An Efficient Synthesis of 2,4,5-Triaryl-1*H*-Imidazole Derivatives Catalyzed by Boric Acid in Aqueous Media Under Ultrasound-Irradiation

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Boric acid (BO_3H_3) is an inexpensive, efficient and mild catalyst for the synthesis of 2,4,5-triaryl-1*H*-imidazoles in excellent yields from the one-pot three-component condensation of benzil/benzoin, an aldehydes and ammonium acetate in aqueous media under ultrasound at room temperature. The remarkable advantages offered by this method are green catalyst, mild reaction conditions, simple procedures, much faster reactions and excellent yield of products.

Key Words: 2,4,5-Triaryl-1*H*-imidazole, Boric acid, Aqueous media, Ultrasound irradiation

Introduction

2,4,5-Triaryl-1*H*-imidazole compounds have gained the remarkable importance due to their widespread biological activities and their use in synthetic chemistry. Imidazole ring system is one of the most important substructure found in a large number of natural products and pharmacologically active compounds such as antiulcerative agent cimetidine,[1] the proton pump inhibitor omeprazole[2] and the benzodiazepine antagonist flumazenil[3] are imidazole derivatives. Trifenagrel[4] 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, Radziszewski and Japp reported the first synthesis of the imidazole from 1,2-dicarbonyl compound, various aldehydes and ammonia, to obtain the 2,4,5-triphenylimidazoles.[5,6] Also, Grimmett *et al.* proposed the synthesis of the imidazole using nitriles and esters.[7] Recently, there are 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,[8] $ZrCl_4$,[9] $NiCl_2{\cdot}6H_2O$,[10] ionic liquid,[11] iodine,[12] sodium bisulfite,[13] acidic Al_2O_3,[14] AcOH,[15] NH_4OAc,[16] $Yb(OTf)_3$.[17] However, these methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles derivatives would be highly desirable.

In 1980, Breslow discovered that the Diels-Alder reaction performed in water could be subjected to huge rate accelerations.[18] To date, many more organic transformations have been carried out in water or aqueous media.[19] In recent years, boric acid (BO_3H_3 or $B[OH]_3$) have gained special attention as catalyst in organic synthesis because many advantages such as excellent solubility in water, uncomplicated handling, inexpensiveness and eco-friendly nature. Recently, several synthetically useful organic transformations using boric acid as a catalyst have been reported in the literature.[20] Ultrasound has increasingly been used in organic synthesis in the last three decades. It has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under ultrasound irradiation.[21]

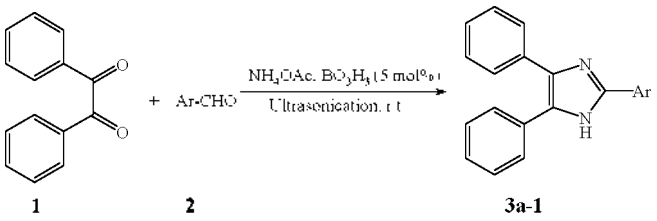
Experimental

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 80 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard. Bandelin Sonorex (35 kHz) ultrasonic bath was used for ultrasonic irradiation. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique.

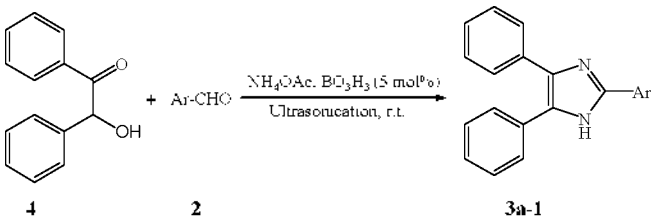
General procedure for the synthesis of 2,4,5-triary-1*H*-imidazoles (3a-l). BO_3H_3 (5 mol%) benzil **1**/benzoin **4** (1 mmol), and ammonium acetate (3 mmol) dissolved in water-ethanol (5:5 mL) were taken in single neck round bottom flask and to this aldehyde (1 mmol) was added. The flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for the prescribed time (Table 2). The progress of the reaction was monitored on TLC (petroleum ether: ethyl acetate = 9:1 as eluent). Then reaction mixture was poured on ice-water (50 mL), and a precipitated solid was filtered, washed with water, dried and recrystallized from ethanol to get the corresponding 2,4,5-triaryl-1*H*-imidazoles (**3a-l**). The products (**3a-l**) were confirmed by comparisons with authentic samples. IR, ^{1}H NMR, mass spectra and melting points.

Result and Discussion

As a part of our ongoing investigation in developing a versatile and efficient method for synthesis of heterocyclic compounds,[19,21d,e,22] we report here an efficient synthetic method for the synthesis of 2,4,5-triarylimidazoles from



Scheme 1



Scheme 2

benzil/benzoin, aldehydes and ammonium acetate in the presence of boric acid (Scheme 1, 2).

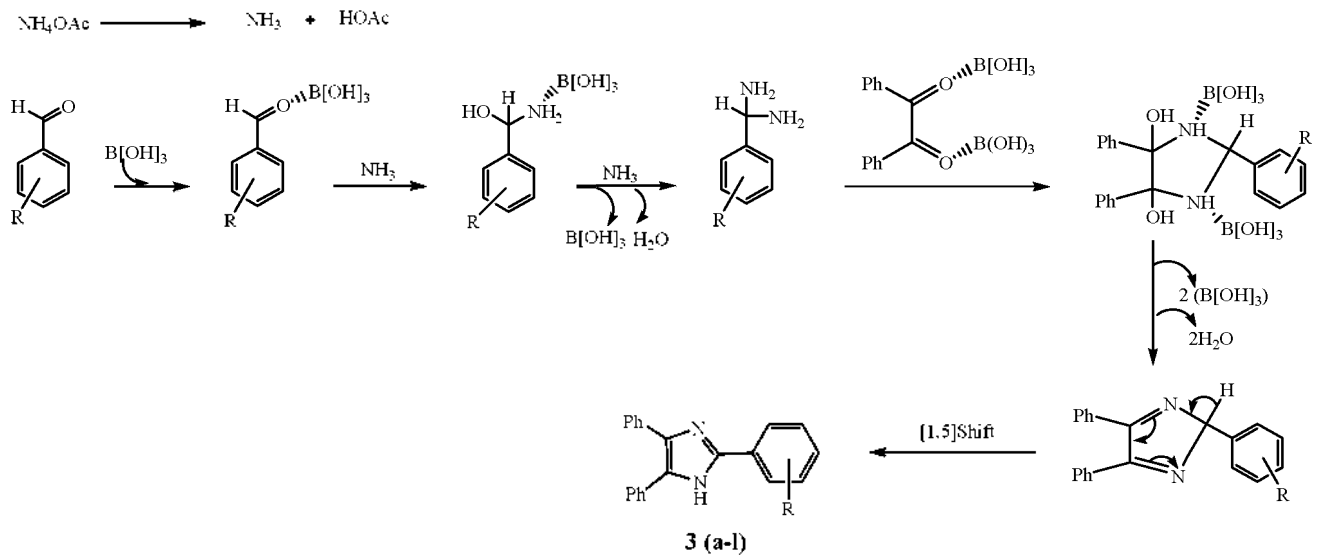
We initially studied the catalytic efficiency of boric acid for the synthesis of 2-(2-chlorophenyl-4,5-diphenyl-1*H*-imidazole (Table 2, compound **3b**) using benzil/benzoin, 2-chlorobenzaldehyde and ammonium acetate in different solvents and various mol% of boric acid (Table 1). From Table 1, the reactions in pure water and ethanol afforded 2-(2-chlorophenyl)-4,5-diphenyl-1*H*-imidazole in low yields after 160 and 180 min, respectively (Table 1, entry 1, 2). The use of THF and CH_3CN as cosolvent delivers low yields (Table 1, entry 3, 4) as compared to optimized reaction condition (Table 1, entry 6). A quantitative yield of desired product was obtained in the presence of 5 mol% boric acid for 40/70 min. indicating that the boric acid (5 mol%) H_2O/EtOH (5:5 mL) catalytic system is highly active for this reaction. Even we changed the ratio of water and ethanol, but we observed that when ratio of water and ethanol is less than 5:5 mL then yield was nearly 67 to 80% (Table 1, entry 8, 9). These results suggest that 5:5 mL ratio of water and ethanol is the best solvent for this condensation reaction. We found that aromatic aldehydes containing different functional group at different positions worked well and did not show remarkable differences in the yield of products and reaction times. Also, the present method was found to be effective for hetero-aromatic aldehydes for the synthesis of 2-heteroaryl-4,5-diphenyl-1*H*-imidazoles with excellent yields (compound **3k**, **3l**). To determine the role of boric acid, the same reaction was carried out in the absence of catalyst under the same conditions, which resulted in no product formation, after 180 min. This result indicates that boric acid exhibit a high catalytic activity in this transformation.

To evaluate the effect of ultrasound for the model reaction (Table 2, compound **3b**), we first examined the reaction without ultrasound at room temperature. We found low yield (40%) with prolonged reaction time (180 min) and using ultrasound at room temperature amazingly we found excellent

Table 1. Optimization of reaction condition and mol% of boric acid using benzil, 2-chlorobenzaldehyde and ammonium acetate under ultrasonication at room temperature (Table 2, compound **3b**).

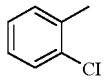
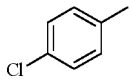
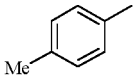
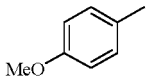
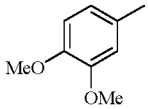
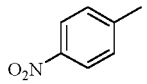
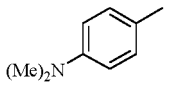
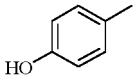
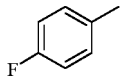
Entry	Solvent (mL)	BO_3H_3 (mol%)	Benzil Time (min)/ Yield(%)[a]	Benzoin Time(min)/ Yield (%)[a]
1	pure H_2O(10)	10	90/70	120/65
2	pure EtOH(10)	10	90/66	110/60
3	H_2O/THF(5:5)	10	60/87	90/80
4	H_2O/CH_3CN(5:5)	10	80/82	100/76
5	H_2O/EtOH(5:5)	10	35/98	60/94
6	H_2O/EtOH(5:5)	5	40/98	70/94
7	H_2O/EtOH(5:5)	2.5	60/87	90/84
8	H_2O/EtOH(2:8)	5	60/76	100/67
9	H_2O/EtOH(3:7)	5	50/80	90/72

[a]Isolated yields.



Scheme 3

Table 2. Syntheses of 2,4,5-triarylimidazoles using boric acid as catalyst under ultrasonication at room temperature.

Compound	Ar-CHO	Reaction time (min)		Yield (%)[a]		M.P. (°C)	
		Benzil	Benzoin	Benzil	Benzoin	Found	Lit.
3a		30	55	98	94	276-278	276-277[8]
3b		40	70	98	94	195-197	195-196[13]
3c		30	50	97	94	260-262	260-262[13]
3d		45	80	96	94	230-232	231-232[8]
3e		50	90	95	90	228-230	227-228[8]
3f		40	70	94	91	220-221	220-221[13]
3g		70	95	92	85	232-233	232-233[13]
3h		60	90	94	89	256-258	257-258[8]
3i		50	80	96	92	269-270	268-270[13]
3j		45	70	97	93	188-190	190[9]
3k		50	80	96	92	200-202	199-201[13]
3l		45	80	95	91	260-262	260-261[12]

[a]Isolated yields.

Table 3. Comparison of a reported procedure with the present method for the synthesis of 2-(4-chlorophenyl)- 4,5-diphenyl-1*H*-imidazole (Table 2, compound **3c**)

Entry[a]	Lit.	Catalyst	Solvent	Reaction condition	Time	Yield (%)[b]
1	Ref. 9	$ZrCl_4$	CH_3CN	r.t., stirring	10 h	93
2	Present	BO_3H_3	H_2O/EtOH	r.t., ultrasound	30 min	97

[a]All reactions were carried out in benzil:4-chlorobenzaldehyde: ammonium acetate (1:1:3) under different reaction conditions. [b]Isolated yield.

yield (98%) with short reaction time (40 min). Therefore, we chose this method to perform the synthesis of all derivatives of 2,4,5-triarylimidazoles under ultrasound irradiation.

In Table 3, we compared our result with result obtained by a reported procedure[9] for the synthesis of 2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazole (compound **3c**). The data presented in this table show the promising feature of this method in terms of reaction rate and the yield of product compared with that reported in the literature. The proposed mechanism of this reaction is as shown in Scheme 3.

Conclusion

In conclusion, we have developed an ultrasound-assisted, efficient and convenient method for the one-pot three-component synthesis of 2,4,5-triarylimidazole derivatives using cheap and readily available boric acid as a catalyst. The

notable merits offered by this methodology are mild reaction conditions, simple procedures, cleaner reactions, short reaction times and excellent yields of products.

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Spectral Data of Principal Compounds.

Compound (**3a**): IR (KBr): 3450 (N-H), 3050 (C-H), 1600 (C=C), 1580 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ): 7.15-8.00 (m, 15H, Ph), 9.20 (br s, NH). EIMS (*m/z*, %): 297 (M+1). Compound (**3b**): IR (KBr): 3450 (N-H), 1600 (C=C), 1580 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ:7.5-7.65 (m, 10H, Ph), 7.42 (d, 1H, *J* = 10 Hz, Ar), 7.33 (d, 1H, *J* = 10 Hz, Ar), 7.20 (t, 1H, *J* =10 Hz, Ar), 7.10 (t, 1H, *J* = 10 Hz, Ar). EIMS (*m/z*, %): 331 (M+1). Compound (**3c**): IR (KBr): 3450 (N-H), 1600 (C=C), 1580 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ):7.10-7.60 (m, 10H, Ph), 7.35 (d, 2H, *J* = 10 Hz, Ar), 7.85 (d, 2H, *J* = 10 Hz, Ar). EIMS (*m/z*, %): 331 (M+1). Compound (**3d**): IR (KBr): 3450 (N-H), 1600 (C=C), 1585 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ): 2.30 (s, CH_3), 7.10-7.60 (m, 10H, Ph), 7.70 (d, 2H, *J* = 10 Hz, Ar), 7.30 (d, 2H, *J* = 10 Hz, Ar). EIMS (*m/z*, %): 311 (M+1). Compound (**3e**): IR (KBr): 3450 (N-H), 1610 (C=C), 1575 (C=N), 1385 (C-O) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ): 3.90 (s, OCH_3), 7.05 (d, 2H, *J* = 8.8 Hz, Ar), 7.30-7.80 (m, 10H, Ph), 7.90 (d, 2H, *J* = 8.8 Hz, Ar). EIMS (*m/z*, %): 327 (M+1). Compound (**3g**): IR (KBr): 3400 (N-H), 1580 (C=N), 1515 (NO_2), 1335 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ): 7.15-7.70 (m, 10H, Ph), 7.90-8.25 (AB, 4H, *J* = 9 Hz, Ar). EIMS (*m/z*, %): 342 (M+1). Compound (**3h**): IR (KBr): 3050 (C-H), 2850 (C-H), 1615 (C=C), 1600 (C=N), 1360 (C-N) cm^{-1}. ^1H NMR ($CDCl_3$, 80 MHz, δ): 2.90 (s, $2CH_3$), 6.60 (d, 2H, *J* = 8.9 Hz, Ar), 7.10-7.60 (m, 10H, Ph), 7.70 (d, 2H, *J* = 8.9 Hz, Ar). EIMS (*m/z*, %): 340 (M+1). Compound (**3k**): IR (KBr): 3316 (N-H), 2993 (C=C-H), 1660 (C=C), 1580 (C=N) cm-1. ^1H NMR ($CDCl_3$, 200 MHz, δ): 7.21 (m, 1H, NH), 7.46-7.58 (m, 4H, Ar), 7.60-7.70 (m, 3H, Ar), 7.96-8.02 (m, 6H, Ar). EIMS (*m/z*, %): 287 (M+1).