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Solvent-free microwave-assisted synthesis of imidazo[1,5-*a*]pyridine and –quinoline derivatives

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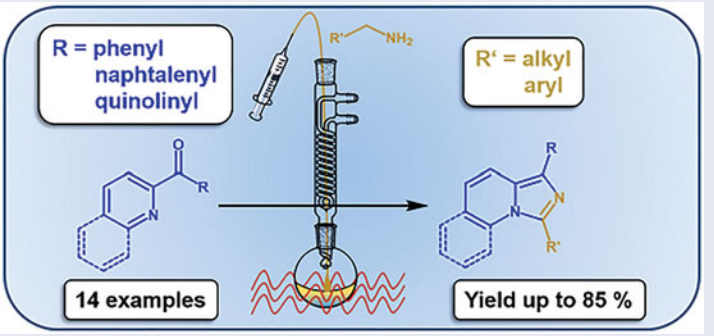
ABSTRACT

A quick and highly efficient microwave-assisted preparation of imidazopyridines and –quinolines is described, starting from the corresponding ketones and amines. The method requires no solvent and uses activated MnO_2 as an oxidant. A mechanism for the cyclization is proposed and discussed.

GRAPHICAL ABSTRACT



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KEYWORDS
Condensation reaction; microwave reaction; MnO_2; imidazo[1,5-a]pyridine; rearrangement

Introduction

Unsaturated N-heterocycles can be found nearly everywhere in nature. Amongst these are alkaloids like caffeine or the nucleobases of DNA. Furthermore, N-heterocycles have found broad applications, ranging from pharmacy to material science.

A special structure class of N-heterocycles is imidazopyridines and –quinolines (IPs and IQs), which are also found in nature.[1] Amongst these especially the 1,3-disubstituted imidazo[1,5-a]pyridines and –quinolines (Figure 1) have been receiving increasing attention in the last years. They are bioactive substances, in relation to arterial

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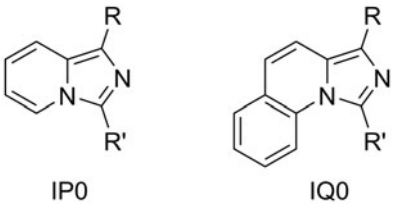


Figure 1. Left: 1,3-disubstituted imidazo[1,5-*a*]pyridine (IP0); right: 1,3-disubstituted imidazo[1,5-*a*]quinoline (IQ0); R and R′: aryl or alkyl.

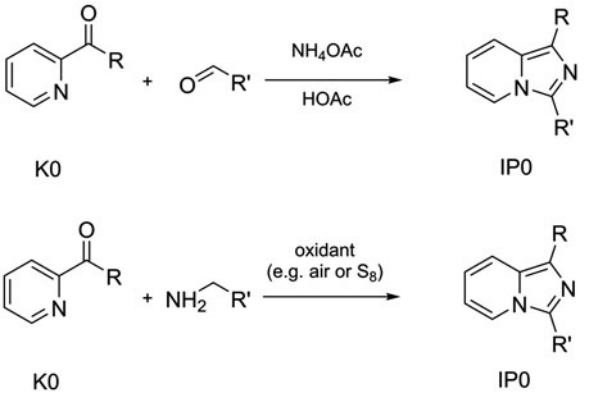
thrombosis,[2] Alzheimer's disease[3] or tumors.[4] Due to their strong fluorescence, IPs and IQs can also be used as fluorescence probes[5–9] or as cell imaging reagents.[10]

Furthermore, because of their characteristic strong (and often blue) fluorescence[11] (quantum yield up to 44%),[10] IPs and IQs are interesting for application in various technical components. For example, Costa et al. prepared a light-emitting electrochemical cell (LEC) based on an IP derivative.[12,13] Other groups investigated the applicability of IPs and IQs for organic light-emitting diodes (OLEDs)[14–17] or for dye-sensitized solar cells (DSSCs).[18] For such applications often the complexes instead of pure IPs and IQs are used, due to triplet state harvesting. Complexes with many different metals were investigated in this context (e.g., Ag,[19] Re,[20–22] Zn,[23] Cu,[13] and Ir[24]). Additionally, there are first investigations of IPs as ligands for Pd-catalyzed reactions.[25]

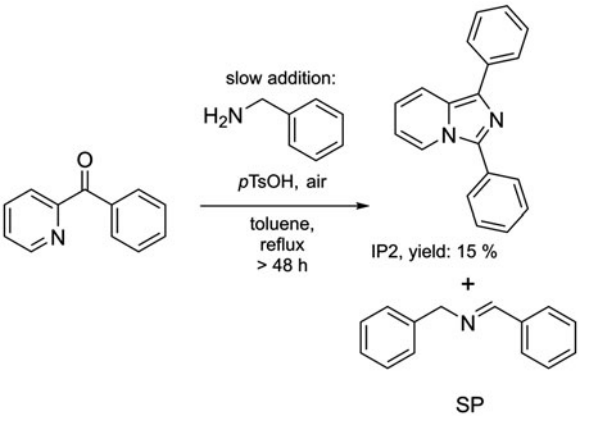
Luminescence materials for the application in OLEDs or comparable techniques are of importance for the generation of power-efficient lighting and displays, thereby reducing energy consumption and CO_2 emissions. Therefore, efficient preparation of luminescence materials for such applications is of general interest. We wanted to study the photo- and electrochemical properties of new imidazopyridines and –quinolines and their derivatives and were interested in an efficient synthetic approach to these compounds.

Currently, two synthetic approaches towards IPs and ICs are known (Scheme 1). The first is a three-component condensation reaction between pyridin-2-yl-methanones, aldehydes, and ammonium acetate in acetic acid.[26–28] This reaction can also be carried out in a microwave reactor with addition of LiCl.[29] The advantage of this approach is the wide scope of products. However, as the reaction is carried out in acetic acid, the compounds must be stable under acidic conditions. The second approach is a condensation reaction between an amine and a carbonyl group including an oxidation step.[30] This reaction is often catalyzed by copper salts with air as an oxidant[31,32] but also an example with elemental sulfur as oxidant is known.[33] The disadvantage of this approach is that the amines can react with oxygen under copper catalysis, leading to undesired side products like imines or N-oxides.[34] Thus, an excess of amine is required for a complete conversion of the carbonyl compound. This also renders the adjustment of the amount of oxidant tricky. Other pathways towards the synthesis of IPs avoid simple amines but use cyanides,[35] amino acids,[36] dithioesters,[37] or nitriles.[38] These require either the use of toxic reagents or long reaction times.

In this work, we report a solvent-free microwave-assisted pathway to synthesize IPs and the less well-known IQs in good yields and short reaction times. The synthesis is based on a condensation reaction between a ketone and an amine, avoiding copper catalysts.



Scheme 1. Synthetic approaches towards IPs and IQs; R and R′: aryl or alkyl.



Scheme 2. Imidazopyridines by condensation using air-oxidation.

Results and discussion

We earlier reported on the preparation of an imidazoquinoline (IQ2) in good yield using a condensation reaction and air as the oxidant.[15] Upon applying the same reaction conditions for the preparation of imidazopyridines the yield decreased significantly (Scheme 2).

Unfortunately, the amount of the side product (SP, imine) increased even though a syringe pump was used for a slow addition of the amine. Surprisingly, notable amounts of reduction products of the ketone and imine were found too. Upon addition of sulfur,[33] this reduction of the ketone could be avoided. Nevertheless, long reaction times and a large excess of amine were necessary to obtain a complete conversion of the ketone and still the yield of the desired product remained only moderate (below 30%).

As many reactions can be drastically accelerated by the application of microwave irradiation,[39] we performed the reaction in a closed microwave reactor. As anticipated this led to a reduced reaction time but also to several unidentified side products. Thus, the yield of the desired product could not be increased significantly. In our working group, activated MnO_2 is often used as a reagent for mild oxidations. Utilization of this

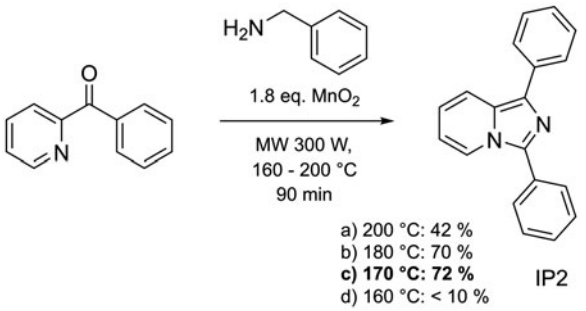
oxidant instead of S_8, lead to higher yields and reduced amounts of side products (Scheme 3). Using these conditions, the best yields were obtained when performing the reaction under solvent-free conditions.

Another advantage of using MnO_2 as the oxidant is its facile removal by filtration. The best yield was obtained with a reaction temperature of 170 °C as shown in Scheme 3.

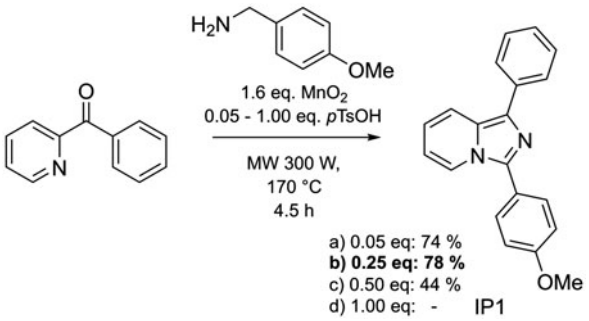
The next goal was to suppress the formation of side products, specifically the above-mentioned oxidation of the amines.[34] The common technique to suppress this reaction is to add the amine to the reaction mixture very slowly. To realize this we had to carry out the reaction in an open microwave vessel equipped with a condenser. We used a Teflon tube to add the amine with a syringe pump. Hereby we were able to reduce the required amount of amine to 1.6 eq. and at the same time suppress the side reaction. However, the slow addition of the amine caused a longer reaction time (Scheme 4).

Using these conditions, we further optimized the reaction by varying the amount of added acid. This is required only in substoichiometric/catalytic amounts with 0.25 eq. leading to the best yield of product (Scheme 4).

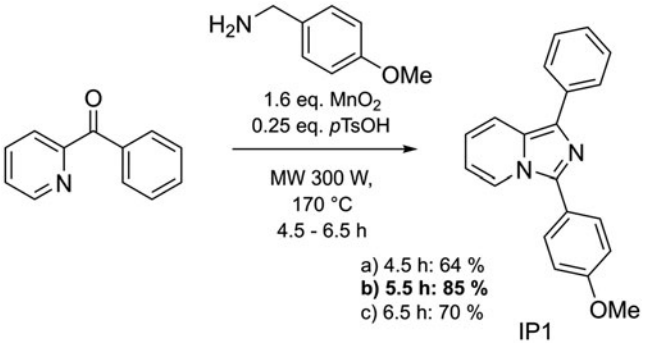
The last optimization step was the variation of the reaction time. The best yields (up to 85%) were obtained with a reaction time of 5.5 h. Longer or shorter reaction times led to reduced yields as depicted in Scheme 5.



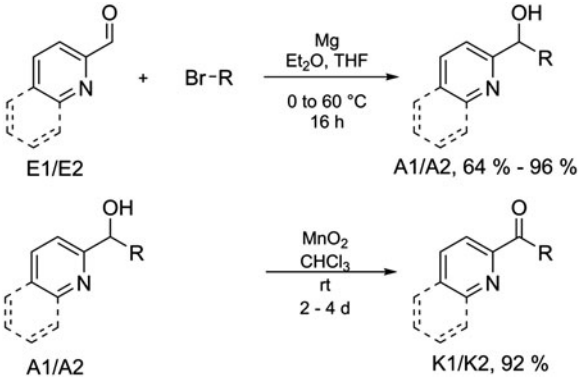
Scheme 3. MnO_2 as oxidant under microwave conditions. The yields are determined using NMR and are not isolated.



Scheme 4. Slow addition of amine to an open microwave reaction, optimization of the added acid.



Scheme 5. Optimization of the reaction time.



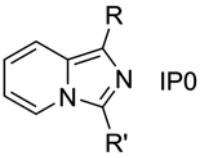
Scheme 6. Preparation of ketones as starting materials; E1/A1/K1 = 2-pyridinyl, E2/A2/K2 = 2-quinolinyl; R = naphtalenyl.

To check the scope of the reaction, we prepared additional ketones as depicted in Scheme 6. We started using the aldehydes E1/E2 which reacted with the corresponding Grignard reagent to obtain the secondary alcohols A1/A2. These were oxidized with activated MnO_2 to the aryl-quinoyl-ketones K1/K2 in excellent yields, which we used as starting materials for our following condensation/oxidation procedure.

The results of these reactions are shown in Table 1. The obtained yields varied with the amines used. For aromatic amines, the yields were best when substituted benzylic amines were reacted. When the aromatic group was electron poor (pyridyl, furanyl, IP4, IP7, and IP9) the yields were only moderate (around 45%). The same held true for IP8, in which an alkylamine was applied. Compared to this, the nature of the ketone seems to be less important (compare IP2 and IP10 as well as IP4 and IP9).

As our developed procedure seems to be rather general for the preparation of imidazopyridines, we wanted to check its applicability for the preparation of imidazoquinolines too. In previous publications, first blue-emitting devices with IQ2 as the emitter were built. Based on these results, other new imidazoquinolines are required to investigate the properties. It was possible to synthesize three new compounds (IQ1, IQ3, and IQ4) as shown in Figure 2. Therefore, our method allows for an efficient and easy preparation to the very interesting but neglected substance class of imidazoquinolines in good yields.

Table 1: Preparation of imidazopyridines applying the optimized MnO_2 and microwave conditions.



IP0

Entry	R	R′	Yield
IP1	Phenyl	4-Methoxyphenyl	85%
IP2	Phenyl	Phenyl	72%
IP3	Phenyl	4-Fluorophenyl	65%
IP4	Phenyl	2-Pyridinyl	41%
IP5	Phenyl	3-CF_3-phenyl	80%
IP6	Phenyl	3-Methoxyphenyl	61%
IP7	Phenyl	2-Furanyl	45%
IP8	Phenyl	Hexyl	42%
IP9	Naphthalenyl	2-Pyridinyl	44%
IP10	Naphthalenyl	Phenyl	79%

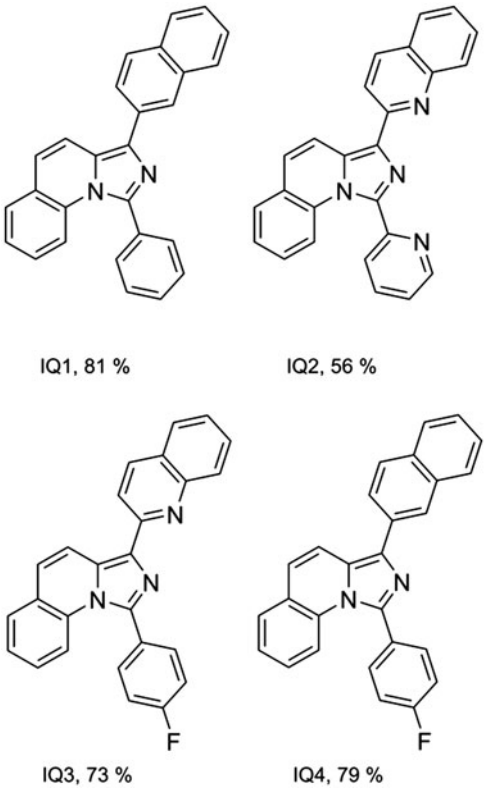
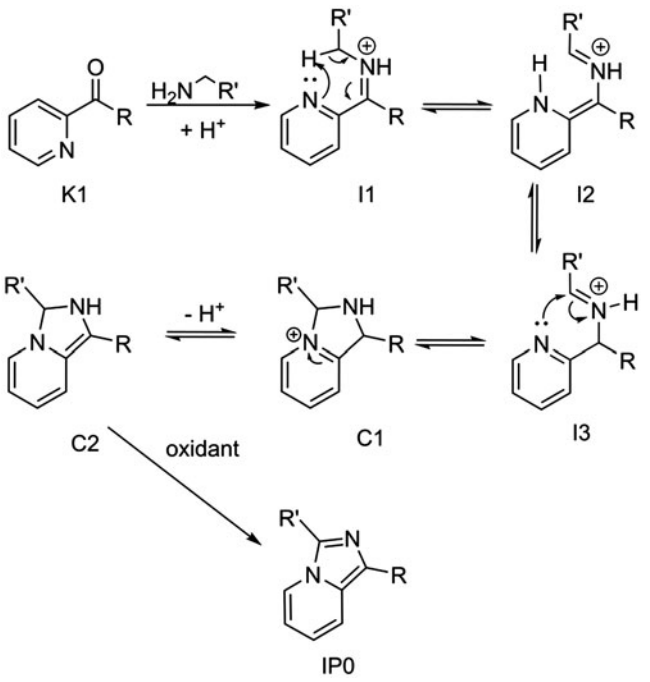


Figure 2. Preparation of imidazoquinolines applying the optimized MnO_2 and microwave conditions.

As with the imidazopyridine examples, again the type of amine used seems to have an influence on the yield obtained with the (pyridine-2-yl)methanamine producing somewhat lower yields than substituted benzylic amines. Furthermore, the benzylic amine carrying a + M-substituent (Table 1, IP1, 4-methoxyphenyl) gave the



Scheme 7. Proposed reaction mechanism.

highest yield. This observation can be explained by the proposed mechanism (Scheme 7). In the first step, the ketone and the amine react to give the iminium ion I1. This is in equilibrium (tautomerism) with the iminium ion I3. This surprising imine isomerization under acidic conditions is probably due to an intramolecular deprotonation of the iminium ion by the pyridine group as shown below (via I2). This could also be described as a 1,5-H-shift. The equilibrium between the two iminium ions depends on the stabilizing effect of the amine-substituent, with electron-donating substituents from the amine (R′) leading to a stronger preference of I3. I3 reacts further to the dihydro-imidazole moiety (C1 and C2) which is finally oxidized to the imidazopyridine system.

From two products single crystals suitable for X-ray structural analysis could be obtained. The obtained X-ray crystal structures of compound IQ4 and IQ3 are shown in Figure 3. IQ4 has a triclinic cell and P1 as space group. The cell dimensions are $a = 5.51904$ Å, $b = 13.4121$ Å, $c = 13.8725$ Å, $\alpha = 115.390°$, $\beta = 95.871°$ and $\gamma = 94.686°$. IQ3 has a triclinic cell and P1 as space group, too. The cell dimensions are $a = 5.5566$ Å, $b = 13.4945$ Å, $c = 13.5592$ Å, $\alpha = 115.012°$, $\beta = 99.583°$ and $\gamma = 96.016°$.

Conclusion

In summary, we have developed an alternative route to synthesize imidazo[1,5-*a*]pyridines and even imidazo[1,5-*a*]quinolones in good yield. Our synthetic procedure is a solvent-free condensation reaction carried out in a microwave reactor. The reaction seems to have a wide scope and tolerates various functional groups, only with non-

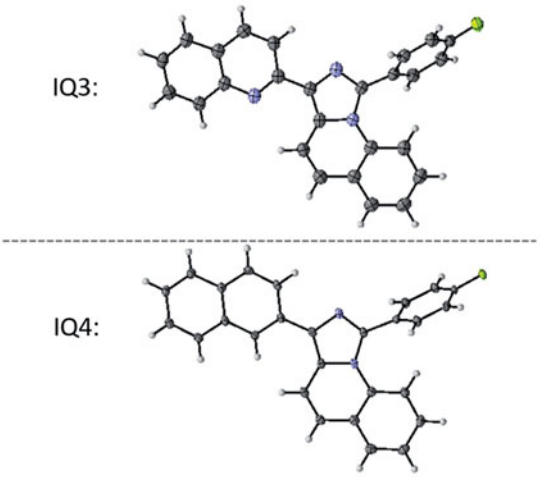


Figure 3. Crystal structures of IQ3 and IQ4.

aromatic amines the yields drop significantly. The new compounds prepared are very interesting for biological[10] as well as technical[12,14] applications. We are currently studying the photochemical and electrochemical properties of these compounds; results will be published in due course.

Experimental

General procedures for the preparation of imidazo[1,5-a]pyridine and –quinoline derivates

Ketone (1.1 mmol), activated MnO_2 (1.8 mmol), and *p*TsOH (0.3 mmol) were stirred briefly in a 15 mL round bottom flask at room temperature for 5 min. Afterward, the mixture was heated in an open microwave reactor (equipped with a condenser) for 5.5 h at 170 °C (max. 300 W). During this time, the amine (1.6 mmol) was added with a syringe pump (PTFE tube). The crude product was purified via flash chromatography or recrystallization.

Full experimental detail, ^{1}H, and ^{13}C NMR spectra, crystallographic data. This material can be found via the "Supplementary Content" section of this article's webpage.

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