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A one-pot synthesis of 1,2,4,5-tetraarylimidazoles using molecular iodine as an efficient catalyst

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Abstract—Molecular iodine is a cheap, nontoxic catalyst, which acts as an efficient catalyst for the synthesis of 1,2,4,5-tetraarylimidazoles using benzoin, an aromatic aldehyde and an amine in the presence of ammonium acetate. The advantage of this method is the direct use of benzoin, which is transformed into benzil in situ and condenses further to generate the imidazole in a one-pot sequence.

The prevalence of imidazole in natural products and pharmacologically active compounds has resulted in a number of synthetic approaches to these heterocycles. However, despite intensive efforts, only a handful of general methods exist for the construction of highly substituted imidazoles. Highly substituted imidazoles could potentially have novel therapeutic activities[1] and thus efforts towards obtaining tetrasubstituted imidazoles have increased. There are several methods reported in the literature for the synthesis of highly substituted imidazoles which include a four component condensation using Wang's resin in refluxing acetic acid,[2] condensation of diones, aldehydes, primary amines and ammonium acetate in phosphoric acid,[3] and in acetic acid,[4] using an organocatalyst in acetic acid,[5] as well as in H_2SO_4[6] and DMSO,[7] N-alkylation of trisubstituted imidazoles,[8] condensation of benzoin or benzoin acetate with an aldehyde, a primary amine and ammonia in the presence of copper acetate,[9] cyclisations of sulfonamides with mesoionic 1,3-oxazolium-5-olates,[10] condensation of β-carbonyl-*N*-acyl-*N*-alkylamines with ammonium acetate in refluxing acetic acid[11] and conversion of *N*-2-oxoamides with ammonium trifluoroacetate[12] under neutral conditions.

However, most of these procedures are lengthy and require expensive and hazardous acid catalysts and result in poor yields. Synthetic alternatives are many and varied, and have resorted to harsh conditions, for example, the formamide synthesis, which requires excess reagents, H_2SO_4 as a condensing agent and high temperature (150–200 °C) affording 40–90% yields of product in 4–6 h. Additionally, reagents for these procedures are not readily or commercially available which is a key deficiency when developing conditions for library synthesis. Therefore, the development of simple, efficient, inexpensive, nontoxic and readily available reagents providing convenient procedures with improved yields, are necessary. Owing to its unique catalytic properties, iodine has been extensively used for a plethora of organic reactions.[13–15]

In a broad programme of developing efficient, selective and eco-friendly synthetic methods for pharmacologically important moieties,[16–18] we explored the catalytic activity of iodine. Herein, we report a simple, rapid and one-pot procedure for the synthesis of 1,2,4,5-tetraarylimidazoles using iodine as the catalyst (Scheme 1).

Initially, a catalytic evaluation of iodine using benzaldehyde **4a** was carried out (Table 1).

The reaction was carried out by adding benzoin **1**, aniline **2** and ammonium acetate **3** to a solution of benzaldehyde **4a** and iodine in ethanol at room temperature. The reaction was complete in 50 min when 10 mol % of iodine was used. Rate enhancement was observed when higher mol ratios were used but no significant improvement in the yield was observed.

Keywords: Molecular iodine; Benzoin; Benzil; 1,2,4,5-Tetraarylimidazoles.
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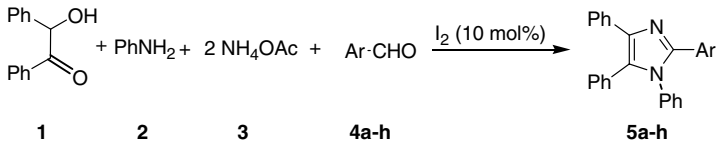


Scheme 1. Iodine catalysed four component synthesis of 1,2,4,5-tetraarylimidazoles.

Table 1. Catalytic activity evaluation for imidazole[a] synthesis

Entry	Iodine (mol %)	Time	Yield[b] (%)
1	0	6 h	0
2	5	3 h	76
3	10	50 min	96
4	15	40 min	97
5	30	30 min	97

[a] 1 equiv of benzoin–1 equiv of **4a**–1 equiv of NH_4OAc–1 equiv of aniline at room temperature.
[b] Isolated and unoptimised yields.

Table 2. Effect of temperature on iodine catalysed imidazole[a] synthesis

Entry	Aldehyde	Product	Temperature (°C)	Time (min)	Yield[b] (%)
1	**4a**	**5a**	Room temperature	50	96
2	**4a**	**5a**	45	40	98
3	**4a**	**5a**	60	30	97
4	**4a**	**5a**	75	20	98

[a] Product **5a** from 1 equiv benzoin–1 equiv of **4a**–1 equiv of NH_4OAc–1 equiv of aniline using 10 mol % of I_2.
[b] Isolated and unoptimised yield.

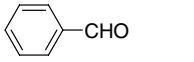
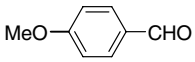
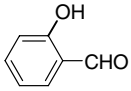
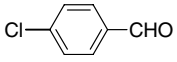
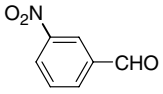
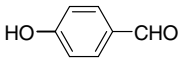
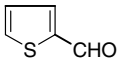
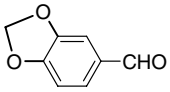
To determine the most appropriate solvent, the reaction was examined using ethanol, dichloromethane, acetonitrile, toluene and xylene. Ethanol and dichloromethane were the best solvents in terms of yields. Ethanol being a 'cleaner' reaction medium was favoured as water could be used for the work-up. Faster reactions occurred on increasing the temperature (Table 2).

Various aldehydes **4a**–**h** (electron withdrawing, electron donating) exemplify the versatility of this simple protocol (Table 3).

Although there are several papers reporting the synthesis of 1,2,4,5-tetraarylimidazoles using 1,2-diketones, there are very few reports in the literature using α-hydroxyl ketones as the starting material. It is worth noting here that 1,2-diketones such as benzil are usually prepared from benzoin **1** catalysed by various toxic oxidants.[19–22] We found that our methodology works very well for α-hydroxyl ketones such as benzoin **1**. Consequently, the direct use of benzoin in our methodology constitutes a significant improvement in the synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a**–**h** in terms of green chemistry.

It is possible that the Lewis acidity of iodine may promote the formation of an α-amino ketone and aryl aldimine, which then condense to form an imidazoline

Table 3. Iodine promoted synthesis of 1,2,4,5-tetraarylimidazoles[a]

Entry	Aldehyde	Product	Time (min)	Yield[b] (%)	Reference
1		**5a**	20	96	8
2		**5b**	20	94	20
3		**5c**	30	97	20
4		**5d**	25	98	21
5		**5e**	30	98	25
6		**5f**	20	97	22
7		**5g**	25	95	25
8		**5h**	25	95	25

[a] 1 equiv of benzoin–1 equiv of **4a**–**h**–1 equiv of NH_4OAc–1 equiv of aniline with 10 mol % of I_2.
[b] Isolated and unoptimised yield.

which is oxidised by iodine to the imidazole. Such oxidation requires a stoichiometric amount of iodine whereas we observed an excellent yield with only 10 mol % of iodine. Hence, this possibility was ruled out and the alternative possibility of benzoin undergoing aerial oxidation to benzil under these conditions was investigated. Thus two sets of control reactions were carried out (Fig. 1).

In the case of refluxing with 10 mol % of iodine, benzoin was oxidised to benzil surprisingly after 1 h whereas only a trace amount was detected after 24 h without iodine. Another set of control reactions under a nitrogen

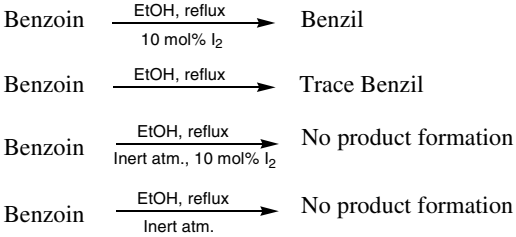


Figure 1.

atmosphere with or without 10 mol % iodine did not give any product. The reactions in Figure 1 highlight the role of molecular iodine in promoting the aerial oxidation to benzil. There are earlier examples of iodine based oxidation of benzoin to benzil under basic conditions,[23] therefore this is not a conceptually unprecedented process.

The Lewis acidity of iodine makes it capable of binding with the aldehyde carbonyl oxygen increasing the reactivity of the parent carbonyl compounds. Iodine reacts initially with aldehyde **4** to produce a diamine intermediate, which condenses with the activated benzil and subsequent elimination of water affords 1,2,4,5-tetraarylimidazoles **5a**–**h**.

In summary, we have developed a simple, convenient and efficient synthetic protocol for 1,2,4,5-tetraarylimidazoles using cheap, readily available and nontoxic iodine in a catalytic amount.[24]

Acknowledgements

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References and notes

1. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. T.; Kumar, S.; Green, D.; McKulty, D.; Blumenthal, M.; Heys, J. R.; Landvatter, S. W.; Strikler, J. E.; McLaughlin, M. M.; Siemen, I. R.; Fisher, S. M.; Livi, G. P.; White, J. R.; Adams, J. L.; Young, P. R. *Nature* **1994**, *372*, 739.
2. Zhang, C.; Moran, E. J.; Woiwade, T. F.; Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 751.
3. Liu, J.; Chem, J.; Zhao, J.; Zhao, Y.; Li, L.; Zhang, H. *Synthesis* **2003**, 2661.
4. Sarshar, S.; Siev, D.; Mjalli, A. M. M. *Tetrahedron Lett.* **1996**, *37*, 835.
5. Frantz, D. E.; Morency, L.; Soheilli, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. O. *Org. Lett.* **2004**, *6*, 843.
6. Weinmann, H.; Hahhe, M.; Koeing, K.; Mertin, E.; Tilstam, U. *Tetrahedron Lett.* **2002**, *43*, 593.
7. Clark, N. G.; Cawkill, E. *Tetrahedron Lett.* **1975**, 2717.
8. Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 319.
9. Lipshutz, B. H.; Morey, M. C. *J. Org. Chem.* **1983**, *48*, 3745.
10. Consonni, R.; Croce, P. D.; Terracioli, R.; Rosa, C. L. *J. Chem. Res. (S)*. **1991**, 188.
11. Evans, D. A.; Lundy, K. M. *J. Am. Chem. Soc.* **1992**, *114*, 1495.
12. Caliborne, C. T.; Liverton, K. J.; Kguyen, K. T. *Tetrahedron Lett.* **1998**, *39*, 8939.
13. Cooke, L. A.; Frauendorf, C.; Gilea, M. A.; Holmes, S. C.; Vyles, J. S. *Tetrahedron Lett.* **2006**, *47*, 719.
14. Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-Fa. *Tetrahedron Lett.* **2005**, *46*, 6345.
15. Jianwei, S.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932.
16. Kidwai, M.; Saxena, S.; Khan, M. R. K.; Thukral, S. S. *Eur. J. Med. Chem. Lett.* **2005**, *40*, 816.
17. Kidwai, M.; Mothsra, P.; Mohan, R.; Biswas, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 915.
18. Kidwai, M.; Mothsra, P. *Synth. Commun.* **2006**, *36*, 817.
19. McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3641.
20. Heinz, J.; Baumgaertel, H.; Zimmermann, H. *Chem. Ber.* **1968**, *101*, 3504.
21. Park, S.; Know, Oh-Hoon.; Kim, S.; Park, S.; Choi, M.-G.; Cha, M.; Park, S. Y.; Jang, Du.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10070.
22. Buttke, K.; Baumgaertel, H.; Nicolas, H. J.; Scheider, M. *J. Parkt. Chem.* **1997**, *339*, 721.
23. Corson, B. B.; McAllister, R. W. *J. Am. Chem. Soc.* **1929**, *51*, 2822.
24. *General procedure for the synthesis of 1,2,4,5-tetraarylimidazoles* **5a**–**h**: A 50 ml round bottom flask was charged with benzoin **1** (10 mmol), aniline **2** (10 mmol), ammonium acetate **3** (10 mmol), aromatic aldehyde **4a**–**h** (10 mmol) and iodine (10 mol %) followed by 5 ml of ethanol. The mixture was then stirred at 75 °C until the reaction was complete (TLC). The reaction mixture was treated with aqueous $Na_2S_2O_3$ solution. The solid imidazole product that separated out, filtered, then washed with water and dried. The crude product, thus obtained was subjected to purification by column chromatography on silica gel (60–120 mesh size) using 25% ethyl acetate in petroleum ether as eluent to yield 1,2,4,5-tetraarylimidazoles **5a**–**h**. The structures of all the products were unambiguously established on the basis of spectral analysis (IR, ^{1}H, ^{13}C NMR and mass spectral data).
25. Spectral data for novel compounds:
2-(3-Nitrophenyl)-1,4,5-triphenyl-1*H*-imidazole (**5e**). Mp 244–246 °C; IR (cm^{-1}, Nujol): 1597 (C=C), 1576 (C=N); ^{1}H NMR ($CDCl_3$/DMSO, 300 MHz): δ 7.31–7.68 (m, 15H), 7.81–8.23 (m, 4H); ^{13}C NMR ($CDCl_3$/DMSO, 75 MHz): δ 123.1, 125.2, 126.0, 128.0, 128.2, 128.4, 128.6, 128.7, 129.9, 130.7, 133.1, 134.6, 137.1, 137.4, 144.3, 153.4; $C_{27}H_{19}N_3O_2$ (417): calcd C, 77.68; H, 4.59; N, 10.07. Found C, 77.69; H, 4.55; N, 10.15.
1,4,5-Triphenyl-2-thiophen-2-yl-1*H*-imidazole (**5g**). Mp 247–251 °C; IR (cm^{-1}, Nujol): 1596 (C=C), 1577 (C=N); ^{1}H NMR ($CDCl_3$/DMSO, 300 MHz): δ 6.73–6.86 (m, 2H), 7.14–7.23 (m, 15H), 7.58–7.61 (m, 1H); ^{13}C NMR ($CDCl_3$/DMSO, 75 MHz): δ 125.3, 126.3, 126.5, 127.0, 127.4, 128.1, 128.4, 129.1, 129.4, 130.0, 131.0, 132.9, 134.0, 132.9, 134.1, 136.1, 136.8, 141.4; $C_{25}H_{18}N_2S$ (378): calcd C, 79.33; H, 4.79; N, 7.40. Found C, 79.33; H, 4.68; N, 7.43.
2-Benzo[1,3]dioxol-5-yl-1,4,5-triphenyl-1*H*-imidazole (**5h**). Mp 194–195 °C; IR (cm^{-1}, Nujol): 1596 (C=C), 1572 (C=N); ^{1}H NMR ($CDCl_3$/DMSO, 300 MHz): δ 6.01 (s, 2H), 6.96–7.42 (m, 18H); ^{13}C NMR ($CDCl_3$/DMSO, 75 MHz): δ 91.6, 113.2, 116.7, 120.9, 125.9, 126.3, 126.6, 127.4, 128.1, 128.3, 129.4, 130.2, 131.0, 132.8, 134.2, 136.6, 137.3, 147.3, 148.1; $C_{28}H_{20}N_2O_2$ (416): calcd C, 80.75; H, 4.84; N, 6.73. Found C, 80.78; H, 4.82; N, 6.78.