SYNTHESIS OF NOVEL 6-ARYL-PHENANTHRIDINES *via* SEQUENTIAL SUZUKI-MIYAURA AND PICTET-SPENGLER REACTIONS UNDER GREEN CHEMISTRY CONDITIONS

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INTRODUCTION

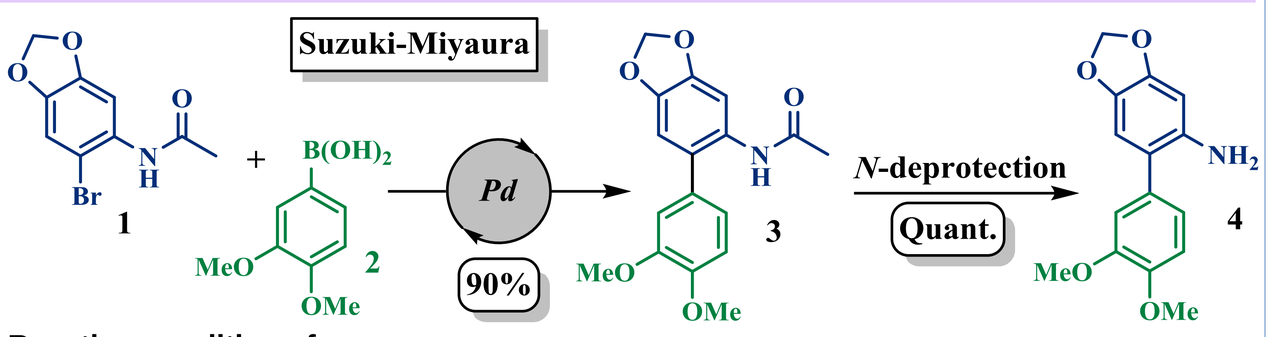
Many phenanthridine derivatives found in nature have proven to be effective anticancer agents, motivating the design and implementation of the synthetic arsenal available for their obtention: versatile and novel synthetic routes leading to the development of structurally richer derivatives with improved biological activities and low toxicity.[1-3]

In this contribution, we present a green approach synthesis of novel 6-aryl-phenanthridines through a sequential Suzuki-Miyaura cross-couplig and Pictet-Spengler reactions, starting from *N*-(6-bromobenzo[*d*][1,3]dioxol-5-yl)acetamide **1** and 3,4-dimethoxyphenylboronic acid **2** to obtain [1,1'-biphenyl]-2-amine **4**. This aniline derivative **4** were used as strategic precursor in the Pictet-Spengler reaction with diverse aromatic aldehydes in choline chloride/zinc chloride deep eutectic mixture and [Bmim]PF_6 as new reaction media for this approach to finally obtain novel 6-aryl-phenanthridines. Green metric analysis showed a favorable environmental impact of this synthetic method.

RESULTS AND DISCUSSION

In this research we focused our task in the construction of this phenanthridine core in an environmentally friendly manner, using the Pictet-Spengler reaction as a determinant synthetic tool. For this purpose, it was necessary to synthesize the strategic precursor [1,1'-biphenyl]-2-acetamide **3** , which served as a building block for the synthesis of phenanthridines. Suzuki-Miyaura cross-coupling was carried out to obtain the new C-C bond in compound **3**, using acetanilide **1** and boronic acid **2** in the presence of palladium as catalyst. The next step consisted in the *N*-deprotection of **3** to finally obtain **4**

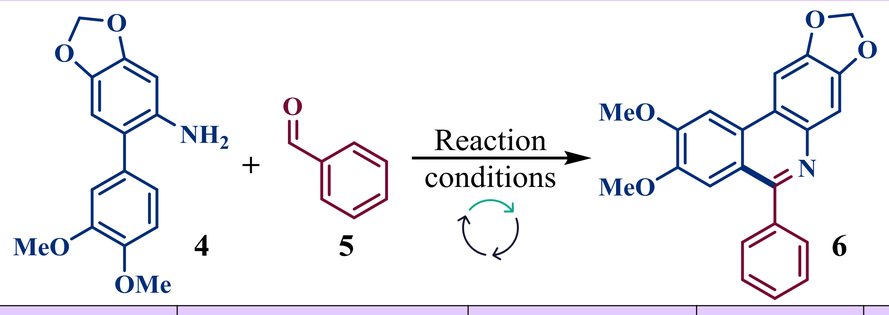
Scheme 1. Synthesis of crucial precursor [1,1'-biphenyl]-2-amine via Suzuki-Miyaura/*N*-deprotection.



Reaction conditions for *Suzuki-Miyaura* = 1 mmol acetanilide **1**, 1.5 mmol phenylboronic acid **2**, 0.05 mmol $Pd(OAc)_2$, 0.05 mmol PPh_3, 3 eq. K_2CO_3 in MeCN, carried out in a Biotage Initiator+ microwave reactor for 15 min at 150 °C. *N-deprotection* = 1 mmol acetamide **3** and 40% KOH/EtOH (10 mL) at 120 °C for 12 min.

Once the precursor [1,1'-biphenyl]-2-amine **4** was obtained, we decided to react this compound with benzaldehyde **5** to obtain phenanthridine **6**. We evaluated different mixtures of eutectic solvents (Table 1). Experiments 1 and 2 showed that the reaction occurs in a relatively short time with equal yields. By varying the ratio of amine and benzaldehyde (1: 2) the yield decreased a little (Exp 3). We discovered that $ZnCl_2$ acts as a catalyst for this reaction, since when changing to urea or $SnCl_2$, the reaction did not proceed. We decided to carry out the reaction using microwave radiation, but unfortunately the yield decreased due to the decomposition of DES (Exp 6). We evaluated the possibility of using $ZnCl_2$ in catalytic amounts in a common solvent (MeCN), but yield did not increase. Finally, we carried out the reaction using ionic liquid [Bmim]PF_6, with $ZnCl_2$ as catalyst. We evaluated the use of microwave radiation and to our delight, the reaction yield increased considerably (Exp 8 and 9).

Table 1. Optimization of the reaction conditions.



Exp[a]	Solvent*	Catalyst	Temp. (°C)	Time	Yield (%)
1	ChCl/$ZnCl_2$		110	1 h	51
2	ChCl/$ZnCl_2$		110	20 min	51
3	ChCl/$ZnCl_2$[b]		110	20 min	44
4	ChCl/urea		110	20 min	NR
5	ChCl/$SnCl_2$		110	20 min	NR
6	ChCl/$ZnCl_2$		150	1 min[c]	23
7	MeCN	$ZnCl_2$ (20 mol%)	84	16 h	36
8	[Bmim]PF_6	$ZnCl_2$ (20 mol%)	110	20 min	50
9	[Bmim]PF_6	$ZnCl_2$ (20 mol%)	150	1 min[c]	65

[a]Reaction conditions: [1,1'-biphenyl]-2-amine (1 mmol), benzaldehyde (1.5 mmol). [b]Reaction carried out employing [1,1'-biphenyl]-2-amine (1 mmol) and benzaldehyde (2 mmol). [c]Reaction carried out in a Biotage Initiator+ microwave reactor at 150 °C. NR: No reaction. *In all the reactions carried out in DES, it was used a 1:2 composition (ChCl:MCl_2 or urea).

Table 2. Substrate scope.

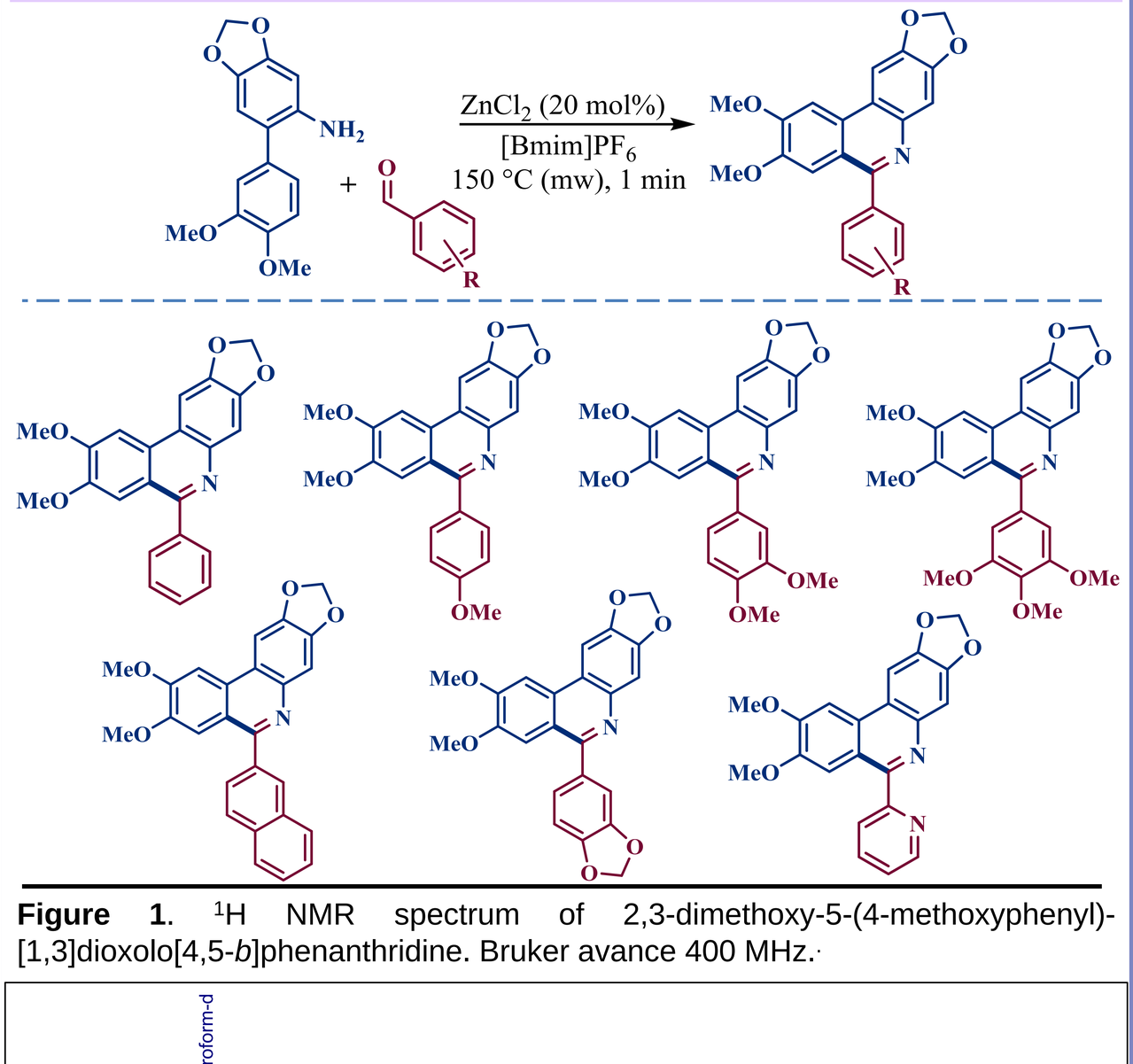
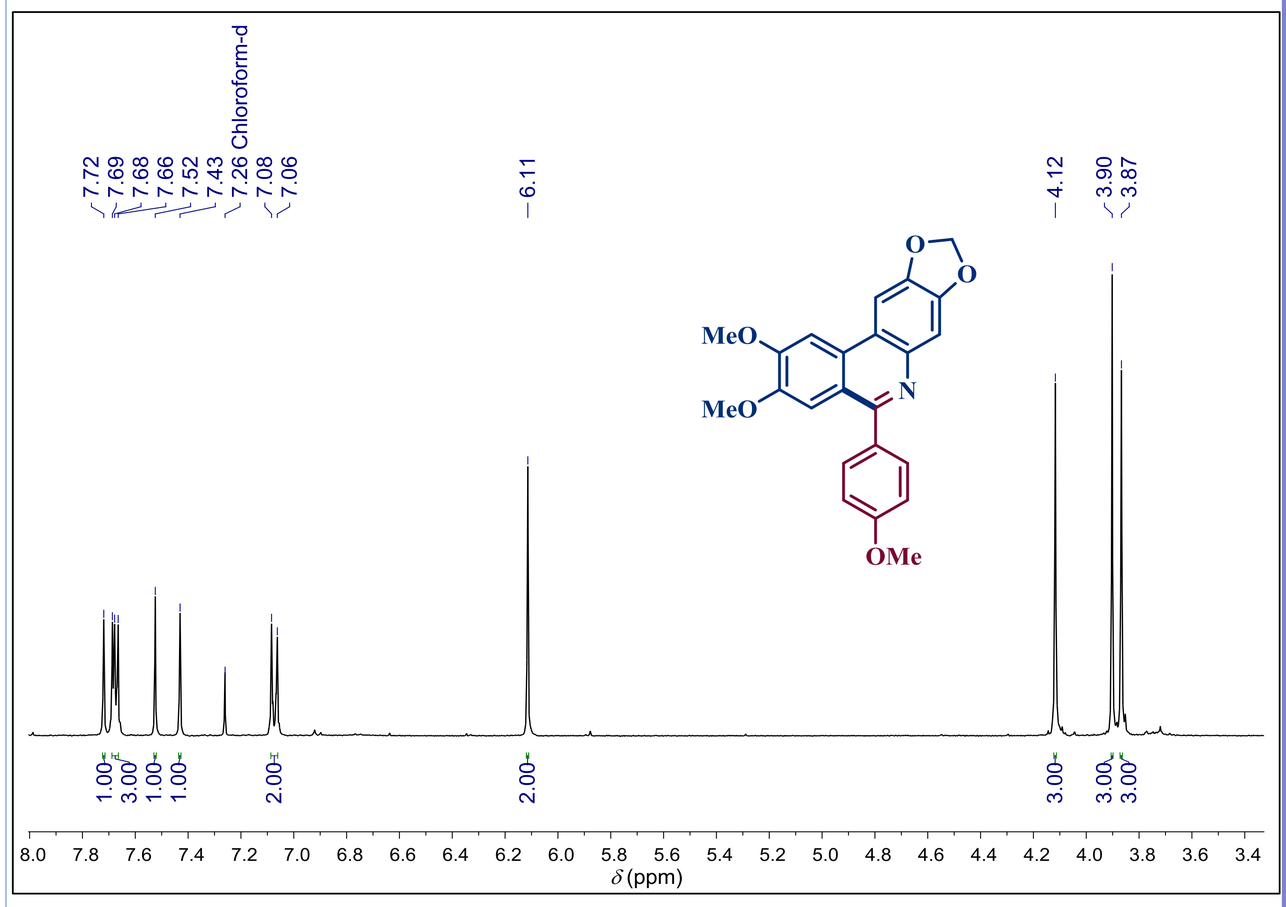


Figure 1. ^1H NMR spectrum of 2,3-dimethoxy-5-(4-methoxyphenyl)-[1,3]dioxolo[4,5-*b*]phenanthridine. Bruker avance 400 MHz.



CONCLUSIONS

In conclusion, we have developed an environmentally friendly methodology to access novel 6-aryl-phenanthridines in short reaction times (1 min in microwave, 20 min conventional heating) in solvents considered "green". The best reaction condition was when the ionic liquid [Bmim]PF_6 and microwave radiation were used with reaction times of 1 min. So far, there is no report in which these *N*-heterocycles are synthesized under conditions consistent with green chemistry.

REFERENCES

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