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Synthesis of 2,4,5-trisubstituted imidazole and 4,5-disubstituted indolylimidazole derivatives by using Amberlyst A-15 as green, recyclable catalyst

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ABSTRACT

Amberlyst A-15 used as a recyclable, an efficient, green and eco-friendly catalyst for one-pot synthesis of highly substituted imidazole derivatives by multi component condensation of benzil, aldehydes and ammonium acetate under microwave irradiation. The key advantages of this process was cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products, excellent yields and very short time reactions.
Keywords : Reusable Catalyst, Multi-Component Condensation, Indolylimidazole, Benzil.

I. INTRODUCTION

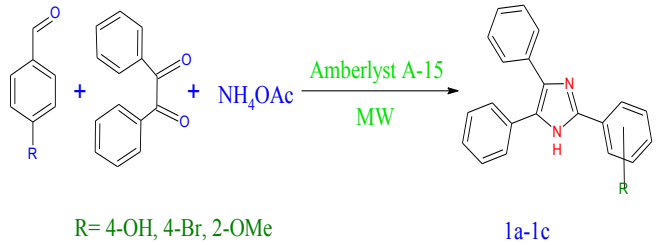
Imidazole derivatives show wide range of pharmacological and therapeutic activities such as anti-histaminic (Cimetidine), anti-hypertensive (Losartan)[1], histamine H_3 antagonist [2,3], farnesyltransferase and geranylgeranyltransferase-I inhibitor [2,4], anti-tumor [5], anti-cancer (Dacarbazine), anti-parasitic (Metronidazole) [6], herbicidal [7], analgesic [8], fungicidal [9], anti-inflammatory [10] and antithrombotic activities [11]. Omeprazole, Pimobendan, Losarton, Olmesartan, Eprosartan and Triphenagrel are imidazole derivatives leading drugs in the market with diverse functionality [12]. The 3- substituted indole alkaloids with additional heterocyclic rings like imidazole and substituted imidazole shows most biological activity and find applications in different fields of science. Indolylimidazole derivatives show different biological and pharmacological activities such as inhibiter against human and murine tumour cells (Topsentin) [13-15], cytotoxicity toward murine tumour cells (Discodermindole, trachyclaindole) [16,17], cytotoxicity toward against P388 cells (Nortopsentins)[18], antidepressants [19], protein kinase C inhibitor [20, 21], interleukin 6 production inhibitor [22], Flt-1 and topoisomerase inhibitor [23], antimicrobial and antifungal activities [24]. Therefore, there is a strong demand for a simple, highly efficient, environmentally benign and versatile method for synthesis of substituted imidazole derivatives due to their great importance.

In recent years, the synthesis of 2,4,5-trisubstituted imidazoles has been catalysed by I_2 [25], $ZrCl_4$ [26], ionic liquid [27], L-proline [28], microwave irradiation [29], $Yb(OPf)_3$ [30], $InCl_3.3H_2O$ [31], $NiCl_2.6H_2O/Al_2O_3$ [32], DABCO [33], magnetic Fe_3O4 nanoparticles [34], nano $MgAl_2O_4$ [35], ZrO_2-β-cyclodextrin [36], [EMIM]OAc [37], NaH_2PO_4 [38], *N*-methyl-2- pyrrolidone hydrogen sulfate [39], europium triflate [40], sulfated zirconia [41], *n*-Bu_4NBr [42], silica-supported Preyssler nanoparticles [43], $(NH_4)6Mo_7O_{24}{\cdot}4H_2O$ [44], nano MgO [45], nano aluminium nitride [46], nano SiO_2-supported ferric hydrogen sulfate (FHS) [47], KSF supported 10-molybdo-2-vanadophosphoric acid [48] and benzyltriphenylphosphonium chloride (BTPPC) [49]. Although some of the methods are actually efficient from the synthetic chemist's points, many of the synthetic protocols for imidazoles reported above suffer from one or more disadvantages, such as harsh reaction conditions, low yields, mixture of products, lack of generality, excess of reagents, high temperature requirement, prolonged reaction time, use of solvents, use of hazardous and often expensive acid catalysts and requirement of excess of catalysts.

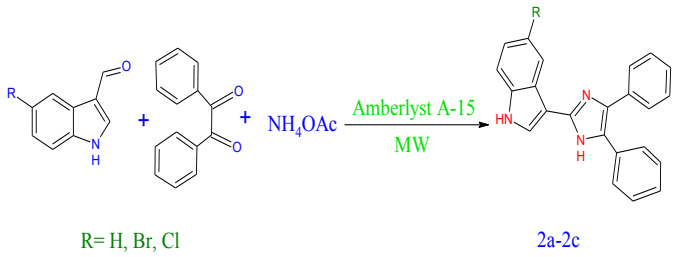
In this paper, Amberlyst A-15 [50-53] catalyst used for the synthesis of substituted imidazole derivatives by the condensation of benzil, aldehyde and ammonium acetate

under MW irradiation. This catalyst was mild, water tolerant, recoverable, non-explosive, easy to handle, and reusable. This method was an efficient, simple, environmentally friendly, low reaction time, high yielding and unique for the synthesis of substituted imidazole derivatives.

Scheme I : Synthesis of 2,4,5- trisubstituted imidazole derivatives



Scheme II : Synthesis of 4,5- disubstituted indolylimidazole derivatives.



II. Experimental

2.1. General

All the melting points were determined by open capillary method and are uncorrected. A domestic microwave oven (IFB, 23BC4, 1400W) was used in all experiments. All melting points are uncorrected and were measured by open capillary method. IR spectra were obtained in KBr by Jasco- FTIR-4100 Spectrometer. 1H NMR spectra were recorded in DMSO with TMS as internal reference on JEOL-400 MHz NMR Spectrometer with multiple probe Facility (AL-400). The Mass spectra were recorded on LCMS SQD-2 with H Class UPLC instruments. All the chemicals and reagents were purchased MERCK and Ranbaxy from Global chemical, Ajmer.

2.2. Experimental Procedure for synthesis imidazole derivatives

2.2.1 General

Synthesis of the tri-phenylimidazole derivative by condensation of benzyl, aldehydes, ammonium acetate and aniline was described [51]. After some modifications, indolylimidazole derivatives were synthesis by multi-component condensation of benzil, indole-3-carbaldehydes and ammonium acetate under Microwave irradiation using Amberlyst A-15 as a reusable catalyst and get a better yield.

2.2.2. Synthesis of 2,4,5-trisubstituted imidazole derivatives 1a-1c:

A mixture of benzil (1 mmol), aldehyde (1 mmol) and NH_4OAc (2 mmol) and Amberlyst A-15 (.14g) into 50ml borosil beaker and irradiated with microwaves at control temperature. The progress of reaction was monitored by TLC using pet. ether and ethyl acetate (9:1). After completion of the reaction the dichloromethane was added and the solid Amberlyst-A-15 was filtered and dried at 80°C and used for its reusability. The organic layer was extracted with H_2O and dried by Na_2SO_4. The Organic layer was removed under reduced pressure. Further, the crude product was purified by column chromatography using pet. ether and ethyl acetate (9:1) on silica gel gave the desire 2,4,5-trisubstituted imidazole (1a-1c) products.

2.2.2. Synthesis 4,5-disubstituted indolylimidazole derivatives 2a-2c:

A mixture of benzil (1 mmol), indole-3-carbaldehyde (1 mmol), NH_4OAc (2 mmol)) and Amberlyst A-15 (.14g) into 50ml borosil beaker and irradiated with microwaves at control temperature. The progress of reaction was monitored by TLC using pet. ether and ethyl acetate (9:1). Above similar procedure was using for further and get better yield of desire products (2a-2c).

2.2.3. Recyclability of the catalyst:

In order to explore the recyclability of the catalyst, the Amberlyst A-15 was used as a catalyst for the same reaction repeatedly. The relation between the number of cycles of the reaction and recyclability in terms of yield of the catalyst is presented in Fig. 1. It was found that Amberlyst A-15 could be reused for seven cycles with negligible loss of their activity.

Table-1. 2,4,5-trisubstituted and 4,5-disubstituted imidazoles, reaction times and yields.

No.	R	Reaction Time (Min.)	% Yield	M.Wt.	M. Formula	M.Pt. (^oC)	M.Pt. (^oC)[a]
1a	4-OH	14	97	312.36	$C_{21}H_{16}N_2O$	267-268	265-267
1b	4-Br	17	95	375.26	$C_{21}H_{15}BrN_2$	248-250	249-252
1c	2-OMe	15	97	326.39	$C_{22}H_{18}N_2O$	211-212	212-213
2a	H	8	97	335.402	$C_{23}H_{17}N_3$	158-160	157-159
2b	Br	13	92	414.297	$C_{23}H_{16}BrN_3$	237-239	237-240
2c	Cl	12	89	369.846	$C_{23}H_{16}ClN_3$	231-233	------

[a] *Melting points are uncorrected and compared with literature reports*[52-57]

Spectral and Analytical Data

1. **4-(4,5-diphenyl-1H-imidazol-2-yl)phenol (1a)**. White solid, M.P. 267-268°C. FTIR (KBr, cm^{-1}): V_{max} 3610, 3434, 2993, 2470, 1638, 1510, 1495, 1465, 1445, 1038, 736, 636; ^{1}H NMR (400 MHz, DMSO-d6): 12.725 (s, 1H, NH), 9.561 (s, 1H OH), 7.925 (d, 2H J=8.4 Hz), 7.932–7.135 (m, 10H, Ar-H), 6.825 (d, 2H, J=8.4Hz). HRMS ((+)-ESI): m/z =312.323 (calcd 312.364)**.**
2. **2-(4-Bromophenyl)-4,5-diphenyl-1H-imidazole (1b):** Colourless solid, M.P. 248-250°C. FTIR (KBr, cm^{-1}): 3420, 3027, 2924, 2835, 1650, 1603, 1501, 1496, 1450, 1069, 826, 728, 715, 696. ^{1}H-NMR (400 MHz, DMSO-d6):) 11.542 (s, 1H, NH), 8.057 (d, 2H, J= 8.2 Hz), 7.702 (d, 2H, J= 8.2 Hz), 7.205-7.692 (m, 10H, Ar-H)ppm. HRMS ((+)-ESI): m/z =375.256 (calcd 375.261)**.**
3. **2-(2-Methoxyphenyl)-4,5-diphenyl-1H-imidazole (1c)**: Colourless solid, M.P. 211-212°C. IR (KBr, cm^{-1}): 3400, 3058, 3036, 2999, 2961, 2838, 1611, 1579, 1542, 1492, 1444, 1073, 1029, 798,768, 696. ^{1}HNMR (400 MHz, DMSO-d6): 12.525 (s, 1H, NH), 8.014 (d, 1H, J=8.79 Hz), 7.534 (d, 1H, J=8.78Hz), 7.036 (d, 2H, J=8.79Hz) 7.531-7.054 (m, 10H, Ar-H), 3.823 (s, 3H) ppm. HRMS ((+)-ESI): m/z =326.140 (calcd 326.142)**.**
4. **3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (2a)-:** Colourless solid, M.P. 158-160°C. FTIR (KBr, cm^{-1}): V_{max} 3412, 3010, 3098, 3055, 1622, 1599, 1577, 1490, 1450, 1336, 1242, 761, 750, 697. ^{1}H NMR (400 MHz, DMSO-d6): 12.447 (s, 1H, imidazole), 11.410 (s, 1H, indole), 8.468 (d, 1H, J= 7.324 Hz), 7.48 (d, 1H, J=7.813Hz), 7.298 (b, 2H, J=37.1Hz), 7.58-7.102 (m, 10H Ar-H)ppm. HRMS ((+)-ESI): m/z =335.34 (calcd 335.4012)**.**
5. **5-Bromo-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (2b)-**: Brownish solid, M.P. 237-239°C. FTIR (KBr, cm^{-1}): V_{max} 3460, 3436, 3195, 3167, 3061, 3018, 3100-3000(Ar-H), 1645, 1603, 1580, 1508, 1454, 1447, 1361, 1268, 1239, 1068, 800, 764, 690. ^{1}H NMR (400 MHz, DMSO-d6): 14.503 (s, 1H, imidazole), 12.524 (s, 1H, indole), 8.484 (s, 1H, J= 2.9Hz), 8.375 (d, 1H. J= 1.46Hz), 7.958 (d, 1H, J= 7.324, 7.813) 7.601 (s, 1H, J= 2.441), 7.592-7.421(m, 10H, Ar-H) ppm. HRMS ((+)-ESI): m/z =414.295(calcd 414.28).
6. **5-Chloro-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1*H*-indole (2c)-**: Colourless solid, M.P. 231-233°C. FTIR (KBr, cm^{-1}): V_{max} 3472, 3445, 3220, 3187, 3110,3085, 3100-3000(Ar-H), 1680, 1635, 1600, 1535, 1462, 1456, 1381, 1278, 1245, 1082, 805, 769, 693. ^{1}H NMR (400 MHz, DMSO-d6): 14.953(s, 1H, imidazole), 13.651(s, 1H, indole), 8.912 (d, 1H, J= 2.9Hz), 8.438 (d, 1H. J= 1.46Hz), 8.258 (d, 1H, J= 7.424, 7.353), 7.953 (s, 1H, J= 2.441), 7.857-7.691(m, 10H, Ar-H) ppm. HRMS ((+)-ESI): m/z =369.8399 (calcd 369.8462).

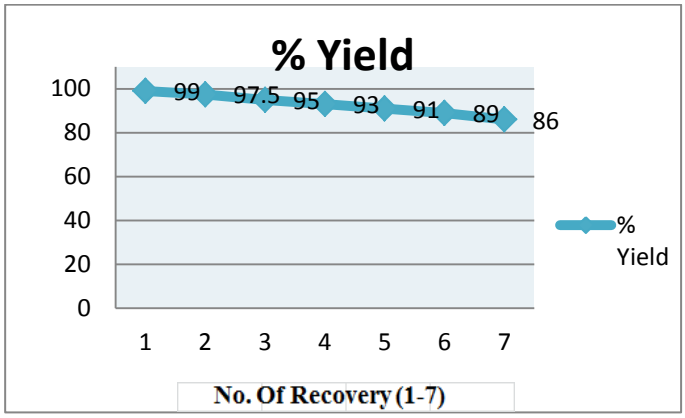


Figure1. The recycling catalyst yield % for modal reaction

III. RESULTS AND DISCUSSION

In this paper, an efficient, green and eco-friendly, one-pot multi-component condensation method for synthesis of 2,4,5-trisubstituted imidazole (1a-1c) by aldehydes, benzil and ammonium acetate have offered in the presence of Amberlyst A-15 as an effective, reusable catalyst under Microwave irradiation and obtained remarkable yields. Similar methodology was applied for the synthesis of 4,5-disubstituted indolylimidazole derivatives (2a–2c) which also produced an excellent yield by the condensation of benzil, indole-3-carbaldehydes and ammonium acetate (table-1) in presence of Amberlyst A-15 under Microwave irradiation. The advantages of this method are short reaction times, high yields, simple work-up, and reusable catalysts. The catalyst Amberlyst A-15 was recycled for the same reaction repeatedly and found that this catalyst could be reused for seven cycles with negligible loss of their activity.

IV. CONCLUSION

In summary, we have presented an efficient, mild and rapid approach for the synthesis of substituted imidazole and indolylimidazole derivatives via condensation of a representative benzil with various aldehydes and ammonium acetate by using Amberlyst A-15 as a new and highly effective catalyst under solvent-free and microwave conditions. Non-corrosiveness, safe, low waste, easy for separation, short time, high yields and environmentally benign are some of the advantages of this methodology.

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