Monatshefte für Chemie 137, 1189–1194 (2006)
DOI 10.1007/s00706-006-0518-9

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Efficient Elemental Iodine Catalyzed One-Pot Synthesis of 2,4,5-Triarylimidazoles

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Received February 2, 2006; accepted (revised) March 7, 2006
Published online August 24, 2006

Summary. Elemental iodine is used as an efficient catalyst for the synthesis of 2,4,5-triarylimidazoles in excellent yields *via* condensation of benzoin, ammonium acetate, and aromatic aldehydes. This is a simple, one-pot, high yielding technique using cheap, non-toxic iodine in catalytic amounts.

Keywords. Elemental iodine; 2,4,5-Triarylimidazoles; Benzoin; Ammonium acetate; Aromatic aldehyde.

Introduction

Compounds with an imidazole ring system are biologically important due to its role in biochemical processes. Substituted imidazoles are well known as inhibitors of P38MAP kinase [1], fungicides and herbicides [2], plant growth regulators [3], and therapeutic agents [4]. Imidazole chemistry, because of its use in ionic liquids [5] and in N-heterocyclic carbenes (NHCs) [6], gave a new dimension in the area of organometallics and ''Green Chemistry''. There are several methods reported for the synthesis of substituted imidazoles [7]. Many of the synthesis protocols for imidazoles reported so far suffer from one or more disadvantages, such as harsh reaction conditions, poor yields, longer reaction time periods, and the use of hazardous and often expensive acid catalysts. In addition, a new method based on a reaction strategy using microwave heating in the solid state has been presented [8], but this requires special instrumentation. Moreover, the syntheses of these heterocycles have been carried out in *DMF*, *DMSO*, and acetic acid leading to complex isolation and recovery procedures.

Thus, the development of a simple, efficient, and versatile method for the preparation of 2,4,5-triarylimidazoles **4** is an active area of research with a scope for further improvements towards milder reaction conditions and higher product yields. In recent times, the use of elemental iodine has received considerable

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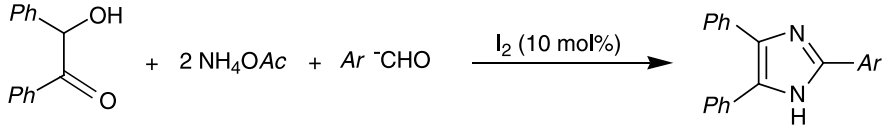
attention as an inexpensive, non-toxic, and readily available catalyst for various organic transformations [9]. The mild *Lewis* acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. During the course of our studies towards the development of new routes to the synthesis of biologically active heterocycles [10], we wish to report a simple and efficient method for the synthesis of 2,4,5-triarylimidazoles **4**.

Results and Discussions

In the present communication we report the condensation of benzoin (**1**), ammonium acetate (**2**), and aromatic aldehydes **3** catalyzed by iodine (Scheme 1). Initially, a systematic study was carried out for catalytic evaluation of iodine for benzaldehyde (Table 1).

The reaction went to completion in 2 h at room temperature with 10 mol% I_2. Accordingly, 10 mol% was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher molar ratios of I_2 were used. However, no product formation was observed in absence of I_2. Toluene, acetonitrile, dichloromethane, and ethanol were suitable solvents, but we proceeded with ethanol,



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

Scheme 1

Table 1. Catalytic evalulation of iodine for the synthesis of **4**[a]

Entry	$c(I_2)$/mol%	Time/h	Yield/%[b]
1	0	4	0
2	5	2	78
3	10	2	97
4	15	1.5	99
5	30	1	99

[a] Product **4a** from benzoin:NH_4OAc:benzaldehyde (**3a**) = 1:2.5:1 at room temperature; [b] isolated and unoptimized yields

Table 2. Effect of temperature on the yields of **4**[a]

Entry	Temperature/°C	Time/min	Yield/%[b]
1	room temperature	120	97
2	45	40	97
3	60	25	97
4	75	15	98

[a] Product **4a** from benzoin:NH_4OAc:benzaldehyde (**3a**) = 1:2.5:1 with 10 mol% I_2; [b] isolated and unoptimized yields

Table 3. Synthesis of 2,4,5-triarylimidazoles **4**[a]

Entry	**3**	*Ar*	Time/min	Product	Yield/%[b]
1	**3a**	C_6H_5	15	**4a**	98
2	**3b**	*p*-*Me*OC_6H_4	30	**4b**	96
3	**3c**	*o*-HOC_6H_4	20	**4c**	94
4	**3d**	*p*-ClC_6H_4	28	**4d**	98
5	**3e**	*m*-$NO_2C_6H_4$	25	**4e**	97
6	**3f**	*p*-HOC_6H_4	20	**4f**	93
7	**3g**	2-thienyl	20	**4g**	94
8	**3h**	3,4-piperonyl	20	**4h**	97

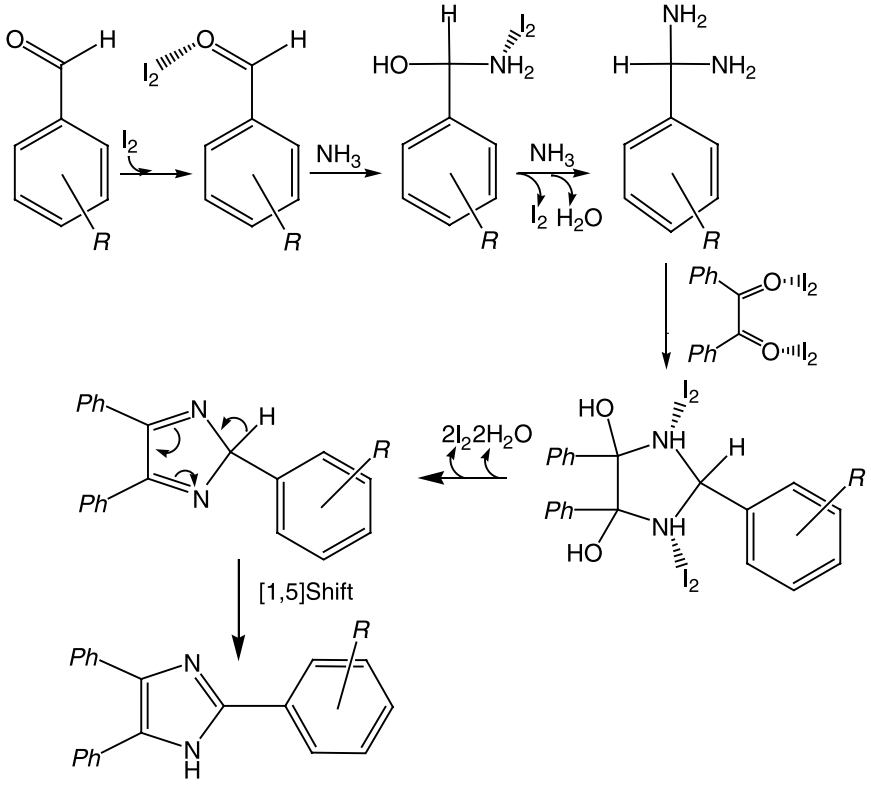
[a] Product **4a** from benzoin:NH_4OAc:benzaldehyde (**3a**) = 1:2.5:1 with 10 mol% I_2 at 75°C; [b] isolated and unoptimized yields

which is considered as a relatively benign organic solvent. It is important to note that in case of ethanol, imidazoles **4** precipitated on dilution of the reaction mixture with an aqueous solution of $Na_2S_2O_3$ and were isolated by simple filtration whereas in other solvents hazardous solvents for the extraction of the products were required. At room temperature, we observed product **4a** after 2 h, however, with increase in temperature, **4a** was obtained within a few minutes (Table 2).

Encouraged by these results, we have extended the methodology to a variety of aldehydes, which are summarized in Table 3. This method is effective for the preparation of **4** from both electron efficient as well as electron deficient aromatic aldehydes **3**. The aryl groups substituted with different groups and also the same groups located at different positions of the aromatic ring did not show any effect on the formation of **4**. However, there are several reports on the synthesis of **4** using 1,2-diketones but α-hydroxyketone usage as a starting material *viz*. benzoin **1**, which we have used, is not very often reported in literature. 1,2-Diketones, such as benzil are usually prepared from benzoin **1** catalyzed by various toxic oxidants [11]. It is worth noting here that the direct use of **1** in our methodology constitutes a significant improvement in the synthesis of **4**. A nearly stoichiometric amount of ammonium acetate was used in the course of the reaction, whereas previously a many-fold of ammonium acetate was required. This is an additional advantage of the novel methodology.

Initially, it was thought that the possible pathway is *via* an imidazoline. The subsequent condensation and intramolecular cyclization of α-aminoketone and aldimine leads to the imidazoline, which dehydrogenates to **4**. It seems probable that the fully conjugated nature of the product results in rapid oxidation aided by I_2, which is a mild oxidizing agent. However, the possibility of dehydrogenation of an imidazoline was ruled out because such kind of oxidation requires stoichiometric amounts of the oxidizing agent and in the present case we obtained the product in excellent yield with only 10 mol% I_2. Alternatively, the probability that **1** itself undergoes aerial oxidation to benzil under these conditions was explored. Thus, two sets of control reactions were carried out to confirm the aerial oxidation. To our surprise, **1** was converted to benzil when refluxed with 10 mol% I_2 for 1 h whereas in absence of I_2, only trace amounts of benzil were detected after 24 h. The same set of reactions was performed under N_2. Under these conditions no trace of benzil was observed (TLC). This shows that aerial oxidation takes place and I_2 only facilitates/catalyzes the transformation. The benzil so formed is a well-known substrate for the synthesis of **4** and can react as shown in Scheme 2.

Molecular I_2 is capable of binding with the carbonyl oxygen increasing the reactivity of the parent carbonyl compound. Iodine facilitates the formation of the diimine intermediate, which under mild



Scheme 2

acid catalysis of I_2 condenses further with the carbonyl carbon of the 1,2-diketone followed by dehydration to afford the iso-imidazole, which rearranges *via* a [1, 5] sigmatropic shift to the required 2,4,5-triarylimidazole **4**.

In conclusion, we have shown that I_2 is an excellent catalyst for the one-pot three-component synthesis of 2,4,5-triarylimidazoles **4**. This simple methodology represents an alternative to existing procedures. This is the first report of an iodine catalyzed synthesis of 2,4,5-triarylimidazoles from benzoin and thus, this new methodology opens an important alternative by the use of elemental iodine.

Experimental

Melting points were determined using a *Thomas Hoover* melting point apparatus. IR spectra were obtained on a Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance Spectrospin 300 (300 and 75 MHz) using *TMS* as internal standard. Elemental analyses were performed on a Hereaus CHN Rapid analyser and the results were found to be in good agreement with the calculated values. Mass spectra were recorded on a JEOL JMS-DX 303. The temperature of the reaction mixture was measured by means of a non-contact infrared thermometer (AZ, Mini Gun type, model 8868). The purity of compounds was checked by TLC on aluminum plates coated with silica gel (Merck).

*General Procedure for the Synthesis of 2,4,5-Triarylimidazoles **4***

A mixture of 10 mmol **1**, 10 mmol **2**, 10 mmol aromatic aldehyde **3**, and I_2 (10 mol%) in 2 cm^3 ethanol was stirred at 75°C for the time specified in Table 3. The completion of the reaction was monitored by

TLC. After completion of reaction, the reaction mixture was diluted with H_2O (containing 15% $Na_2S_2O_3$). The solid products, which separated, were filtered off, washed with H_2O, and dried. The crude products thus obtained were pure and subjected to further purification by column chromatography on silica gel (60–120 mesh size) using 25% ethylacetate in petroleum ether as eluent to yield **4**.

2,4,5-Triphenyl-1H-imidazole (**4a**)
Mp 272–274°C (Ref. [7a] 276–277°C); IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are in accordance with published data [7h, 8f].

2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (**4b**)
Mp 222–224°C (Ref. [7b] 222°C); IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are in accordance with published data [7h, 8f].

2-(4,5-Diphenyl-1H-imidazol-2-yl)phenol (**4c**)
Mp 202–204°C (Ref. [7d] 202°C); IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are in accordance with published data [7h, 8f].

2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (**4d**)
Mp 262–264°C (Ref. [7c] 261–262°C); IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are in accordance with published data [8f].

2-(3-Nitrophenyl)-4,5-diphenyl-1H-imidazole (**4e**)
Mp 300–305°C (Ref. [8f] >300°C); ^{13}C NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 122.7$, 124.2, 127.9, 128.5, 129.4, 132.8, 133.1, 146.3, 157.8 ppm; IR, ^{1}H NMR, and mass spectra are in accordance with published data [8f].

4,5-Diphenyl-2-thien-2-yl-1H-imidazole (**4f**)
Mp 255–256°C (Ref. [8b] 254–255°C); ^{13}C NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 122.2$, 125.3, 126.2, 126.5, 127.40, 128.13, 129.4, 136.7, 141.35 ppm; IR, ^{1}H NMR, and mass spectra are in accordance with published data [8b].

4-(4,5-Diphenyl-1H-imidazol-2-yl)phenol (**4g**)
Mp 260–261°C (Ref. [7d] 256–257°C); IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are in accordance with published data [7h 8f].

2-Benzo[1,3]dioxol-5-yl-4,5-diphenyl-1H-imidazole (**4h**)
Mp 248–250°C (Ref. [8f] 300°C); ^{13}C NMR ($CDCl_3$/*DMSO*-d_6): $\delta = 92.8$, 113.6, 117.2, 121.3, 122.7, 126.3, 127.3, 129.1, 136.8, 147.8, 149.7 ppm; IR, ^{1}H NMR, and mass spectra are in accordance with published data [8f].

Acknowledgements

P. M. thanks the Council of Scientific and Industrial Research, New Delhi, for the award of a Junior Research Fellowship.

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