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Comparison of Sonochemical and Conventional Methodologies for the Efficient Multicomponent one-pot Synthesis of Tetra-Substituted Imidazoles

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Abstract

Sonochemical reactions are one of the most explored synthetic methodologies in the current era. The combination of green approach, efficiency and selectivity of sonochemical synthesis makes it a quite worth exploring filed. Imidazoles are interesting heterocyclic compounds that are integral part of a number structural scaffolds of medicinal, synthetic and industrial importance. The presented work is centered around comparison of different conventional and nonconventional synthetic strategies, including sonochemistry, for the synthesis of tetrasubstituted imidazoles using facilie method(s) that would afford product in high yields.

The work involved multicomponent reaction between aromatic aldehydes, aniline, benzil and ammonium acetate in presence of Lewis acid catalysts. Best yields were obtained when FeCl3 was used as catalyst whereby 87% yield of product was obtained at 30C with in 30 min of reaction time.

Keywords: ***Tetrasubstituted imidazole, Sonochemistry, Green Chemistr, Lewis acid catalysts***

Introduction

The imidazoles are one of important classes of heterocyclic compounds which is found extensively in nature. Apart from their applications as useful intermediates in reaction chemistry, these heterocycles have found a plethora of medicinal importance; which includes but not limited to: antiedema [1], anti-inflammatory [2], analgesic [3], anthelmintic [4], anti-bacterial [5], antitubercular [6], anti-fungal [7], antitumor [8], anticancer [9] and antiviral activities [10], β-lactamase inhibitors, (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, *trans*-[Ru(3-hydroxy-2-methylpyran4-onato)$_2$ (2-methyl-5-nitro-1H-imidazol-1-ethanol)$_2$] CF_3SO_3 and *trans*-[Ru(2-ethyl-3-hydroxypyran-4-onato)$_2$ (2-methyl-5-nitro-1H-imidazol-1-ethanol)$_2$] CF_3SO_3 were shown to exhibit anti-cancer activity comparable to cisplatin [11]. 2-substituted benzimidazole. Several of the synthesized products were subjected for anticancer screening which revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma [12]. Many imidazoles have been prepared as pharmacological agents Azomycine, Clotrimazole, Miconazole, Ergothionine, Clonidine and Moxonidine. One of the most important applications of imidazole derivatives is their used as material for treatment of denture stomatitis [13]. The general synthesis of benzimidazoles is by the condensation reaction of 1,2-phenylenediamine with carboxaldehydes, carboxylic acids [14,15] or their derivatives [16,17] such as, chlorides, nitriles, and orthoesters, under strong acidic conditions, with high temperatures. Benzimidazoles have also been prepared on a solid phase to prove a

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combinatorial approach [18]. The most popular strategies for their synthesis utilize N-alkylation of unsubstituted benzimidazoles [19]. Ammonium salts are also useful for the synthesis of highly substituted imidazole scaffold [20].

Tetrasubstituted imidazoles are generally synthesized in a four-component condensation of aldehydes, 1,2-diketones, amines, and ammonium acetate in the presence of various catalysts such as silica gel or HY zeolite [21], silica gel/$NaHSO_4$ [22], $K_5CoW_{12}O_{40}$ [23], I_2 [24], $HClO_4$-SiO_2 [25], polyacids [26], $InCl_3$ [27], $FeCl_3$ [28], BF_30-SiO_2 [29], Al_2O_3 [30], $Cu(OAc)_2$ [31], DABCO [32], ionic liquid [33], $Zr(acac)^4$ [34], nano-$TiCl_4.SiO_2$ [35] and under microwave conditions [36].

Sonochemical synthesis is one of the non-conventional methods in synthetic chemistry which is being extensively explored. Considering the scope of research in this field, it was planned to synthesize tetra-substituted imidazoles by conventional and non-conventional (sonochemical) methods and to compare the outcome of the two strategies.

Materials and Methods

The TLC was carried out on pre-coated silica gel (0.25 mm thick layer over Al sheet, Merck) with fluorescent indicator. The spots were visualized under UV lamps (365 and 254 nm λ) of 8W power. The compounds were purified either on glass column packed silica gel (0.6-0.2 mm, 60 A mesh size, Merck) or by crystallization. All solutions were concentrated under reduced pressure (25 mm of Hg) on a rotary evaporator (Laborota 4001, heidolph) at 35-40°C. Melting points were determined using a MF-8 (Gallenkamp) instrument and are reported uncorrected. IR-spectra are recorded on Prestige 21 spectrophotometer (shimadzu) in diffused reflectance mode. Ultrasonication was performed in a Greatsonic, China ultrasound cleaner with a frequency of 50 kHz and an output power of 200 W.

Representative procedure for conventional synthesis of 1, 2, 4, 5-tetraphenyl-1H-imidazole

The reaction mixture comprising of equimolar amount of benzaldehyde (0.01 mmol), aniline (0.01 mmol), NH_4OAc (0.01 mmol) and benzil (0.01 mmol) in EtOH (20 mL), H_2SO_4 (1-2 mL) was added and the reaction was subjected to reflux. Progress of reaction was monitored by TLC. By the end of reaction, the product was obtained as pale yellow solid upon cooling the reaction mixture to room temperature. Yield: 67%

Representative procedure for sonochemical synthesis of 1, 2, 4, 5-tetraphenyl-1H-imidazole

The reaction mixture comprising of equimolar amount of benzaldehyde (0.01 mmol), aniline(0.01 mmol), NH_4OAc (0.01 mmol) and benzil (0.01 mmol) in EtOH (5 mL), 0.05 mol% of different Lewis acids (H^+, $FeCl_3$, $NiCl_2$) was added and the resulting mixture was subjected to ultrasound for appropriate time (Table 1). Progress of reaction was monitored by means of TLC. By the end of reaction, the product got precipitated as pale yellow solid.

Appearance: pale yellow solid; Rf (n-hexane/EtOAc; 3:1): 0.56; IR (KBr) cm-1: 2987 (=C-H), 1510(C=C), 1496 (C=N), 1448 (C=C, aromatic) pale yellow solid; $\mathbf{R_f}$ (n-hexane/EtOAc; 3:1): 0.56; MP: 214-216°C [37]**; IR** (KBr) cm^{-1}: 2987 (=C-H), 1510(C=C), 1496 (C=N), 1448 (C=C, aromatic); Offwhite solid; UV (λmax, ethanol) = 286 nm; 1 H NMR (400 MHz, DMSO): 7.15–8.11 (m, 20H, Ar–H) ppm; 13C NMR (100 MHz, DMSO): 125.1 (2×CH_{arom}), 126.3 (CH_{arom}), 126.4 (CH_{arom}), 127.2 (CH_{arom}), 128.0 (CH_{arom}), 128.1 (CH_{arom}), 128.2 (CH_{arom}), 128.2 (CH_{arom}), 128.3 (CH_{arom}), 128.4 (CH_{arom}), 128.6 (CH_{arom}), 128.7 (CH_{arom}), 129.1 (CH_{arom}), 129.4 (CH_{arom}), 129.5 (CH_{arom}), 130.3 (CH_{arom}), 131.0 (CH_{arom}), 131.2 (CH_{arom}), 131.3 (CH_{arom}), 132.1 (C_{arom}), 134.3 (CH_{arom}), 135.5 (CH_{arom}), 136.6 (CH_{arom}), 136.8 (C_{arom}), 145.4 (CH_{arom}), 145.9 C_{arom}).

TABLE 1. **Optimization of conditions for sonochemical synthesis of 1, 2, 4, 5-tetraphenyl-1H-imidazole**

	Catalysts	Temperature (°C)	Reaction time (min)	Yield (%)
1	-	25	20	-
2	-	30	20	-
3	-	35	20	-
4	-	40	20	-
5	-	50	20	>10
6	-	55	30	>10
7	H_2SO_4	25	20	15
8	H_2SO_4	50	30	18
9	$FeCl_3$ (0.05 mol%)	25	10	69
10	$FeCl_3$ (0.05 mol%)	30	10	87
11	$FeCl_3$ (0.05 mol%)	50	10	78
12	$NiCl_2$ (0.05 mol%)	25	10	52
13	$NiCl_2$ (0.05 mol%)	30	10	68
14	$NiCl_2$ (0.05 mol%)	50	10	63

Results and Discussion

Considering the importance of imidazole scaffold in pharmaceutical and industrial chemistry, the presented work was carried out to compare the effectiveness of conventional (reflux) and non-conventional sonochemical method for the synthesis of tetra-substituted imidazoles.

The strategy involved multicomponent reaction between aldehyde, benzil, ammonium acetate and aniline (scheme 1)

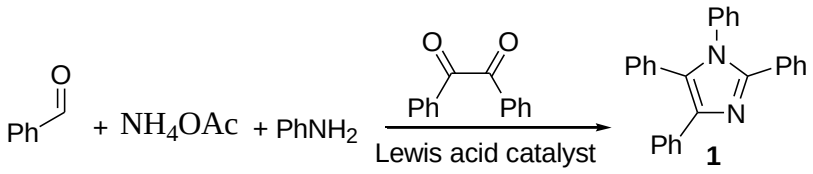

FIG. 1. **To study the outcome of this comparative study, synthesis of 1, 2, 4, 5-tetraphenyl-1H-imidazole 1 was under taken as model study.**

Conventional method

In this method, all components of the reaction were taken in one reaction flask and reaction was subjected to reflux in presence of 1-2 mL of H2SO4 used as a catalyst and EtOH was used as solvent. The reaction progress was monitored by means of TLC. The reaction was complete in 20 min and once the reaction mixture approached room temperature, the product got precipitated out as pale yellow sold.

The formation of product was confirmed by nitrogen test (Lassigne test method). The negative test with 2, 4-DNP dip further confirmed absence of any carbonyl functionality. The spectroscopic evidence also confirmed the absence of C=O stretching vibrations in IR spectrum. Furthermore, the FTIR spectrum also indicated absence of any N-H stretching; thus confirming the formation of desired product 1. The appearance of 20H in aromatic region in 1H NMR and appearance of doublet carbons and singlet carbons in 13C NMR confirm formation of product beyond doubt.

Sonochemical method

In this method, all components of the reaction were taken in one reaction flask and reaction was subjected to reflux in presence of 0.05 mol% of different Lewis acid catalyst and EtOH was used as solvent. The reaction progress was monitored by means of TLC (table 1).

The absence of Lewis acid catalyst resulted in no progress in reaction. However when H_2SO_4 was added as catalyst, the reaction progress was not quite significant and >10% of product yield was obtained. These findings suggested that H_2SO_4 is not suitable in sonochemical conditions as catalyst although it was quite effective under conventional reaction conditions. This also suggests that sonochemical method follows an entirely different mechanistic pathway as compared to the conventional method.

Use of $FeCl_3$ and $NiCl_2$ as Lewis acid catalysts made a significant difference; $FeCl_3$ being more effective than $NiCl_2$. The effect of temperature indicated that yield increases with increase in temperature however after certain temperature limit, the yield decreases instead of increasing. Therefore finding optimum temperature for a certain catalyst and for specific substrate is important when designing a sonochemical synthetic method for a give substrate.

Conclusion

The synthesis of 1, 2, 4, 5-tetraphenylimindazole was successfully carried out under conventional conditions of refluxing the reactants in presence of H_2SO_4 in alcoholic solvent. The reaction was complete in 20 min in 67% yield. In comparison to conventional methodology, the sonochemical methodology of the same substrate resulted in formation of product in 10 min in 69% yield at 20℃ and 87% yield in 10 min at 30℃. These findings indicate that temperature of 30℃ is optimum for synthesis of tetrasubstituted imidazoles under sonochemical conditions. Furthermore, the sonochemical method is a total failure if no catalyst is used. The best results were obtained when $FeCl_3$ was used as a catalyst.

The successful model studies are quite promising it is desired to utilize same strategy for the synthesis of libraries of tetraaryl substituted imidazoles by this green protocol.

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