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Research Article

Synthesis of 2,4,5- triaryl imidazoles using catalytic amount of Et_4NBrO_3

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Key words: substituted imidazole, three component reaction, tetraethylammonium bromate, phase transfer catalyst. 1,2 diketones

Abstract: Tetraethylammonium bromate catalyzes the condensation of 1,2-diketones, aldehydes and ammonium acetate in a three component reaction under mild condition and in a short time to afford the 2,45-triarylimidazoles in high yield.

Introduction

Imidazole and its derivatives are an important class of bioactive molecules and are widely used as analgesic[1] , antibacterial[2], antifungal[3], antiviral[4], and as antitubercular[5] agents and also as COX-2/LOX inhibitor[6,7] . They have been reported for their application as melanocortin-4 receptor (MC4-R) antagonists[8]. The imidazole ring system is of interest for being a component of histidine that produces histamine in the metabolic process.[9]

By far the most common method used for the synthesis of imidazole derivatives is based on the condensation of arylamines , aldehydes and ammonia[10,11]. Specific methods include the condensation of aryldiamines and aldehydes with $ZrOCl_2 \cdot 8H_2O$ as catalyst under solvent free conditions[12]. Condensation of aromatic diamines, 1,2 diketones and ammonium acetate using $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$[13] is reported to be a green method of synthesis. Improved methods of synthesis includes the use of ionic liquid in the presence of catalytic amounts of p-toluene sulphonic acid[14], a four component condensation of aromatic aldehydes , primary amines and ammonium acetate catalyzed by zeolite HY and silica gel under microwave irradiation[15], CAN mediated synthesis [16-17] , Pd catalyzed continuous flow method at high pressure [18] and by the condensation of arylglyoxal, 1^0-amines, carboxylic acids and isocyanides with solid supported reagents[19] besides others. As part of our on going interest in the synthesis of heterocyclic compounds using new reagents, we report for the first time the use of tetraethylammonium bromate for carrying out a facile three component condensation reaction for the synthesis of 2,4,5-triarylimidazoles.

Results and discussion

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The use of quaternary ammonium salts have immense synthetic value . Besides being cheap and readily available, the quaternary ammonium salts can be modified to suit the requirement of a particular synthetic method. The unique property of these salts is that they are soluble in organic solvents as well as in water and hence can be used according to the demand of the reaction conditions. A simple , efficient and environmentally acceptable method for the synthesis of 2,4,5-trisubstituted imidazole mediated by tetraethylammonium bromate is reported. We observed that an aqueous solution of tetraethylammonium bromate can be conveniently used for carrying out a three component condensation reaction for the synthesis of 2,4,5-substituted imidazole using 1,2-dicarbonyls , aldehydes and ammonium acetate in acetic acid at 60^0C. The reaction was completed in a short time and yields have been found to be good. Apart from acetic acid , other solvent like ethanol, methanol, ethanol-water (1:1), DCM, CH_3CN, $CHCl_3$ are also used however, best yields were obtained with acetic acid as the solvent . In a typical procedure , the 1,2 diketone , aromatic aldehyde and ammonium acetate were dissolved in aqueous acetic acid (50% v/v) and to this an aqueous solution of tetraethylammonium bromate was added and the reaction solution kept at 60-^{o}C under constant stirring . On completion of the reaction, as indicated by TLC, the reaction was quenched with a large volume of water and the product trisubstituted imidazole precipitated out and recovered by simple filtration. Purification was done by column chromatography. The products were identified by spectroscopic methods and by comparing their melting points with those reported in literature . The reaction is shown in **Scheme 1.** The results are listed in **Table I**. The reaction is clean as no undesirable side products are observed. The spent bromate being soluble in water could be easily separated from the products.

Scheme 1

Synthesis of 2,4,5-trisubstituted imidazoles catalyzed by Et_4NBrO_3

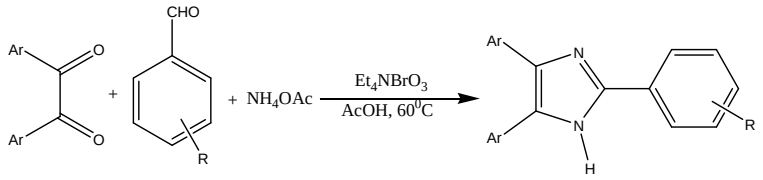

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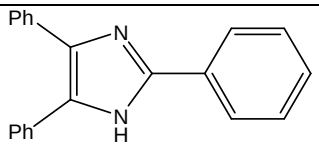
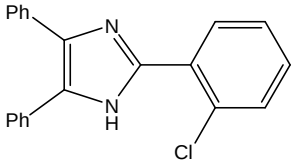
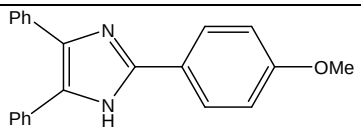
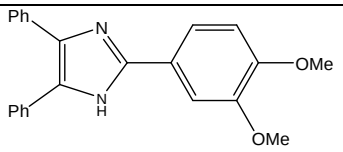
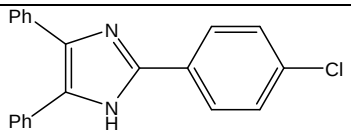
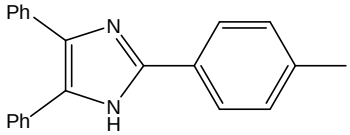
Table: 1 Physical characteristics of the 2,4,5-triaryl imidazoles

Entry	Ar	R	Product	Yield (%)	**Time** (min)	Melting Point	
						Obs.(^{0}C)	Lit. .(^{0}C) [20,21,22]
1	Ph	H		92	45	266-268	267-269
2	Ph	2-Cl		88	60	188-190	190-191
3	Ph	4-OMe		87	50	219-221	220-223
4	Ph	3,4-diOMe		85	75	215-216	218
5	Ph	4-Cl		81	60	260-261	262-264
6	Ph	4-Me		75	120	229-231	233-235

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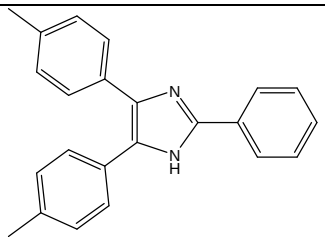
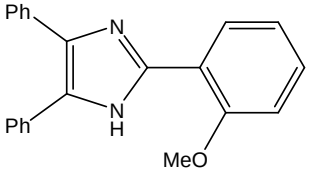
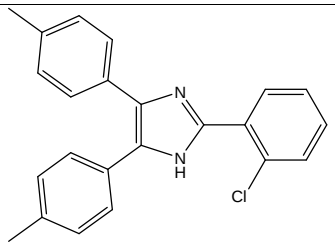
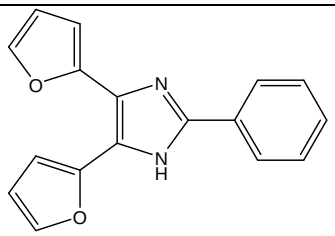
7	4-MeC_6H	H		86	90	253-254	254
8	Ph	2-OMe		78	100	208-209	210-211
9	4-MeC_6H_4	2-Cl		83	115	190-192	195
10	2-furyl	H		79	95	213-215	218

Materials and method

All aromatic 1,2-diketones and aromatic aldehydes were purchased from Sigma Aldrich. The 1,2-diketones and the aldehydes were used without purification however , some liquid aldehydes were purified by distillation before use. The products 2,4,5-triaryl imidazoles were identified from their reported Mp[16,17,18]. IR recorded in Perkin elmer FTIR 1600 , ^1H and ^{13}C NMR spectra were recorded on a Bruker Bio-Spin spectrometer at 300 MHz using TMS as the internal standered (in $CDCl_3$) , Mass spectra ESIMS were recorded in waters Q-Tof Premier & Aquity UPLC, LC-MS/MS system and the results compared with those reported in literature. Meting points were recorded in open capilliaries and tetraethylammonium bromate was prepared by a method reported earlier [23].

Experimental Section

General procedure:

Synthesis of 2,4,5-triarylimidazoles using tetraethylammonium bromate : 1,2-diketones (1 mmol) , aromatic aldehydes (1.2 mmol) and ammonium acetate (4 mmol) were added sequentially to a round bottomed flask containing 5 mL of acetic acid (50% v/v) with constant stirring. To this mixture an aqueous solution of tetraethylammonium bromate (10 mol%) was added and the solution was kept at 60^0C in a water bath using a reflux condenser. The progress of the reaction

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was monitored by TLC in prepared silica gel plates with ethylacetate: *n*-hexane (1:9 or 10% ethyl acetate) as the eluent. The completion of the reaction was indicated by the absence of the starting material in the TLC plates. The reaction mixture was then cooled and poured into ice water and on standing the product precipitated out which was filtered , washed with aqueous sodium bicarbonate (50mLx3) and distilled water . Further purification was done by column chromatography in silica gel (Merck) 60-120 mesh using ethylacetate and *n*-hexane as the eluent. All the products were found to be solid and are characterized by comparing their melting point with those reported in literature, IR, ^{1}H NMR, ^{13}C NMR, Mass spectra of the compounds.

Some spectral characteristics of the 2,4,5-triaryl imidazoles:

Product 1: ***2,4,5-triphenylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 8.035 (d, J= 6.9Hz, 2H, ArH); 7.61-7.49 (m, 4H, ArH); 7.37-7.322 (m, 2H, ArH); 7.28-7.16 (m, 7H, ArH). FT-IR (KBr, cm^{-1}): 1485, 1583, 1636, 3451.

Product 2: ***2-(2-Chlorophenyl)-4,5-diphenylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 8.408 (d, J= 6Hz, 1H, ArH); 7.56 (d, J= 5.4Hz, 4H, ArH); 7.43 (d, J= 6Hz, 1H, ArH); 7.39-7.24 (m, 8H, ArH). FT-IR (KBr, cm^{-1}): 1446, 1498, 1571, 1600, 2954, 3062, 3445.

Product 3: ***2-(4-Methoxyphenyl)-4,5-diphenylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 7.97 (d, J= 8.4Hz, 2H, ArH); 7.52 (d, J= 7.2Hz, 4H, ArH); 7.29-7.197 (m, 6H, ArH); 6.89 (d, J= 8.7Hz, 2H, ArH); 3.793 (s, 3H, -OCH_3). ^{13}C NMR: (75MHz, $CDCl_3$/DMSO-d_6) ∂ 159.53, 146.31, 133.21, 128.15, 127.92, 126.94, 126.75, 123.28, 113.72, 55.11. FT-IR (KBr, cm^{-1}): 1252, 1510, 1622, 2990, 3032, 3451.

Product 4: ***2-(3,4-Dimethoxyphenyl)-4,5-diphenylimidazole:*** ^{1}H NMR: 300MHz, $CDCl_3$/DMSO-d_6) ∂ 7.525 (s, 2H, ArH); 7.167-7.148 (m, 4H, ArH); 7.083-7.07 (m, 6H, ArH); 6.69 (d, J= 6.6Hz, 1H, ArH); 3.635 (s, 3H, -OCH_3); 3.593 (s, 3H, -OCH_3). ^{13}C NMR: (75MHz, $CDCl_3$/DMSO-d_6) ∂ 159.23, 139.52, 138.82, 136.58, 131.16, 121.19, 65.94. FT-IR (KBr, cm^{-1}): 1483, 1512, 1602, 1647, 2999, 3421.

Product 5: ***2-(4-Chlorophenyl)-4,5-diphenylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 7.82 (d, J= 6.3Hz, 2H, ArH); 7.49 (d, J= 5.4Hz, 4H, ArH); 7.36 (d, J= 6.3Hz, 2H, ArH); 7.32-7.24 (m, 6H, ArH). FT-IR (KBr, cm^{-1}): 1320, 1640, 3020, 3430.

Product 6: ***4,5-Diphenyl-2-p-tolylimidazole:*** ^{1}H NMR: (300MHz, DCl_3/DMSO-d_6) ∂ 7.78 (d, 6Hz, 2H, ArH); 7.45 (d,6Hz, 4H, ArH); 7.27-7.19 (m, 6H, ArH); 7.17 (d, 5.7Hz, 2H, ArH); 2.344 (s, 3H, -CH_3).FT-IR (KBr, cm^{-1}): 1315, 1483, 1512, 1600, 3002, 3436.

Product 7: ***2-Phenyl-4,5-di-p-tolylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 8.04 (d, J= 7.2Hz, 2H, ArH); 7.42-7.28 (m, 6H, ArH); 7.24 (d, J= 6.9Hz, 1H, ArH); 7.07 (d, J= 7.5Hz, 4H, ArH); 2.299 (s, 6H, $2CH_3$). ^{13}C NMR: (75MHz, $CDCl_3$/DMSO-d_6) ∂ 145.81, 136.45, 130.70, 128.97, 128.48, 128.03, 127.90, 125.47, 21.23. FT-IR (KBr, cm^{-1}): 1502, 1634, 2990, 3434.

Product 8: ***2-(2-Methoxyphenyl)-4,5-diphenylimidazole:*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 10.52 (s, br, 1H, NH); 8.5 (d, J= 6.6Hz, 1H, ArH); 7.6 (s, 4H, ArH); 7.375-7.39 (m, 7H, ArH); 7.132 (t, J= 7.5Hz, 7.5Hz, 1H, ArH); 7.04 (d, 8.1Hz, 1H, ArH); 4.037 (s, 3H, -OCH_3).^{13}C NMR: (75MHz, $CDCl_3$/DMSO-d_6) ∂ 155.65, 144, 129.49, 128.54, 127.74, 127.16, 121.62, 118.03, 111.12, 55.83.FT-IR (KBr, cm^{-1}): 1500, 1620, 2950, 3010, 3433.

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Product 9: ***2-(2-Chlor-phenyl)-4,5-di-p-tolylimidazole*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 10.237 (s, br, 1H, NH); 8.4 (d, J= 7.8Hz, 1H, ArH); 7.48-7.36 (m, 6H, ArH); 7.3 (d, J= 7.8Hz, 2H, ArH); 7.18 (d, J= 7.5Hz, 3H, ArH); 2.442 (s, 3H, CH_3); 2.388 (s, 3H, CH_3). ^{13}C NMR: (75MHz, $CDCl_3$/DMSO-d_6) ∂ 142.79, 130.76, 130.36, 129.51, 129.38, 127.98, 127.57, 127.41, 21.26.FT-IR (KBr, cm^{-1}): 1520, 1620, 2995, 3438.

Product 10: ***4,5-Difuran-2-yl-2-phenylimidazole*** ^{1}H NMR: (300MHz, $CDCl_3$/DMSO-d_6) ∂ 12.42 (s, br, 1H, NH); 7.22–7.48 (m, 5H, ArH); 7.18 (s, 2H, ArH); 6.85–6.89 (d, J=8 Hz, 2H, ArH); 6.13–6.18 (dd, J= 7.5 Hz, 2H, ArH).FT-IR (KBr, cm^{-1}): 1450, 1600, 3030.

Conclusion

In conclusion, we report ,for the first time, the use of tetraethylammonium bromate as a catalyst for the synthesis of 2,4,5-trisubstituted imidazoles. One major advantage of this method is the easy removal of the water soluble spent catalyst. By products of over oxidation was not observed. In other words, the use of tetraethylammonium bromate gave clean products and elaborate purification procedures was not necessary. Easy work-up, short reaction time and good yield are some notable features.

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