Synthesis of 2,4,5-triarylimidazoles in aqueous solution, under microwave irradiation†

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A series of 2,4,5-triarylimidazoles was synthesized from a new, highly efficient and green method. The reaction is performed in water, without the presence of any catalyst, and under microwave irradiation. This provides new opportunities for the rapid screening of a wide range of compounds, either for the development of new drugs, or original compounds for the material scientist.

1. Introduction

Imidazoles and more specifically 2,4,5-triarylimidazoles have proven to be key compounds for the synthesis of therapeutic agents (anti-inflamatory,[1,2] analgesic,[3] glucagon receptor antagonists[4]…). In addition, their optical properties (fluorescence[5,6] and chemiluminescence) are of particular concern for material scientists. In this context, they have received great attention for the development of fluorescence labelling agents,[7–9] materials for biological imaging application,[10] blue-light emitting materials,[11] luminophores for optoelectronic applications[12] or chromophores for non linear optic systems.[13] Recently, some distriarylimidazoles have been investigated for their piezochromism, photochromism and thermochromism properties, and the results reported suggest potential applications in molecular photonics and sensing.[14] The synthesis of 2,4,5-triphenylimidazole (Lophine) has been known for a long time.[15,16] Such a compound and its derivatives are principally obtained by a multi-component reaction involving benzil (or a substituted benzil), an aryl aldehyde and ammonium acetate as an ammonia source. In the last decade, increasing interest has been devoted to optimize the reaction conditions in order to reach very high yields and highly pure products. For this purpose, many catalysts have been investigated (silica/sulfuric acid,[17,18] $Yb(OTf)_3$,[19] $NiCl_2{\cdot}6H_2O$,[20] oxalic acid,[21] iodine,[22] sulfanilic acid,[23] tetrabutyl ammonium bromide,[24] cerium ammonium nitrate,[10] $Zr(acac)_4$,[25] $InCl_3{\cdot}3H_2O$[26]…) as well as different activation modes (thermal activation, microwave irradiation[27,28] or ultrasounds[10,25]). These reactions are performed either in solution (AcOH,[19,28] EtOH,[20,22] EtOH–H_2O[21,29,30]), in solventless conditions[17,27,31] or in ionic liquids.[32,33]

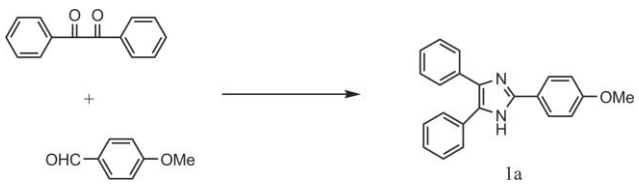
In order to face current environmental preoccupations, the development of green organic syntheses, sustainable and environmentally benign protocols appears essential. In this respect, the replacement of hazardous organic reaction media with water is particularly relevant.

It is well-known that at high temperature, water behaves like a pseudo-organic solvent.[34,35] As a result, some organic reactions can be performed at high temperature in a homogeneous medium, whereas the reactants and/or the products are not soluble in water at room temperature. Since the pioneering work of Strauss and co-workers,[36–38] the development of new synthetic protocols involving both water and microwave irradiation has recently received a considerable interest.[39–41] Some reviews[42,43] report a wide range of chemical reactions (eliminations, reductions, cyclodehydration, Suzuki-coupling…) and recently, a specific attention has been devoted to the synthesis of heterocyclic compounds.[44–48]

In continuation of our work related to the synthesis of aromatic and heterocyclic structures by environmentally-friendly procedures,[49,50] this paper reports a very efficient and green process for the synthesis of 2,4,5-triaryimidazoles, without any catalyst, in water and under microwave irradiation.

2. Results and discussion

In this work, a three-component reaction between benzil, anisaldehyde and ammonium acetate was chosen as a benchmark reaction for the formation of a 2,4,5-triarylimidazole compound (Scheme 1).



Scheme 1 Synthesis of 2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazole.

Pressure and temperature were monitored during the whole reaction by a pressure sensor and an optical fibre dipping in the medium. For safety reasons, a maximum pressure threshold was fixed at 30 bars. Owing to the direct in-core heating nature of microwave irradiation and thanks to an efficient magnetic stirring, a uniform temperature profile was produced in the

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† Electronic supplementary information (ESI) available: Temperature and pressure profiles during reactions, HPLC UV chromatograms, NMR spectra, and synthesis and characterization of a benzoxazole compound. See DOI: 10.1039/b925177d

reaction mixture. The reaction temperature was varied from 180 to 210 °C.

During microwave irradiation, the temperature increase was extremely rapid. One most probable reason is the very efficient microwave heating of aqueous media. In the case of a high irradiation power (800 W), the temperature increase was even faster than the optical fibre time-delay, which results in slightly higher temperatures than the initially fixed temperature (temperature oscillations with maximum values up to 10 °C above the threshold—Fig. 1).

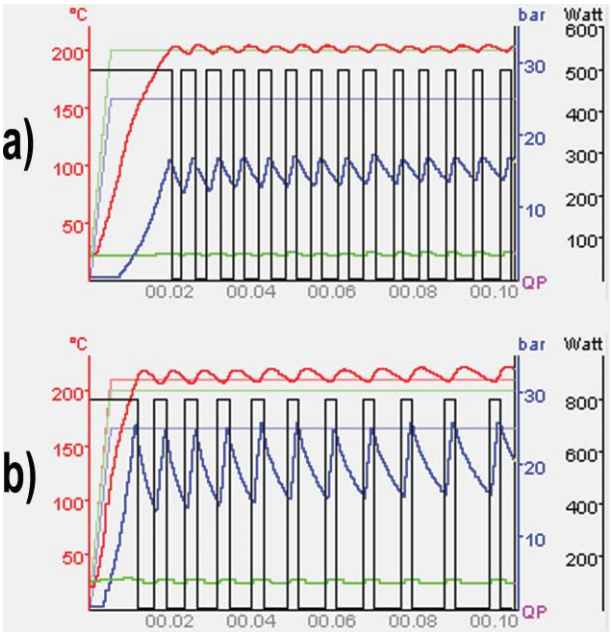


Fig. 1 Typical temperature and pressure profiles recorded during a synthesis of 2,4,5-triarylimidazole. (a) Reaction with 500 W irradiation. (b) Reaction with 800 W irradiation. In red: temperature profile; in blue: pressure profile; in black: irradiation power.

Typically, a maximum pressure of 27 bars was observed during the reaction. The pressure profile (see Fig. 1) recorded as a function of reaction time was not constant, which could be accounted for by different phenomena. Indeed, besides the autogenic pressure of water (leading to a near supercritical character), gaseous ammonia is produced *in situ* (by the thermal decomposition of ammonium acetate) and consumed in the course of the reaction. After cooling, the product formed precipitates, which can be simply isolated by filtration, and rinsed with water. This very convenient work-up avoids time-consuming or energy-costly additional steps such as column chromatography, extraction or re-crystallization, and confers an additional green character to this process. Different parameters such as the reaction time, reaction temperature, and solid content were studied in order to provide optimized reaction conditions. The results are reported in Table 1.

Each crude sample has been analyzed by high performance liquid chromatography (HPLC). The analytical conditions were set up in order to identify the presence of eventual residual reagents as well as the final product. For a given microwave irradiation power, a reaction time increase (entry 5 and 6 *vs.* entry 8 and 10) results in a systematic yield increase,

Table 1 Optimization of 2,4,5-triarylimidazole synthesis in water, under microwave irradiation

Entry	SC (%)[b]	Power/W	Reaction time/min	T_1/°C[c]	T_2/°C[d]	Yield (%)[e]
1	15	500	10	180	188	74
2	15	500	15	180	190	86
3	15	800	10	180	185	79
4	15	500	10	200	205	87
5	15	500	5	210	212	73
6	15	500	10	210	215	89
7	27	500	10	210	216	93
8	27	800	5	210	214	90
9[a]	27	800	10	210	220	88
10	27	800	10	210	219	98

[a] With 5 equivalents of NH_4OAc instead of 10 equivalents. [b] Solid content SC (%) = (theoretical mass of triarylimidazole formed / (theoretical mass of triarylimidazole formed + volume of water)) × 100. [c] Reaction temperature. [d] Maximum observed temperature. [e] Isolated yield, analytically pure compounds obtained after filtration and washing with petroleum ether. For details, see the ESI.†

suggesting that 5 min reaction is not sufficient to complete the reaction. This hypothesis was confirmed by the presence of residual benzyl and aldehyde by HPLC. Besides the triaryl imidazole product (elution time 10.8 min), excepted in entry 10, traces of a secondary product was evidenced (15.7 min). On the basis of a mass spectroscopy analysis, this product was identified as a benzoxazole. The formation of such a compound has already been mentioned by Davidson and coworkers,[51] by the action of ammonia on esters of benzoin. An additional experiment reacting exclusively benzyl and ammonium acetate was performed, and the expected benzoxazole was isolated and thoroughly characterized (see the ESI†), confirming the formation of this species in the course of the reaction.

Whereas this benzoxazole was produced in significant amounts when the reaction was performed in the absence of aldehyde, its proportions remained almost negligible in the typical reaction conditions studied in this work (Fig. 2a). In order to remove any traces of this undesired compound, all crude products were slightly rinsed with petroleum ether, yielding analytically pure compounds (Fig. 2b).

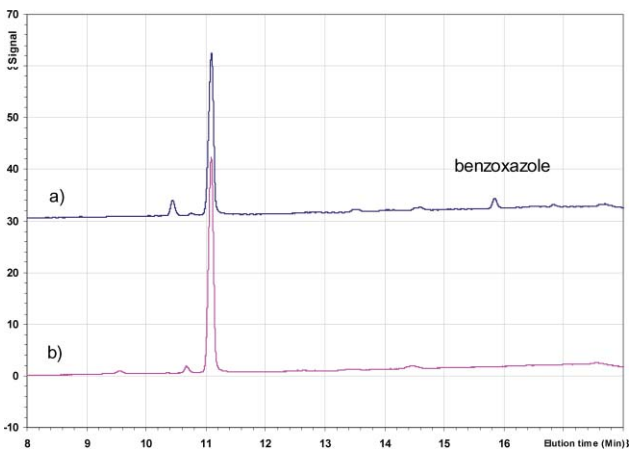
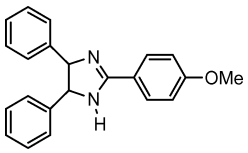
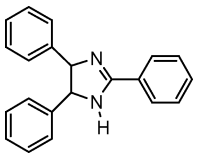
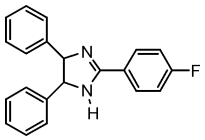
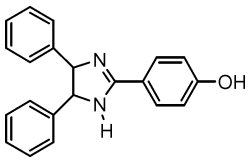
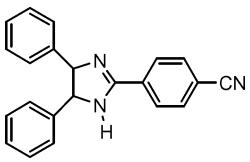
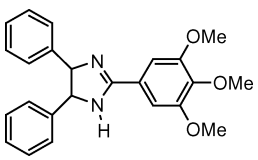
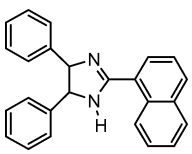
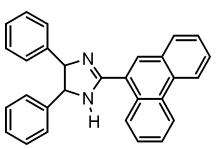
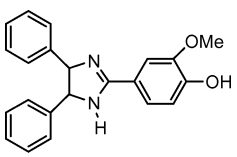


Fig. 2 HPLC traces of (a) crude product and (b) pure product (after washing in petroleum ether).

Table 2 High yield syntheses of various 2,4,5-triarylimidazoles

Entry	Product	Yield (%)[a]	Mp/°C found	Mp/°C (Lit.)
1		98	232–234	230–231[52]
2		81	275–277	275–277[31,52,53]
3		99	251–252	250–251[52]
4		99	256–258	256–257[21]
5		96	264–265	—
6		99	251–253	—
7		96	286–287	—
8		88	267–270	—
9		97	253–254	—

[a] Isolated yield, analytically pure compounds obtained after filtration and washing with petroleum ether. For details, see the ESI.†

From the results obtained, it appeared that the reaction strongly depends on the reaction medium temperature. When the recorded temperature was less than 190 °C, the yields were lower than 85%. The presence of benzil confirmed an incomplete reaction. At higher temperatures (200–220 °C), the yields are better. The reaction time appears also to be important parameter as 5 min irradiation was not sufficient to complete the reaction (entry 6 and 8). The last point concerns the amount of ammonium acetate necessary: 10 equivalents were required whereas 5 equivalents were not sufficient (entry 9). Taking these parameters into account, the optimal reaction conditions were found to be a 10 min reaction at 210 °C (800 W microwave power), using 10 equivalents of ammonium acetate, and in a highly concentrated medium (27 wt%). In these conditions an analytically pure compound was isolated with 98% yield. It is worth mentioning that these reactions are performed using stoichiometric amounts of benzil and aryl aldehyde, and can be realized in a highly concentrated medium, which minimizes the amount of chemical waste. Based on these experimental conditions, different aldehydes have been involved in the three-component reaction to synthesize different 2,4,5-triarylimidazoles. The results are reported in Table 2.

In all cases, excellent yields were obtained, whatever the nature of the substituent present on the aldehyde (electron-donating or electron-withdrawing). This confirms the reliability of the synthetic method. Comparing the results obtained with those reached in solvent-free conditions, in the presence of zeolite HY,[31] the yields obtained in this study are very similar (81% in both cases for the synthesis of product 2, Table 2; 98 and 92% for the synthesis of product 1, Table 2, respectively, in water and in the presence of zeolite HY). This suggests that both processes are very effective.

From an economical point of view, according to the results reported by Gronnow *et al.*,[54] the use of microwave irradiation heating process is expected to significantly reduce (up to 85-fold) the amount of energy required to perform the reaction (by comparison with what would be necessary in a thermal conventional way). In this respect, this procedure can also be considered as a green process.

3. Experimental

3.1 Characterization and methods

Microwave experiments were performed with a Milestone ETHOS multi-mode dedicated oven. NMR spectra were recorded on a Bruker 200 MHz spectrometer. Deuterated dimethylsulfoxide (DMSO-d_6 + ATF) was used as solvent. Tetramethylsilane (TMS) was used as chemical shift reference. Melting points were measured by using the capillary method, on a STUART SMP3 melting-point apparatus, at 2 °C min^{-1}. All spectra were recorded at 25 °C. HPLC analyses were carried out using an Agilent Technologies instrument (1200 series) equipped with a LC/MSD (1956A)VL mass detector. Separation was performed on a Modulo-cart QK Uptisphere 5HDO column (150*2.0 mm—5 microns). The experimental conditions were the following: $T = 0$ min. 70% H_2O (pH = 7)–30% CH_3CN / $T = 15$ min. 100% CH_3CN—$T = 20$ min. 100% CH_3CN—back to initial conditions—oven temp. = 40 °C—flow: 0.4 ml min^{-1}.

In these experimental conditions, the eventual presence of anisaldehyde and benzyl were respectively evidenced by their elution at 4.8 min and 10.4 min.

3.2 2,4,5-Triarylimidazole synthesis

Optimized general procedure for the preparation of 2,4,5-triarylimidazole:

Benzil (1.8 g, 8.5 mmol), aldehyde (8.5 mmol) and ammonium acetate (6.6 g, 85 mmol) were suspended in 7.5 mL of water in a high pressure Teflon reactor equipped with a magnetic stir bar, a pressure sensor and an optical fibre. The reaction mixture was submitted to microwave irradiation in a Milestone Ethos multi-mode cavity at 800 W for 10 min. For security reasons, the maximum temperature allowed was set to 210 °C and the maximum pressure was 25 bars. Pressure and temperature were monitored during the whole reaction by a pressure sensor and an optical fibre dipping in the medium. The temperature and pressure profiles recorded for all compounds syntheses are reported in supporting informations. After cooling, the crude product was isolated by simple filtration. The resulting compounds were further rinsed with water, petroleum ether and dried under vacuum at 50 °C, to afford an analytically pure products (see thorough characterization in the ESI†).

4. Conclusions

In this paper, the efficient synthesis of 2,4,5-triarylimidazoles in water, under microwave irradiation and without catalyst has been described. The three-component reaction involving benzil, an aryl aldehyde and ammonium acetate proceed expeditiously (completion of the reaction within 10 min) and with excellent yields (from 88 to 99% yields, in analytically pure and isolated compounds). A wide range of aromatic aldehydes were tested, bearing either electron-donating or electron-withdrawing substituents, suggesting that this method can be used to synthesize a large variety of compounds. It has therefore been demonstrated that using water as the solvent and microwave irradiation as the heating source is ideally suited for the synthesis of 2,4,5-triarylimidazoles. This high throughput method can be considered as a green process, as it fulfils many required criteria, including the use of an environmentally friendly solvent (water), cost effectiveness thanks to microwave heating efficiency, a convenient and rapid isolation procedure (simple filtration), no catalyst, and minimum chemical waste. Such a green and efficient process provides new opportunities for the rapid screening of a wide range of compounds, either for the development of new drugs, or original compounds for the material scientist. In the emerging field of green chemistry, the synthetic strategies involving processes associating water and microwave irradiation open new perspectives for the sustainable development of environmentally friendly chemistry and technology.

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