was an intermediate in the studied reaction. In the literature two mechanisms for analogous reactions are proposed. According to the first one (Scheme 3, route A), the reaction takes place *via* attack of the exocyclic amine group on bromomalonaldehyde, followed by the elimination of water and formation of an intermediate imine **5a'** or enamine **5a**. Then, *via* intramolecular cyclization and expulsion of the bromide anion, the final product is formed [17]. The second mechanism [25,26] involves attack of the endocyclic nitrogen atom, which expels the bromine anion, forming a pyridinium salt, with subsequent closure of the imidazole ring (Scheme 3, route B). To the best of our knowledge, it has never been experimentally determined which mechanism operates in this reaction.

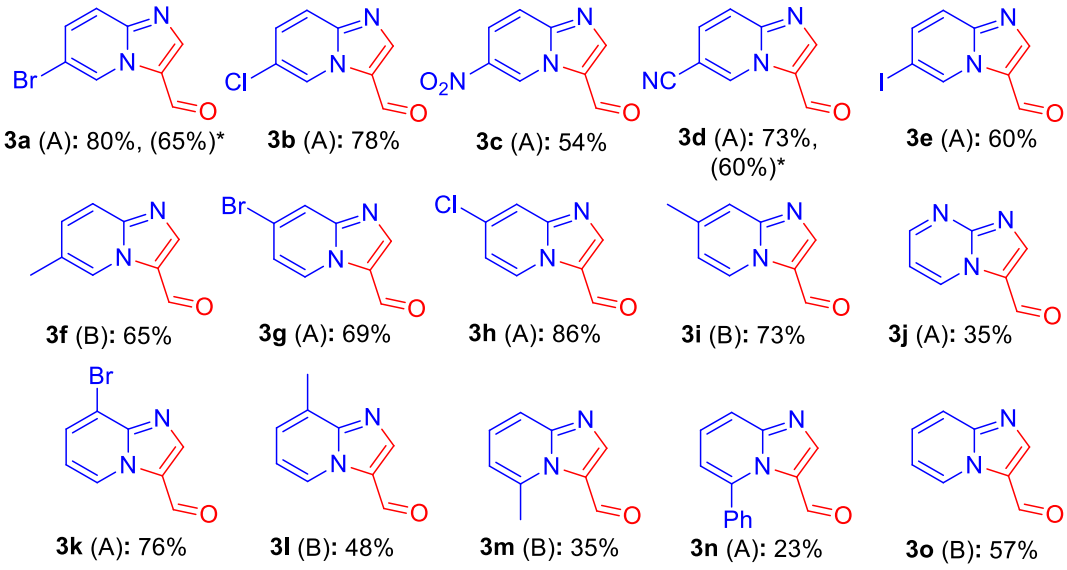

Figure 3. Scope of the method. Reagents and conditions: (A) MW, EtOH:H_2O (1:1, v/v), **2** (1.5 eq.), 110 °C, 10 min; (B) MW, EtOH:H_2O (1:1, v/v), **2** (1.5 eq.), 100 °C, 20 min; * Yields for the scale-up experiments (12 mmol).

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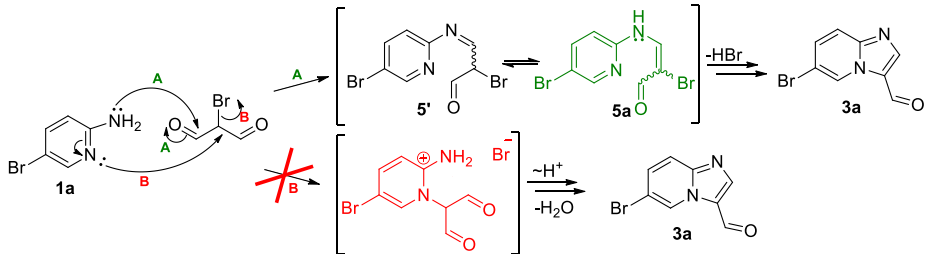

Scheme 3. Plausible reaction mechanisms. The isolated intermediate is presented in green.

Herein, evidence is provided for one of the proposed routes (Scheme 3, route A) by the isolation of compound **5** and its transformation into the expected product **3**. The structure of isolated compound **5a** was determined by MS spectrometry, and ^{1}H and ^{13}C NMR spectroscopy. Compound **5a** contains a bromine atom and according to NMR mainly exists in the enamine form. The distinction between imine **5'** and enamine **5a** was made based on the following features in the NMR spectra: (1) lack of coupling between the CH and formyl group, suggesting that they are separated by more than 3 bonds; (2) two additional non-aromatic signals at 8.88 ppm (d, $J = 12.2$) and at 10.25 ppm (d, $J = 12.2$) in DMSO d_6, with the latter significantly shifted downfield, showing no coupling with carbon, and disappearing in $CDCl_3$. Based on such spectroscopic properties, we have identified it as the signal for the N—H proton. If compound **5'** was the prevailing tautomeric form, the presence of two CH signals, coupled with each other, would be expected. However, we cannot exclude that **5'** also plays a role in this reaction, being present in minute amounts under the reaction conditions.

In order to establish if **5** can be transformed into the final aldehyde, we subjected model enamine **5a** to the microwave irradiation in ethanol/water. Within 10 min almost complete conversion of **5a** into aldehyde **3a** was observed (see Fig. S38-S39). That result together with the spectroscopic data discussed above, strongly supports mechanistic pathway (A) proceeding *via* imine/enamine formation.

In summary, we have developed mild, rapid and metal-free, MW-assisted synthesis of imidazo[1,2-*a*]pyridine 3-carbaldehydes. It represents a convenient alternative compared with the existing methods, as it requires readily available starting compounds, it is carried out in environmentally friendly solvent mixture (EtOH:water, 1:1), and is compatible with diverse substituents on the 2-aminopyridine. We have also isolated the intermediate enamine **5** formed in this reaction, supporting one of the two mechanisms proposed in the literature.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151244.

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