One-Pot Synthesis of 2,4,5-Triaryl-1*H*-imidazoles from Arylaldehydes, Benzyl Alcohols, or Benzyl Halides with Hexamethyldisilazane in Molten Tetrabutylammonium Bromide

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Abstract: A simple and efficient method for the synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives in good to excellent yields by reaction between hexamethyldisilazane and arylaldehydes, benzyl alcohols, benzyl halides in molten tetrabutylammonium bromide as an inexpensive and non toxic solvent has been developed. The remarkable advantages of this method are the simple workup procedure, high yields of products, the use of an ionic liquid as a green solvent, and the availability of reagents.

Key words: 2,4,5-triaryl-1*H*-imidazole, hexamethyldisilazane, ionic liquids, aldehydes

2,4,5-Triaryl-1*H*-imidazoles have gained the remarkable importance due to their widespread biological activity and their use in synthetic chemistry. The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds, such as the antiulcerative agent cimetidine,[1] inhibitors of P38MAP kinase,[2] fungicides and herbicides,[3] plant growth regulators,[4] and therapeutic agents.[5] Trifenagrel[6] is a 2,4,5-triaryl-1*H*-imidazole that reduces platelet aggregation in several animal species and humans.

Due to their great importance, many synthetic strategies have been developed. In 1882, Adziszewski and Japp reported the first synthesis of an imidazole from a 1,2-dicarbonyl compound, various aldehydes, and ammonia, giving 2,4,5-triphenyl-1*H*-imidazoles.[7,8] Also, Grimmett et al. proposed the synthesis of imidazole using nitriles and esters.[9]

Recently, there have been several methods reported in the literature for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzil/benzoin, aldehydes, and ammonium acetate using different catalyst such as zeolite HY/silica gel,[10] zirconium tetrachloride,[11] nickel(II) chloride hexahydride,[12] iodine,[13] sodium bisulfite,[14] acidic aluminum oxide,[15] acetic acid,[16] ammonium acetate,[17] ytterbium triflate.[18,19] The application of these methods suffer from some disadvantages such as the use of costly or less easily available reagents, harsh reaction conditions, long reaction times, poor yields, and the use of toxic solvents. Therefore, despite a number of precedents, an efficient, practical and facile method for these transformations is desired.

Today, one of the biggest problems of chemists is the use of hazardous and unrecoverable chemicals that pollute the world. The use of ionic liquids as reaction media and catalyst can offer a solution to solvent emission and catalyst recycle problems.[19] Ionic liquids possess a number of interesting properties, especially their lack of vapor pressure, a widely accessible temperature range with lack of flammability, and ease of product recovery that reduce environmental emissions.[20]

In a further extension of our work in the context of economical chemistry,[21] herein, we would like to report the use of molten tetrabutylammonium bromide as an inexpensive ionic liquid for the efficient one-pot synthesis of 2,4,5-triaryl-1*H*-imidazoles **1** (Table 1) in high yields.

Among the various ionic liquids {tetrabutylphosphonium bromide, tetrabutylammonium chloride, tetrabutylammonium fluoride, and butylpyridinium tetrachloroferrate ([bpy]$FeCl_4$)} studied for this reaction, molten tetrabutylammonium bromide gave better yields with short reaction times. However, in the absence of an ionic liquid, the reaction did not yield any product even after a long reaction time (15–20 h).

We initially performed the reaction with benzaldehyde derivatives and hexamethyldisilazane in molten tetrabutylammonium bromide at 100 °C in presence of trifluoromethanesulfonic acid–silica gel as catalyst, 2,4,5-triaryl-1*H*-imidazole derivatives **1** were formed in high yields (Table 1).

The proposed mechanism for this reaction is given in Scheme 1.

In continuation of this work, we were interested in expanding this method by using benzylic alcohols and benzylic halides. These reagents were separately treated with bismuth(III) nitrate pentahydrate and hexamethyldisilazane in molten tetrabutylammonium bromide at 100 °C; 2,4,5-triaryl-1*H*-imidazole derivatives **1** were formed in high yields (Table 1).

In conclusion, we have demonstrated a new, straightforward, and efficient method for the one-pot synthesis of 2,4,5-triaryl-1*H*-imidazole derivatives using molten tetrabutylammonium bromide as a commercially available

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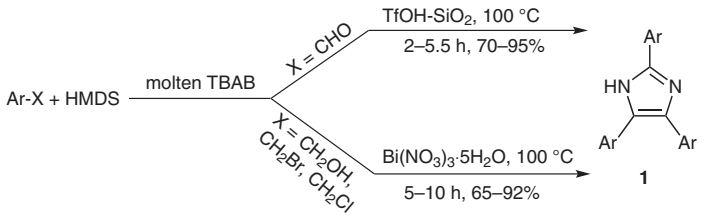
Table 1 Reaction of Arylaldehydes, Aryl Alcohols, Aryl Halides with Hexamethyldisilazane To Form 2,4,5-Triaryl-1*H*-imidazoles



Entry	Ar	X	Product[a]	Time (h)	Yield[b] (%)
1	Ph	CHO	**1a**	3.5	90
2	4-ClC_6H_4	CHO	**1b**	3.5	92
3	4-$O_2NC_6H_4$	CHO	**1c**	3	90
4	2-ClC_6H_4	CHO	**1d**	3.5	95
5	3-$O_2NC_6H_4$	CHO	**1e**	3	92
6	2-furyl	CHO	**1f**	2	95
7	4-MeC_6H_4	CHO	**1g**	5.5	70
8	4-$MeOC_6H_4$	CHO	**1h**	5	75
9	Ph	CH_2OH	**1a**	5	87
10	4-ClC_6H_4	CH_2OH	**1b**	5.5	92
11	4-$O_2NC_6H_4$	CH_2OH	**1c**	10	65
12	2-ClC_6H_4	CH_2OH	**1d**	5	92
13	3-$O_2NC_6H_4$	CH_2OH	**1e**	10	60
14	2-furyl	CH_2OH	**1f**	5	90
15	Ph	CH_2Br	**1a**	5	90
16	Ph	CH_2Cl	**1a**	5.5	88
17	4-ClC_6H_4	CH_2OH	**1b**	5	90
18	4-$O_2NC_6H_4$	CH_2OH	**1c**	10	60
19	4-$O_2NC_6H_4$	CH_2OH	**1c**	10.5	62
20	3-$O_2NC_6H_4$	CH_2OH	**1e**	7	87

[a] All products were characterized with IR and ^1H and ^{13}C NMR.
[b] Isolated yields.

ionic liquid. The significant features of this method include: (a) operational simplicity, (b) the use of available and inexpensive reagents, (c) high yields of products, and (d) the use of an ionic liquid as a green solvent.

Reaction progress was monitored by TLC using silica gel Polygrams SIL G/UV254 plates. IR spectra were obtained using a Shimadzu 470 spectrophotometer. ^1H NMR spectra were run on a Bruker Avance 200 MHz NMR spectrometer. Melting points were determined in open capillaries with a Gallenkamp melting point apparatus and are corrected. Chemicals were either prepared in our laboratories or purchased from Fluka and Merck chemical companies.

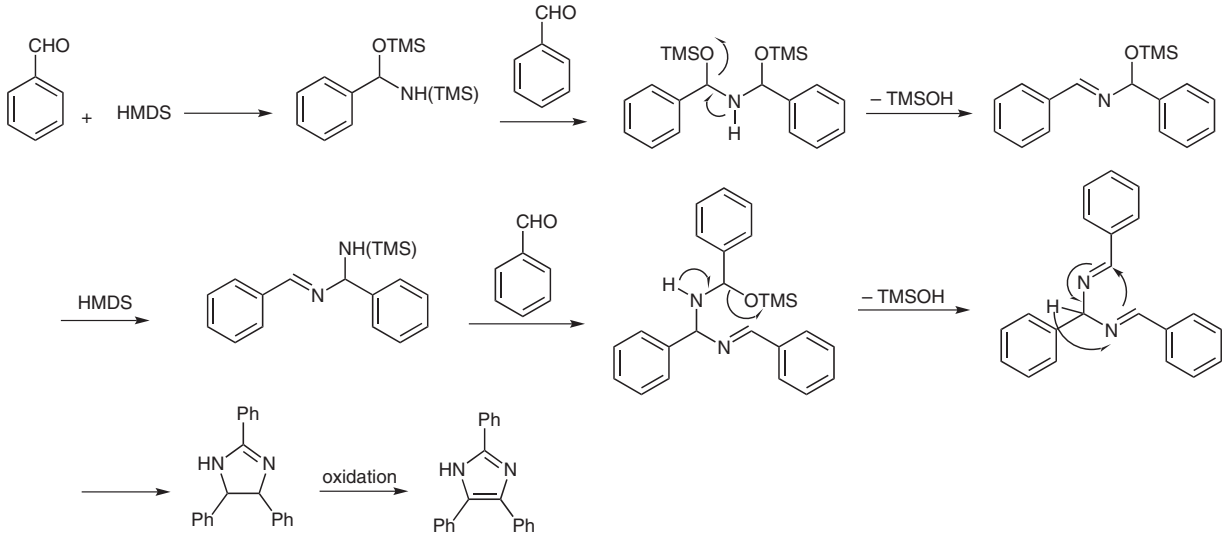
Compound **1a** is known;[22] spectral data for new compounds are given below.

Trifluoromethanesulfonic Acid on Silica Gel Support

To MeCN (20 mL) were added TfOH (1.5 mg) and silica gel (0.5 g) and the mixture was stirred at r.t. for 30 min. Evaporation of MeCN gave the corresponding TfOH-silica gel.

2,4,5-Triaryl-1*H*-imidazoles 1 from Arylaldehyde Derivatives; General Procedure

To the molten salt TBAB (321 mg, 1 mmol) were added arylaldehyde (1 mmol), HMDS (1 mmol), and TfOH-silica gel (0.06–0.1 g); the mixture was stirred at 100 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, H_2O–EtOH (2:1) was added to mixture and the solid thus formed was filtered



Scheme 1

and then washed with cooled EtOH (2 × 10 mL). The solid was recrystallized (EtOH) to give the pure product in 70–95% yield.

2,4,5-Triaryl-1*H*-imidazoles 1 from Benzyl Alcohols or Benzyl Halides; General Procedure

To the molten salt TBAB (1 mmol, 321 mg) were added benzyl alcohol or benzyl halide (1 mmol), HMDS (1 mmol), and $Bi(NO_3)_3·5H_2O$ (1.2 mmol); the mixture was stirred at 100 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, Et_2O (10 mL) was added to the mixture, which was filtered and then H_2O–EtOH (2:1) was added to the filtrate, the solid thus formed was filtered and washed with cooled EtOH (2 × 10 mL). The solid was recrystallized (EtOH) to give the pure product in 62–92% yield.

2,4,5-Triphenyl-1*H*-imidazole (1a)

Mp 273–276 °C.

IR (KBr): 3434, 2993, 2470, 1638, 1216 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 7.42–8.12 (m, 15 H, Ar), 12.61 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 122.1, 127.2, 128.5, 129.1, 136.5.

2,4,5-Tris(4-chlorophenyl)-1*H*-imidazole (1b)

Mp 275–276 °C.

IR (KBr): 3417, 1600, 1481, 1411, 1094, 810 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 7.35 (d, *J* = 10 Hz, 6 H, Ar), 7.85 (d, *J* = 10 Hz, 6 H, Ar), 12.51 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 123.3, 128.8, 129.2, 133.2, 134.2, 136.5.

2,4,5-Tris(4-nitrophenyl)-1*H*-imidazole (1c)

Mp 273–274 °C.

IR (KBr): 3408, 1612, 1523, 1347, 1091, 820 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 7.78 (d, *J* = 9 Hz, 6 H, Ar), 8.50 (d, *J* = 9 Hz, 6 H, Ar), 12.55 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 122.1, 124.1, 127.1, 136.2, 141.1, 147.1.

2,4,5-Tris(2-chlorophenyl)-1*H*-imidazole (1d)

Mp 268–270 °C.

IR (KBr): 3200, 1635, 1475, 1420, 1084, 785 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 7.42 (d, *J* = 10 Hz, 3 H, Ar), 7.33 (d, *J* = 10 Hz, 3 H, Ar), 7.20 (t, *J* = 10 Hz, 3 H, Ar), 7.10 (t, *J* = 10 Hz, 3 H, Ar), 12.6 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 124.1, 127, 128.4, 129.3, 129.9, 132.1, 136, 136.7.

2,4,5-Tris(3-nitrophenyl)-1*H*-imidazole (1e)

Mp (decomposed before melting).

IR (KBr): 3405, 1600, 1520, 1347, 1089, 900, 820, 710 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 7.2–8.3 (m, 12 H), 12.41 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 122.1, 124.1, 128.6, 133.2, 136.2, 137.6, 148.7.

2,4,5-Tri-2-furyl-1*H*-imidazole (1f)

Mp (decomposed before melting).

IR (KBr): 3040, 1601, 1445, 850, 718 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 6.13–6.18 (d, *J* = 7.5 Hz, 3 H, Ar), 6.85–6.89 (d, *J* = 8 Hz, 3 H, Ar), 7.18 (s, 3 H, Ar), 12.42 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 103, 112, 122, 136.2, 143.1, 153.3.

2,4,5-Tri-4-tolyl-1*H*-imidazole (1g)

Mp 256–258 °C.

IR (KBr): 3451, 2990, 2450, 1625, 1210 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 2.36 (s, 9 H, CH_3), 7.14–7.18 (m, 12 H, Ar), 12.58 (br s, 1 H, NH).

^{13}C NMR (DMSO, $CDCl_3$): δ = 21.2, 122, 127, 129.1, 133.2, 136.2, 138.1.

2,4,5-Tris(4-methoxyphenyl)-1*H*-imidazole (1h)

Mp 225–228 °C.

IR (KBr): 3418, 2856, 2435, 1625, 1214 cm^{-1}.

^1H NMR (DMSO, $CDCl_3$): δ = 3.85 (s, 9 H, CH_3), 6.93–6.96 (d, *J* = 8.8 Hz, 6 H, Ar), 8.02–8.05 (d, *J* = 8.8 Hz, 6 H, Ar), 12.52 (br s, 1 H, Ar).

^{13}C NMR (DMSO, $CDCl_3$): δ = 58, 114.2, 122, 128, 128.7, 136, 161.

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