An Efficient Synthesis of 2,4,5-Trisubstituted and 1,2,4,5-Tetrasubstituted-1H-imidazoles

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Since the appearance of the first paper on the application of microwave irradiation in the chemical synthesis[1] the approach has blossomed into a useful technique for a variety of applications in organic synthesis[2] and functional group transformations.[3] In moving towards sustainable technologies the focus has now shifted to less cumbersome solventless methods wherein solid supported[4] microwave synthesis[5,6] has played an important role. This technique eliminates the use of solvent during the reaction stage but requires an appreciable amount of solvent for the adsorption of reagents and elution of product. The emergence of neat reaction is a recent approach under the new paradigm of green chemistry[7] where the neat reactants undergo facile reaction to provide high yield of pure products thus eliminating or minimizing the use of organic solvents. These no solvent[8] reactions are not only advantageous for environmental reasons but also offer benefits of enhanced reaction rates, greater selectivity and experimental ease of manipulation.

The imidazole ring system is of particular interest as it is a component of histidine that produces histamine in metabolic process.[9] The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals which are present in many protein active sites (*eg.* Zn, Fe, Mg).[10] Triaryl imidazoles are used in photography[11] as photosensitive compounds. In addition, they are of interest because of their herbicidal,[12] analgesic,[13] fungicidal,[14] antiinflammatory[15] and antithrombotic activities.[16]

The original synthesis of imidazole utilized glyoxal, formaldehyde and ammonia and established that the formation of four N–C bonds was a viable route.[17,18] Although classical methods were derived from this early success, the reactions suffered low yields, mixture of products and lack of generality. Synthetic methodology alternatives are many[13] and varied[19,20] and have resorted to harsh conditions (eg. the formamide synthesis, which requires excess reagents, H_2SO_4 as a condensing agent, 150-200 °C, 4-6 h, 40-90%).[21,22] Also, reagents for these procedures are not readily available, a key deficiency for library synthesis.

In continuation to our endeavour towards green chemistry[23] and the biological importance of substituted imidazole derivatives we have developed an ecologically safe strategy for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives employing neat reaction conditions using MWI.

Results and Discussion

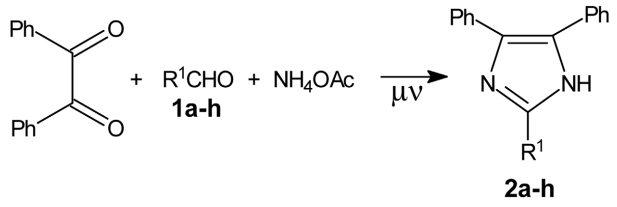
The synthesis of tri/tetra substituted imidazoles by the condensation of aldehyde, benzil, ammonium acetate and amine in refluxing acetic acid for a few hours is a well established procedure.[24] However, this method suffers from drawbacks which include drastic reaction conditions, longer reaction time with tedious work up and low yield of products. In contrast to the drawbacks of classical procedure an improved methodology for the synthesis of 2,4,5-trisubstituted and 1,2,3,4-tetrasubstituted imidazoles using zeolite, silica gel and acidic alumina under MWI is reported.[19] But this technique does not exactly meet the definition of 'no solvent' as it requires the use of an appreciable amount of solvent at the pre and post reaction stages.

We have modified the solid supported technique to an environmentally friendly neat synthesis[25] in which the reaction is carried out in the absence of solvent, solid support and acid. Equimolar amount of neat reactants viz. benzil, aldehydes **1a-h** and excess of ammonium acetate on exposure to microwave irradiation gave excellent yield (Table 1) of 2,4,5-trisubstituted 1H imidazoles **2a-h** (Scheme 1) after

Table 1. Reaction Times and Yields for Compounds **2a-h** and **4a-h**

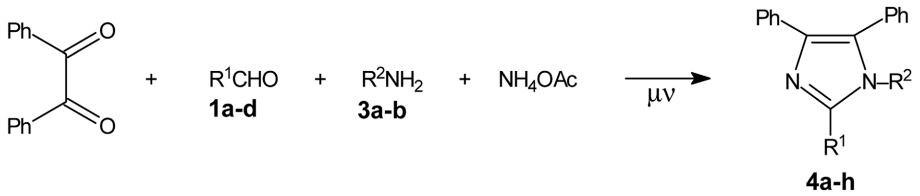
Compd. No.	R^1	R^2	mp/°C	Time (min.)	Yield (%)
2a	Phenyl	–	276-277[26a]	1.5	96
2b	4-Cl-Phenyl	–	263-264[26b]	1.8	94
2c	Piperonyl	–	201-202	2.1	93
2d	2-chloro-3-quinolyl	–	137-138	2.8	90
2e	4-OH-Phenyl	–	256-257[27a]	2.5	91
2f	Indolyl	–	298-299	3.1	92
2g	4-$N(CH_3)_2C_6H_4$	–	259-260[26b]	2.6	95
2h	Furyl	–	235-237	2.3	90
4a	Phenyl	Phenyl	217-218[28]	2.1	93
4b	Phenyl	Benzyl	160-162[27]	2.9	91
4c	4-Cl-Phenyl	Phenyl	158-160	2.7	95
4d	4-Cl-Phenyl	Benzyl	164-165[13]	3.0	90
4e	Piperonyl	Phenyl	198-199	2.5	95
4f	Piperonyl	Benzyl	148-150[13]	2.9	94
4g	2-chloro-3-quinolyl	Phenyl	107-108	2.1	89
4h	2-chloro-3-quinolyl	Benzyl	94-95	2.0	88

Microwave heating (800 W, 2450 MHz, 110-120 °C, 1 min)



Scheme 1

triturating with few drops of methanol. Inspired by the positive results obtained for the synthesis of 2,4,5-trisubstituted imidazoles similar technique was applied for the synthesis of 1,2,4,5-tetrasubstituted 1H imidazoles **4a-h** which were also obtained in high yields within few minutes of MWI by the four component condensation of benzil, aldehyde **1a-d**, aromatic amine **3a-b** and ammonium acetate (Scheme 2). The neat reaction was also attempted under conventional heating, keeping similar reaction conditions. Direct heating of reactants without solvent took more time for completion of reaction and gave the products in low yields and in most cases, lead to charring. The structure of the synthesized compounds was confirmed by spectroscopic and analytical data (Table 2). In the IR spectra the absence of the carbonyl and aldehyde bands are in the accordance with



Scheme 2. R^1 = a = phenyl, b = 4-Cl-phenyl, c = piperonyl, d = 2-chloro-3-quinolyl, e = 4-OH-phenyl, f = indolyl, g = 4-N(CH_3)$_2$-phenyl, h = furyl. R^2 = a = phenyl, b = benzyl

Table 2. Analytical and Spectral Data for Compounds **2a-h** and **4a-h**

Compd. No.	Molecular Formula	% CHN, Found (Calcd)			IR (in KBr) cm^{-1}	^{1}H NMR ($CDCl_3$ + DMSO, δ, 300 MHz)
		C	H	N		
2a	$C_{21}H_{16}N_2$	85.18 (85.13)	5.33 (5.40)	9.38 (9.45)	1600 (C=C), 1580 (C=N), 3445 (N–H)	7.15-7.92 (m, 15H, Ar-H), 9.20 (brs, NH)
2b	$C_{21}H_{15}ClN_2$	76.18 (76.24)	4.58 (4.53)	8.40 (8.47)	1615 (C=C), 1584 (C=N), 3452 (N–H)	7.10-7.60 (m, 10H, Ar-H), 7.35 (d, 2H, Ar), 7.85 (d, 2H, Ar), 9.30 (brs, NH)
2c	$C_{22}H_{16}N_2O_2$	77.58 (77.64)	4.76 (4.70)	8.18 (8.23)	1607 (C=C), 1589 (C=N), 3440 (N–H)	5.90 (s, 2H, OCH_2O), 6.71-7.20 (m, 3H, piperonal), 7.32-7.82 (m, 10H, Ar-H), 9.41 (brs, NH)
2d	$C_{24}H_{16}ClN_3$	75.43 (75.49)	4.12 (4.19)	11.08 (11.00)	1625 (C=C), 1578 (C=N), 3435 (N–H)	7.21-8.35 (m, 15H, Ar-H + Quinolyl), 9.32 (brs, NH)
2e	$C_{21}H_{16}N_2O$	80.82 (80.76)	5.15 (5.12)	8.92 (8.97)	1615 (C=C), 1582 (C=N), 3200 (OH), 3450 (N–H)	6.70-7.61 (m, 15H, Ar-H), 9.52 (brs, NH)
2f	$C_{23}H_{17}N_3$	82.20 (82.14)	5.28 (5.35)	12.42 (12.50)	1628 (C=C), 1588 (C=N), 3452 (NH)	7.12-7.91 (m, 15H, Ar-H), 9.20 (brs, N–H), 10.21 (s, 1H, NH indole)
2g	$C_{23}H_{21}N_3$	81.47 (81.41)	6.12 (6.19)	12.30 (12.38)	1620 (C=C), 1598 (C=N), 3415 (N–H)	2.90 (s, 2CH_3), 6.60 (d, 2H, Ar-H), 7.10-7.62 (m, 10H, Ar-H), 7.70 (d, 2H, Ar-H), 9.12 (brs, NH)
2h	$C_{19}H_{14}N_2O_2$	75.42 (75.49)	4.58 (4.63)	9.21 (9.27)	1624 (C=C), 1594 (C=N), 3430 (N–H)	6.12-6.40 (m, 2H, furan), 7.20-7.92 (m, 11H, Ar-H + furan), 9.30 (brs, NH)
4a	$C_{27}C_{20}N_2$	87.15 (87.09)	5.32 (5.37)	7.58 (7.52)	1625 (C=C), 1596 (C=N)	7.03-7.61 (m, 20H, Ar-H)
4b	$C_{28}H_{22}N_2$	87.10 (87.04)	5.62 (5.69)	7.28 (7.25)	1621 (C=C), 1589 (C=N)	5.16 (s, 2H, –CH_2–), 6.68-7.71 (m, 20H, Ar-H)
4c	$C_{27}H_{19}ClN_2$	79.76 (79.70)	4.62 (4.67)	6.82 (6.88)	1605 (C=C), 1594 (C=N)	7.10-7.60 (m, 15H, Ar-H), 7.32 (d, 2H, Ar), 7.80 (d, 2H, Ar)
4d	$C_{28}H_{21}ClN_2$	79.96 (79.90)	4.92 (4.99)	6.88 (6.65)	1615 (C=C), 1598 (C=N)	5.15 (s, 2H, –CH_2–), 7.10-7.60 (m, 15H, Ar-H), 7.35 (d, 2H, Ar), 7.85 (d, 2H, Ar)
4e	$C_{28}H_{20}N_2O_2$	80.71 (80.76)	4.86 (4.80)	6.78 (6.73)	1619 (C=C), 1587 (C=N)	5.92 (s, 2H, OCH_2), 6.70-7.62 (m, 18H, Ar-H)
4f	$C_{29}H_{22}N_2O_2$	80.98 (80.93)	5.17 (5.11)	6.56 (6.51)	1611 (C=C), 1587 (C=N)	5.12 (s, 2H, –CH_2–), 6.05 (s, 2H, OCH_2), 6.69-7.60 (m, 18H, Ar-H)
4g	$C_{30}H_{20}ClN_3$	78.62 (78.68)	4.32 (4.37)	9.12 (9.18)	1614 (C=C), 1578 (C=N)	7.21-8.32 (m, 20H, Ar-H + Quinolyl)
4h	$C_{31}H_{22}ClN_3$	78.83 (78.89)	4.58 (4.66)	8.96 (8.90)	1619 (C=C), 1583 (C=N)	5.1 (s, 2H, –CH_2), 7.20-8.35 (m, 19H, Ar-H)

the structure of the product. The appearance of band at 1585 and 1600-1625 cm^{-1} due to C=N and C=C respectively further confirmed the formation of the products.

Experimental Section

Microwave irradiations were carried out in Kenstar Microwave Oven, Model No. OM9925E (2450 MHz, 800 W) and IR spectra were recorded on a Perkin Elmer FTIR-1710 spectrophotometer using KBr pellets. ^1H NMR spectra were recorded on Bruker Avance 300 Spectrospin (300 MHz) instrument. Temperature of the reaction mixture was measured through AZ, Mini Gun Type, Non Contact IR thermometer, Model No. 8868. The melting points were determined on a Thomas Hoover melting points apparatus and are uncorrected. Chemical shifts, δ, for ^1H NMR, are given in ppm, relative to internal reference, tetramethylsilane (TMS) and IR frequency, ν (KBr pellets), in cm^{-1}. The purity of compounds was checked on aluminium plates coated with silica gel (Merck).

General procedure for the synthesis of 2-substituted 4,5-diphenyl-1H-imidazole derivatives (2a-h). A mixture of 0.02 mol of benzil, 0.02 mol of aldehyde **1a-h** and 0.07 mol of ammonium acetate were taken in an Erlenmeyer flask and was subjected to microwave irradiation. On completion of reaction as monitored by TLC at an interval of 30 seconds the sticky solid obtained was triturated with few drops of methanol to obtain the desired product **2a-h** which was recrystallized from aqueous methanol.

General procedure for the synthesis of 1-phenyl/benzyl-2-substituted-4,5-diphenyl-1H-imidazole derivatives 4a-h. A mixture of 0.02 mol of benzil, 0.02 mol of aldehyde **1a-d**, 0.02 mol of aromatic amine **3a-b** and 0.07 mol of ammonium acetate were taken in an Erlenmeyer flask and was subjected to microwave irradiation. On completion of reaction as monitored by TLC at an interval of 30 seconds the sticky product obtained was triturated with few drops of appropriate solvent (methanol for **4a**, **b**, **c**, **f** and mixture of benzene: petroleum ether for **4d**, **e**, **g**, **h**) to obtain the required product **4a-h**.

Conclusion

An highly efficient microwave assisted rapid synthesis of tri/ tetrasubstituted 1H imidazoles has been developed. This solvent free neat reaction is not only of interest from an ecological viewpoint but also offer considerable synthetic advantages in terms of yield, selectivity and simplicity of the reaction procedure. Though these solventless reactions are more appropriate for small scale productions but these results may stimulate interest among researchers involved in industrial scale up of reactions.

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