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One-pot synthesis of 2,4,5-tri-substituted-1H-imidazoles promoted by trichloromelamine

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2,4,5-Trisubstituted imidazoles have many pharmaceutical properties and can be prepared via reaction of 1, 2-diketones with aldehydes in the presence of an acidic catalyst. In this work, we have prepared 2,4,5-trisubstituted imidazoles in the presence of trichloromelamine as a source of positive chlorine. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.

1. Introduction

2,4,5-Trisubstituted imidazoles are used as fungicides, herbicides, plant growth regulators, inhibitors of IL-1 or p38 MAP kinase, CB1 cannabinoid receptor antagonists[1], antibacterial[2], antitumor[3], and glucagon receptors[4].

There are several reported methods for the synthesis of 2,4,5-trisubstitutedimidazoles such as the hetero-Cope rearrangement[5], and four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin[6]. Recently, the synthesis of 2,4,5-trisubstituted imidazoles has been catalyzed by $ZrCl_4$[7], ionic liquid[8], silica gel or Zeolite HY[9], $InCl_3.3H_2O$[10], DABCO[11], PEG-400[12], Wells–Dawson heteropolyacid supported on silica (WD/SiO_2)[13],

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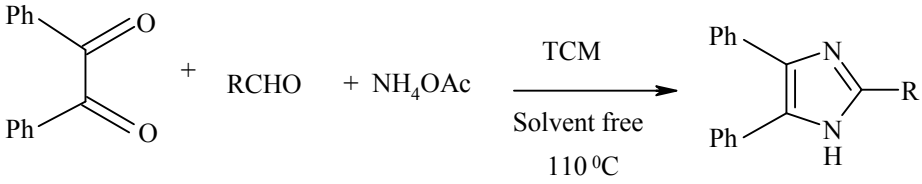
[EMIM]OAc[14], NaH_2PO_4[15], *N*-methyl-2-pyrrolidone hydrogen sulfate[16], K10[17], ZMS-5[17], sulfated zirconia[17], *n*-Bu_4NBr[18], $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$[19], nano MgO[20] and KH_2PO_4[21].

N-halo reagents with high active *N*-X bond have the potential to promote some important reactions. Trichloromelamine (TCM) as a common *N*-halo reagent is used as bleaching agents, disinfectants and bactericides and promoted some organic reactions such as *N*-nitrosation of secondary amines[22], oxidation of alcohols[23,24], and trimethylsilylation of hydroxyl group[25].

2. Results and disscusion

In continuation of our investigations on solid acids in organic synthesis[26-30], we report here on applying trichloromelamine as an efficient Cl^+ catalyst source for synthesis of 2,4,5-trisubstituted imidazoles *via* reaction of benzil, aldehydes and ammonium acetate. For investigation the efficiency of trichloromelamine in preparation of 2,4,5-trisubstituted imidazoles, we have examined the reaction of benzaldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2 mmol) as model reaction. The reaction in different conditions in the presence of trichloromelamine revealed that the best condition was 0.07 g of trichloromelamine under solvent-free condition at 110 °C (Entry 2, Table 1).

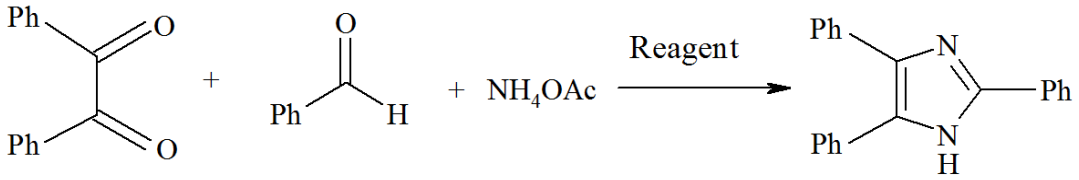
Table 1 Synthesis of 2,4,5-triphenyl-1*H*-imidazole under various conditions[a]



Entry	Reagent (g)	Condition	Time (h)	Yield (%)[b]	Ref.
1	TCM (0.05)	solvent free/ 110 °C	1	87	-
2	TCM (0.07)	solvent free/ 110 °C	1	92	-
3	TCM (0.1)	solvent free/ 110 °C	1	92	-
4	TCM (0.1)	*n*-hexan/ reflux	24	-	
5	P_2O_5/SiO_2 (0.1)	solvent free/ 110 °C	3	90	31
6	[EMIM]OAc (0.017)	ultrasound/ r.t.	0.7	87	14
7	NaH_2PO_4 (0.33 mmol)	solvent free/ 120 °C	0.5	99	15
8	DABCO (0.7 mol%)	*t*-BuOH/ 65 °C	12	92	11
9	*N*-methyl 2-pyrrolidone hydrogen sulfate (0.08)	solvent free/ 100 °C	1.5	87	16
10	K10 (0.01)	EtOH/ Reflux	1.5	85	17
11	ZMS-5 (0.01)	EtOH/ Reflux	1.8	84	17
12	Sulfated zirconia, SZ (0.01)	EtOH/ Reflux	1.6	82	17
13	*n*-Bu_4NBr (0.032)	*i*-PrOH/ 82 °C	0.3	95	18
14	$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (0.12 g)	solvent free/ MW	0.16	94	19
15	Nano MgO (0.008 g)	solvent free/ 100 °C	0.5	94	20
16	KH_2PO_4 (0.5 mol %)	EtOH/ Reflux	0.6	93	21

[a] 1 mmol of benzil, 1 mmol of benzaldehyde and 2 mmol of ammonium acetate were used.
[b] Isolated yield.

Benzil, ammonium acetate and various aldehydes were then used as substrates for the synthesis of 2,4,5-tri substituted imidazoles (Table 2, scheme 1). Most of the products were known and identified by spectroscopic data and comparison with literature.



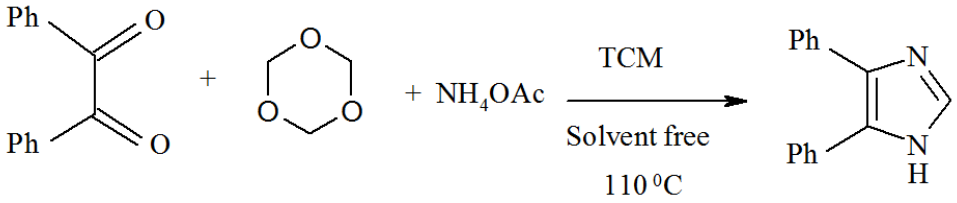
Scheme 1: Synthesis of 2,4,5-tri substituted imidazoles in the presence of trichloromelamine (TCM).

Table 2 Synthesis of 2,4,5-triaryl (alkyl)-1*H*-imidazoles promoted by trichloromelamine[a]

Entry	R	time(h)	yield (%)[b]	m.p. °C		ref.
				obtained	reported	
1	C_6H_5	1	90	274-275	275-276	14
2	4-$(CH_3)_2CHC_6H_4$	1	94	253-255	-	-
3	4-$CH_3OC_6H_4$	1.5	90	226-228	227-228	18
4	2-$CH_3OC_6H_4$	1.5	88	209-211	207-208	14
5	2-ClC_6H_4	2	89	197-199	197-199	14
6	4- ClC_6H_4	3.5	88	261-263	260-262	17
7	2,4-$Cl_2C_6H_3$	11	78	174-175	174-175	16
8	4-BrC_6H_4	2.5	90	264-265	263-265	19
9	2-$NO_2C_6H_4$	6.5	87	228-230	230-231	31
10	3-$NO_2C_6H_4$	3	86	268-269	269-271	19
11	4-$NO_2C_6H_4$	7	89	237-238	239-242	14
12	$(CH_2O)_3$	3	43	101-103	-	-
13	3,4-$(HO)_2C_6H_3$	4.5	-	270-271	272	18

[a]The ratio of benzil (mmol): aldehyde (mmol):ammonium acetate (mmol): trichloromelamine (g) is 1:1:2:0.07
[b]Isolated yield

For synthesis of two substituted imidazole, we have used 1,3,5-trioxane as formaldehyde source (Scheme 2).

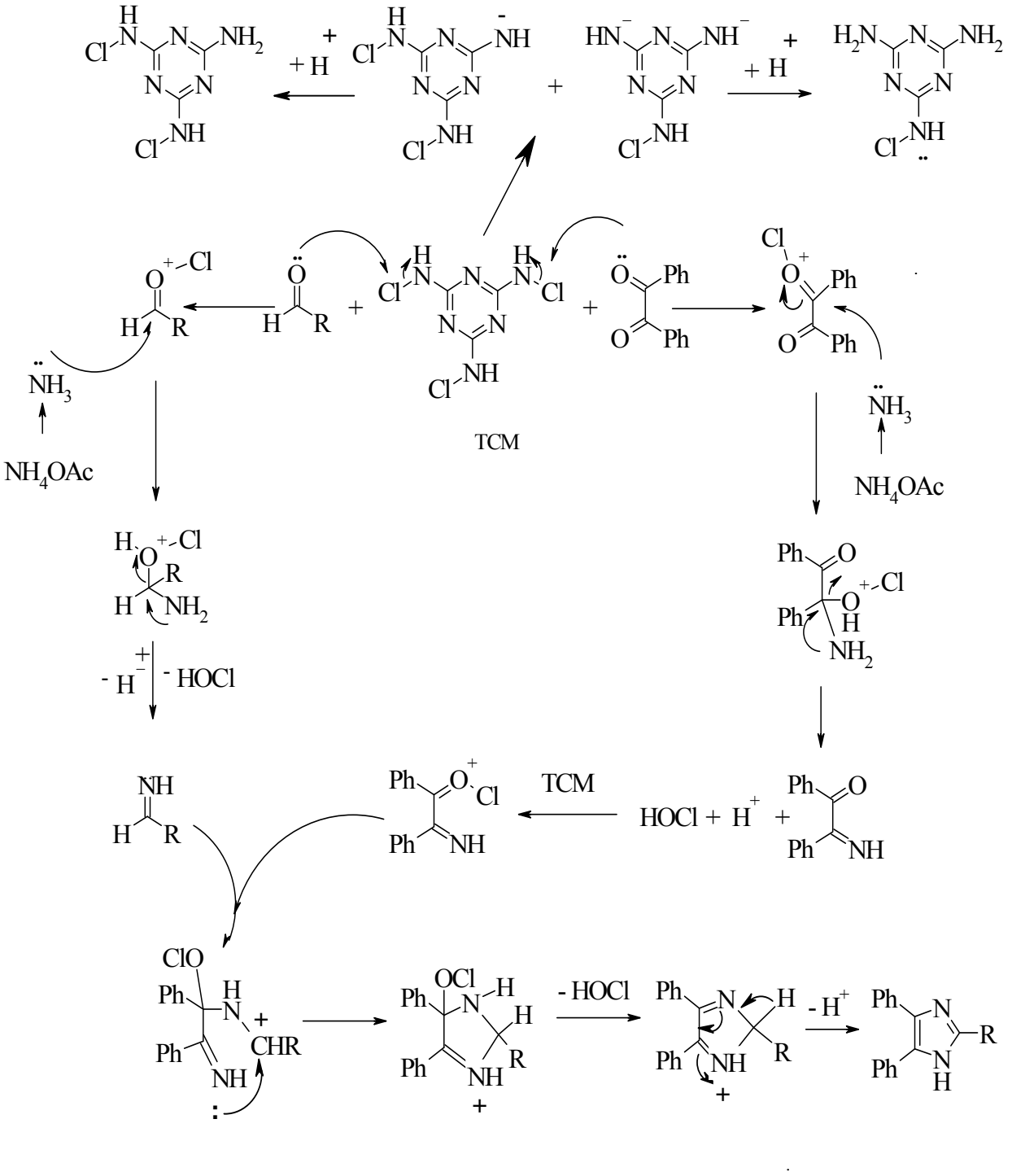


Scheme 2: Synthesis of 4, 5-diphenyl imidazole in the presence of trichloromelamine (TCM).

The presence of one broad singlet signal in δ=7.22 ppm, proves the formation of 4,5-diphenyl imidazole. According to our investigation about the mechanism of 2,4,5-trisubstituted imidazole synthesis in the presence of trichloromelamine, we have found that one or two NHCl group in this reagent converts to NH_2 group. The reusability of trichloromelamine in this reaction is 2 or 3 times. Thus, we have proposed a mechanism for preparation of 2,4,5-trisubstituted imidazole in the presence of trichloromelamine as positive chlorine catalyst in scheme 3.

3. Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of 2,4,5-trisubstituted imidazoles using trichloromelamine as an eco-friendly, inexpensive, and efficient reagent. Short reaction times, high yield, simplicity of operation and easy work-up are some advantages of this method.



Scheme 3. A proposed mechanism for the synthesis of 2,4,5- trisubstituted imidazoles in the presence of TCM.

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Experimental

The chemicals were used without any additional purification. The products were characterized by FT-IR (ATR), ^{1}H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H-NMR spectra. Elemental analyses were done by Costech ECS 4010 CHNS-O analyser.

General procedures for the synthesis of 2,4,5-trisubstituted imidazoles in the presence of trichloromelamine

A mixture of benzil (1 mmol), aldehyde (1 mmol), ammonium acetate (2 mmol) and trichloromelamine (0.07 g) was heated with stirring at 110 °C. After completion of the reaction (monitored by TLC), acetone was added to the cold reaction mixture and the catalyst was recovered by filtration and washed with acetone (2 × 5 ml). By adding water to the filtrate, a milky to yellow solid was obtained. The dried solid was washed with hot *n*-hexane to obtain highly pure product. Most of the products were known and identified by comparison of their physical and spectral data with those of authentic samples.

Selected spectroscopic data

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

FT-IR: ῡ (KBr) = 3443 (N-H), 3038, 1602, 1504, 1461, 766, 697 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.68 (s, 1 H, N-H), 8.09 (d, ^3J = 7.5 Hz, 2 H, Ar-C-H), 7.38 (t, ^3J = 7.2 Hz, 2 H, Ar-C-H), 7.31 (brs, 2 H, Ar-C-H), 7.23 (brs, 1 H, Ar-C-H), 7.45-7.55 (m, 8H, Ar-C-H) ppm.

2-(4-Isopropyl phenyl)- 4, 5-diphenyl-1*H*-imidazole (Table 2, entry 2)

FT-IR: ῡ (KBr) = 3029, 2961, 1602, 1490, 837,765, 696 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): 12.60 (s, 1 H, N-H), 8.01 (d, ^3J = 8.2 Hz, 2 H, Ar-C-H), 7.35 (d, ^3J = 8.2 Hz, 2 H, Ar-C-H), 7.38-7.52 (m, 10 H, Ar-C-H), 2.94 (sep, ^3J = 6.9 Hz, 1 H, C-H), 1.25 (d, ^3J = 6.9 Hz, 6 H, 2CH_3) ppm. Elemental analysis. Found, %: C 85.03; H 6.61; N 8.36. $C_{24}H_{22}N_2$. Calculated, %: C 85.17; H 6.55; N 8.28,

2-(2-Chlorophenyl)-4, 5-diphenyl-1*H*-imidazole (Table 2, entry 5)

FT-IR: ῡ (KBr) = 3026, 1600, 1482, 1069, 826, 766, 695 cm^{-1}, ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 7.27 (brs, 3 H), 7.42 (brs, 5 H), 7.49 (brs, 3 H), 7.67 (brs, 2 H), 8.55 (brs, 1 H), 12.5 (s, 1 H, N-H).

2-(4-Chlorophenyl)-4, 5-diphenyl-1*H*-imidazole (Table 2, entry 6)

FT-IR: ῡ (KBr) = 3026, 1600, 1482, 1069, 826, 766, 695 cm^{-1}, ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 12.8(s, 1 H, N-H), 8.14(s, 1 H, C-H), 8.04 (d, 1 H , ^3J= 7 Hz), 7.25-7.55 (m, 12 H, Ar-H).

2-(4-Bromophenyl)-4, 5-diphenyl-1*H*-imidazole (Table 2, entry 8)

FT-IR: ῡ (KBr) = 2963, 1452, 1490, 835, 764, 694 cm^{-1}, ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 7.35 (brs, 7 H), 7.56 (brs, 3 H), 7.61(brs, 4 H).

2-(4-Nitrophenyl)-4, 5-diphenyl-1*H*-imidazole (Table 2, entry 11)

FT-IR: ῡ (KBr) = 3061, 1599, 1487, 1516, 1339, 1108, 854, 765, 695 cm^{-1}, ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): 7.29 (brs, 3 H), 7.40 (brs, 3 H), 7.52 (brs, 2 H), 7.67 (d, ^3J=8, 4 H), 8.07 (m, 2 H), 11.81(s, 1 H, N-H).

4, 5-Diphenyl-1*H*-imidazole (Table 2, entry 12)

Yield: 43%, white solid, m.p. 101-103 ˚C.
FT-IR: ῡ (KBr) = 3436, 3050, 1600, 1460, 1127, 765, 697 cm-1, ^{1}H-NMR (500 MHz, DMSO-d6): 12.68 (s, 1H, N-H), 8.08 (d, 3J = 6 Hz, 2 H), 7.46-7.54 (m, 4 H, Ar-C-H), 7.38 (brs, 2 H, Ar-C-H), 7.30 (brs, 2 H, Ar-C-H), 7.22 (brs, 1 H) ppm. Elemental analysis. Found, %: C 81.68; H 5.55; N 12.77. $C_{15}H_{12}N_2$. Calculated, %: C 81.79; H 5.49; N 12.72.

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