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One pot Solvent free synthesis of 2, 4, 5-Trisubstituted Imidazoles using wet cyanuric chloride

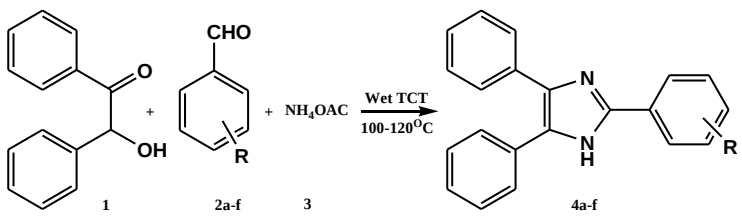
Madhuri S Kulkarni, Ritu Mamgain, Ketaki Saravate and Revati R Nagarkar

Abstract
One-pot three component synthesis of 2, 4, 5-trisubstituted imidazoles using wet Cyanuric chloride as an efficient organic catalyst is explored. The advantages of this methodology are solvent free synthesis, high yields, easy workup, short reaction times and atom economy.

Keywords: One pot synthesis, wet cyanuric Chloride, 2, 4, 5-trisubstituted imidazoles

1. Introduction
Imidazole is a five-membered planer aromatic heterocycle which consists of two nitrogen atoms at 1 and 3 positions. It is an important pharmacophore involved in many biological activities such as anti-inflammatory [1, 2], antitumor [3], antiparasitic [4], antiprotozoal [5, 6], antidiabetic [7], antibiotic [8, 9], antifungal [10], antimalarial [11], antiulcerative [12] and analgesic [13].
One pot synthesis is the strategy to conduct several reaction sequences in one reaction vessel. It has advantages of atom economy, easy workup procedure and improved yields. One pot synthesis of 2, 4, 5-trisubstituted imidazoles by the reaction of substituted aromatic aldehydes, ammonium acetate and benzoin/ benzil have been carried out using a variety of catalysts viz., silica sulfuric acid [14], $NiCl_2.6H_2O/Al_2O_3$ [15], sodium bisulfite [16], potassium aluminium sulphate [17], polymer-supported $ZnCl_2$ [18], phosphomolybdic acid [19], $ZrOCl_2.8H_2O$ [20], L-proline [21] and PTSA [22], $InCl_3.3H_2O$ [23].
Many of the above mentioned synthetic protocols suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged reaction time and use of polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO. This results into tedious workup which generates waste solvent, which have to be recovered, treated and disposed off.
As a part of our program aiming at developing new methodologies for the preparation of heterocyclic compounds containing nitrogen [24], here we would like to report new routes for the direct synthesis of 2, 4, 5-trisubstituted imidazoles using wet cyanuric chloride (wet 2, 4, 6-trichloro-1, 3, 5-triazine/ wet TCT) as an efficient catalyst under solvent free condition.

2. Results and Discussion
On reacting substituted benzaldehydes with benzoin and ammonium acetate in presence of catalytic amount of wet cyanuric chloride (Wet TCT), we obtained 2, 4, 5 tri-substituted imidazoles in good yield (Scheme 1).



Scheme 1

Different reaction conditions were employed to achieve best results. When the reaction was carried out in ethanol without catalyst, no product was obtained even after prolonged heating. On using TCT as catalyst without solvent at high temperature and in ethanol at 80 °C resulted

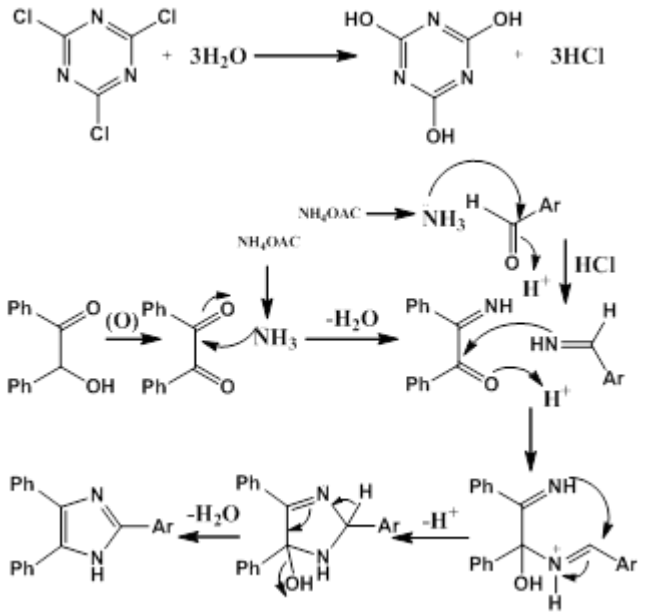
in low yields. When the reaction was carried out in wet TCT, product was obtained in high yield (Table: 1).

The use of 10 mol % of wet TCT afforded good yields. However, on increasing catalyst to 30 mol % no change in yield was found. Similar reaction was carried out in microwave at 700 W. The product was obtained in 6 min along with few side products which were difficult to separate, consequently this methodology was not further explored.

Table 1: Catalytic evolution for synthesis of 4a under different conditions.

Entry	Catalyst	Solvent	Temp (° C)	Yield %
1	No catalyst	Ethanol	80	0
2	TCT	Ethanol	80	20
3	TCT	-	120	20
4	Wet TCT	-	120	90

The reason for high yield is in-situ generation of HCl from TCT in presence of water (Scheme 2). The HCl generated oxidises benzoin to benzil. It also acts as a protic acid to activate the carbonyl oxygen of benzil for imine formation with ammonia released from ammonium acetate. This imine reacts with imine of substituted aldehyde to form the derivatives of 2, 4, 5 trisubstituted imidazoles. [25] All the aldehydes gave good yield except hydroxy substituted aldehyde such as salicylaldehyde which resulted in poor yield. We were able to improve yield only by increasing the equivalents of aldehyde. The reason for above observation can be explained by the interaction of hydroxy group of salicylaldehyde with TCT.



Scheme 2: Plausible mechanism of 2, 4, 5-trisubstituted imidazole formation.

3. Experimental

3.1 General

Melting points were determined using a Thiele's tube and are uncorrected. IR spectra were obtained on Perkin-Elmer FTIR-1710 spectrophotometer using KBr/Nujol film. ^{1}H NMR spectra were recorded on Bruker at 400 and 300 MHz, respectively, using TMS as an internal standard. Analytical TLCs were performed on pre-coated Merck silica gel 60 F254 plates; the spots were detected either under UV light or by placing in iodine chamber. All melting points compared satisfactorily with those reported in the literature.

Table 2: Wet TCT catalysed synthesis of 2, 4, 5 trisubstituted imidazole

Entry	R	Yield %*	MP °C	
			Found	Reported
4a	3,4- OMe	90%	220	215[a]
4b	4-NO_2	86%	200	196[a]
4c	4-Cl	88%	260	262[a]
4d	4-OMe	90%	225	222-223[a]
4e	2-NO_2	85%	228	224[b]
4f	2-OH	65%	206	-

(a- ref. 23, b- ref 26), *Crude yield

3.2 General Procedure for the synthesis of 2, 4, 5-trisubstituted imidazoles (4a-f)

A mixture of substituted benzaldehyde (2a-f) (1 mmol), benzoin (1 mmol) and ammonium acetate (3 mmol) and wet TCT 10 mol% was stirred and heated at 120 °C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with diethyl ether. Ether layer was dried over Na_2SO_4 and evaporated. Crude imidazole obtained was recrystallised from ethanol (4a-f). The results are summarized in Table 2. All the products are known compounds were characterized by IR and ^{1}H NMR. All melting points compared satisfactorily with those reported in the literature.

3.2 Spectroscopic data of synthesized compounds

(4a) 2-(3, 4-dimethoxyphenyl)-4, 5-diphenyl -1 *H*-imidazole: solid M.P: 220 °C, IR (cm^{-1}, KBr): 3446, 1633, 1545; ^{1}H NMR ($CDCl_3$): δ 7.24- 7.56 (m, 13H), 6.87-6.89 (d, 1H), 3.90 (s, 3H), 3.89 (s, 3H).

(4b) 2-(4-Nitrophenyl)-4, 5-diphenyl -1 *H*-imidazole: solid M.P: 200 °C, IR (cm^{-1}, KBr): 3456, 1640, 1589, 1523, 1348; ^{1}H NMR ($CDCl_3$/DMSO-*d6*): δ 12.61 (br, s, 1H); 7.26-8.48 (m, 14H).

(4c) 2-(4-Chlorophenyl)-4, 5-diphenyl-1 *H*-imidazole: solid; M.P. 260 °C; IR (cm^{-1}, KBr): 3447, 1620, 1519. ^{1}H NMR ($CDCl_3$/DMSO-*d6*): *δ* 12.60 (br, s, 1H), 7.76-7.90 (d, 2H), 7.44- 7.51 (d, 2H), 7.12-7.45 (m, 10H).

(4d) 2-(4-Methoxyphenyl)-4, 5-diphenyl -1*H*-imidazole: solid; M.P: 225 °C; IR (cm^{-1}, Nujol): 3433, 1619, 1527; ^{1}H NMR ($CDCl_3$/DMSO-*d6*): δ 12.48 (br, s, 1H), 7.82–7.85 (d, 2H), 7.18–7.31 (m, 10H), 6.92–6.96 (d, 2H), 3.72 (s, 3H).

(4e) 2-(2-nitrophenyl)-4, 5-diphenyl -1*H*-imidazole: solid; M.P 228 °C; IR (cm^{-1}, Nujol) 1601, 1524, 1502, 1364, 724, 694. ^{1}H NMR (DMSO-*d6*): δ 12.98 (br, s, 1H), 8.00 (d, 1H), 7.93 (d, 1H), 7.79 (t, 1H), 7.64 (t, 1H), 7.35-7.60 (m, 8H), 7.31 (t, 1H), 7.23 (t, 1H).

(4f) 2-(2-Hydroxyphenyl)-4,5- diphenyl -1*H*-imidazole: solid; M.P: 206 °C; ^{1}H NMR ($CDCl_3$/DMSO-*d6*): δ 7.25-7.55 (m, 12 H), 7.05-7.08 (d, 1H), 6.87-6.91 (t, 1H).

4. Conclusion

Wet cyanuric chloride was optimized for the synthesis of trisubstituted imidazoles. The present one-pot synthetic method provides an alternate methodology to obtain excellent yield of product, in less reaction time under solvent free condition with 10 mol% of wet TCT. The catalyst in presence of water gives cyanuric acid as by product that can be easily removed by washing. Hence our protocol is a good choice for chemical industries.

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