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AN ORGANOCATALYZED EXPEDITIOUS SYNTHESIS ROUTETO BENZIMIDAZOLESUNDER ULTRASOUND TECHNIQUE

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Abstract: Thecyclocondensation of *o*-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes catalyzed by organocatalyst 3-morpholinopropane-1-sulfonic acid (MOPS) in alcohol under ultrasound technique at 50-60 °C has been reported for the first time. A potentially valuable reaction medium in the presence of MOPS in ethanol has been reacted smoothly retaining near-neutral pH with a pKa of 7.20 and contributed a lot for the synthesis of benzimidazole derivatives which resulted into facile, sustainable and high yielding methodology.

Keywords: Organocatalyst, Benzimidazoles, 3-Morpholinopropane-1-sulfonic acid

Introduction

In this day and age an embryonic awareness of the environmental consequences of the chemical output and protocol by which they are produced has led to the gentle concept of "Sustainable (Green) Chemistry" [i]. Green chemistry has produced itself the landlord of organic chemistry, since its fundamental scientific methodologies can protect human health and the environment in an economically beneficial manner [ii].Literature assessment revealed that organocatalysts are successfully utilized for various organic transformations [iii]. Hence, MOPS could be a dedicated organocatalyst for ultrasound accelerated expeditious synthetic route to benzimidazoles. Literally, several biochemical applications of MOPS have been found as it is an excellent buffer for many biological systems at near-neutral pH with a pKa of 7.20 [iv]. Chemical structure of MOPS contains a morpholine ring having propane sulfonic acid as a substituent at nitrogen atom.

In the review, great number of organic reactions can be carried out obtaining high yields and mild reaction condition under ultrasonication[v]. Herein, double goal has been achieved by using MOPS as a mild organocatalyst and ultrasound irradiation as an energy source for benzimidazole synthesis.

In the last few decades benzimidazoles have been much utilized for the synthesis of diverse highly functionalized molecules because of their broad spectrum of biological/pharmacological activities [vi]. It has been observed that numerous

benzimidazolederivatives are successfully commercialized as potent Active Pharmaceutical Ingredients (APIs). Several benzimidazole derivatives find application as promising drugs in different therapeutic categories as potential anticancer agent [vii], antitubercular [viii], antifungal [ix], antiprotozoal and antibacterial [x], anthelmintic agent [xi], antiviral and antitumor [xii], anti-inflammatory and analgesic [xiii], lipase inhibition and antioxidant [xiv], aurora A/B kinase inhibitor [xv], H_4 receptor antagonists [xvi] and antidiabetic[xvii] activity.

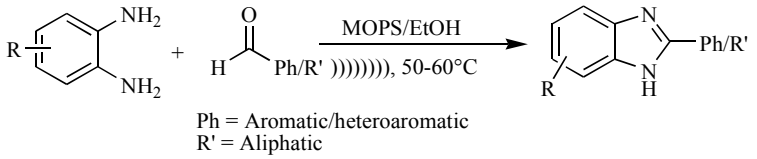
Realizing the importance of benzimidazole derivatives in the synthesis of various drug sources, numerous routs have been reported [xviii]. Some of the other methods involve the use of catalysts like $ZnCl_2$-SiO_2 under microwave irradiation [xix], CAN in PEG-400 [xx], boron sulfonic acid [xxi], $NaHSO_4$ in DMF [xia] at 80 °C, $NaHSO_4$-SiO_2 under solvent free condition [xxii] at 100 °C, and $CdCl_2$ in acetonitrile [xxiv] at 80-85 °C. Apart from this, the present methodologymay help to improve the further aspects of sustainability. Herein, attempt has been made to perform the cyclocondensation of o-phenylinediamine and aromatic/heteroaromatic/aliphatic aldehydes catalyzed by MOPS in ethanol under ultrasonic irradiation to sustain the benign environment (**Scheme 1**).

Result and Discussion

In continuation of author's interest to develop greener research methodologies [xxv] for the synthesis of various heterocyclic compounds herein, for the first time MOPS catalyzed synthesis of benzimidazoles in ethanol under ultrasonic irradiation has been described. The use of organocatalyst under ultrasonic technique is one of the concept of sustainable science.

Initially the reaction of equimolar quantity of *o*-phenylinediamine and benzaldehyde catalyzed by MOPS under ultrasonic irradiation at 50-60 °C has been considered as a standard model reaction. To evaluate the effect of solvent, model reaction was performed in the presence of catalytic amount of MOPS in different solvents. Here, time period 112 mins has been kept constant because while optimizing reaction condition we found complete transformation in ethanol within 112 mins. and only solvents get varied.

Scheme: 1



Ph = Aromatic/heteroaromatic
R' = Aliphatic

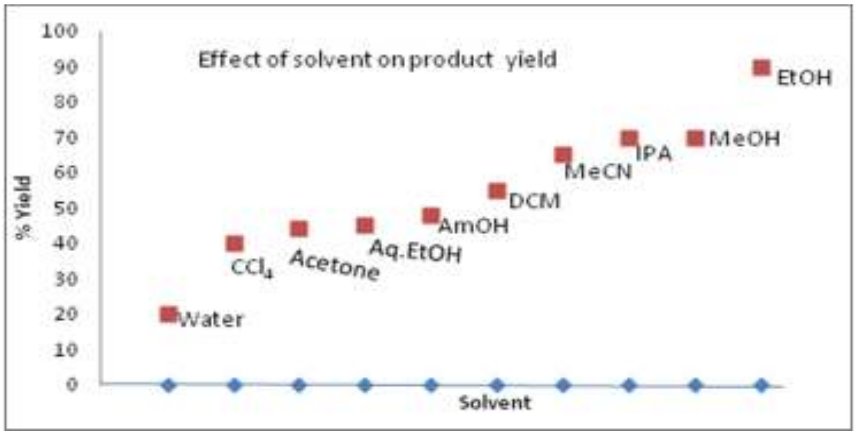


Figure 1: Effect of solvent on yield of the product.

As per **Figure 1**it has been observed that among the different solvents ethanol/MOPS combination shows best auxiliary condition for the desired product benzimidazoles. Rather, methanol and isopropyl alcohol converts somehow appreciable yield of product than other solvents such as acetone, acetonitrile, dichloromethane and carbon. It is also observed that in the combination of water/MOPS only Schiff's base is formed in more extent rather than cyclised product *i.e.* benzimidazole. Hence, authors were delighted to report that among the conditions screened the corresponding benzimidazole was obtained quantitatively high with MOPS at 50-60 °C temperature in ethanol.

In the next study (**Figure 2**), to determine the proper concentration of the catalyst, we have examined the concentration of catalyst as 2, 4, 6, 8, 10, and 12 mol %. The obtained results revealed that, when the reaction was carried out in the presence of 2, 4, 6 mol% of catalyst it gives lower yield of product even after prolonged reaction time.

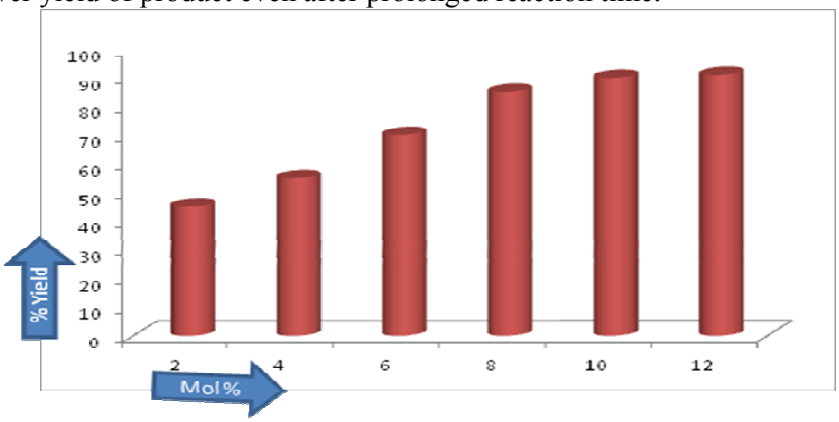


Figure 2: Screening of catalyst concentration for model reaction.

At the same time when the concentration of catalyst was 10 or 12 mol% we got the excellent yields of product 90 and 91 % respectively in short span. Even after increasing the catalyst concentration the yields of the products were found to be constant. This indicates that 10 mol % of MOPS is enough to carry out the reaction efficiently.

The plausible step-up interactions of substrate molecules with MOPS in alcohol medium aredescribed according to the structural reactivity (**Figure 3**).

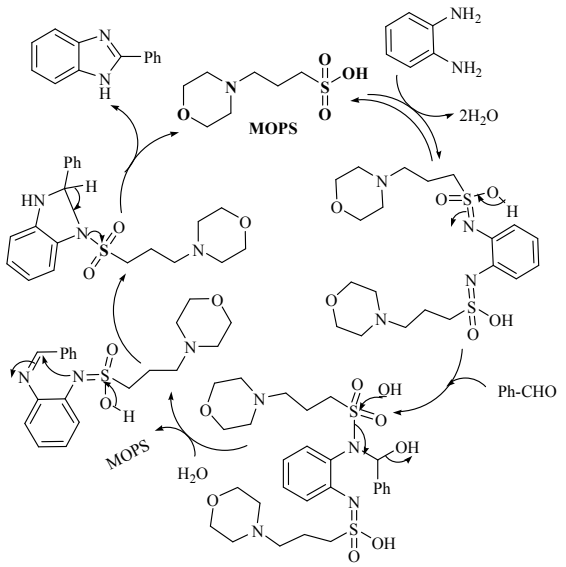


Figure 3: Organocatalyzed mechanism for the synthesis of benzimidazole derivatives.

As in the structure of MOPS, propane side chain imparts inductive donation to deficient sulfur as a result, sulfonic acid proton is not that much anxious to protonate carbonyl group of benzaldehyde or other electronegative groups in the substrate molecules. Consequently, in the reaction mixture MOPS forms benzene disulfonamide intermediate followed by dehydration reaction. This on interaction with benzaldehyde through cyclocondensation obtains desired benzimidazole. During this reaction course neither any harmful substance is formed nor is poisonous gas evolved as a result reaction smoothly runs at near neutral pH contributing wide advantages of sustainable technique. Hence, it is proved that MOPS is suitable organocatalyst to the present reaction scheme, because it can typically be run under aerobic condition and also possess environmentally/user friendly behavior.

Table 1. Sonochemical effect on the synthesis of benzimidazoles.

Entry	Ar	R	Time (hr)	Yield[a,b] (%)
1	C_6H_5	H	4.5	91
2	2Cl- C_6H_4	H	6	84
3	4 Cl- C_6H_4	H	5	89
4	4 OMe- C_6H_4	H	5	87
5	3 OMe- C_6H_4	H	6	81
6	3 OMe, 4 OH- C_6H_3	H	5.5	90
7	4 $N(Me)_2$ C_6H_4	H	5	90
8	Furfural	H	4.5	91
9	C_6H_5	Me	7	80
10	C_3H_7	H	10	78
11	C_6H_5	EDA	15	75

[a]Isolatedyield.[b]Compounds were characterised by ^{1}H NMR, MS spectral data and their physical constant.

To establish the scope and generality of the optimized reaction conditions, various aldehydes such as aromatic, heteroaromatic and aliphatic aldehydes with different substituent and diamines were allowed to undergo this cyclocondensation reaction with remarkable results (**Table 1**).

Almost all the aromatic aldehydes proved to be amenable to these reaction conditions. Interestingly, no significant substituent effect was found on the yield of the products and reaction also proceeds smoothly. Nevertheless, aliphatic aldehydes and ethylene diamine

gives comparatively less yields and takes more time for completion of reaction. The formations of products were confirmed by physical constant and spectroscopic analysis and are in good agreement with reported data.

Experimental

All chemicals were purchased and used without any further purification. Melting points were determined in open capillaries in a Thiele tube filled with paraffin oil and are uncorrected. Equitron ultrasonic bath with a frequency of 42 kHz (2.5 Ltr) and power80 Wattequipped with heater was used for ultrasonic irradiation.

General experimental procedure

In the hard glass test tube, benzaldehyde (0.212g, 0.002 mol) in the solution of MOPS (10 mol%) in ethanol (5 mL) was irradiated in ultrasonic bath at 50-60 °C for 5 minutes. To this solution o-phenylinediamine (0.216g, 0.002 mol) was added and the reaction mass was subjected to ultrasound irradiation for 112 minutes at about same temperature. Progress of the reaction was monitored after interval of each half hour by TLC (n-hexane/ethyl acetate 7:3). After completion of the reaction, the reaction mixture was poured into crushed ice (10 mL). The obtained solid product was filtered and purified by recrystallization from ethanol. Similar procedure was used for the synthesis of other compounds. All synthesized compounds were characterized by their physicochemical and spectral data.

Spectral data and physical constant of representative compounds

2-Pheny-1*H*-benzo[*d*]imidazole (Table 1, entry 1): m.p.291-293 °C, ^{1}H NMR (DMSO-*d6*, 400 MHz, δ ppm): 5.50 (br s, ^{1}H, NH), 8.09 (d, *J* = 7.4 Hz, 2Ar-H), 7.56–7.66 (m, 1, Ar-H), 7.57–7.51 (m, 4Ar-H), 7.21–7.17 (m, 2Ar-H); MS m/z: 194 (m+).

2-(furan-2-yl)-1*H*-benzo[*d*]imidazole (Table 1, entry 8): m.p. 284-286 °C, ^{1}H NMR (DMSO-*d6*, 400 MHz, δ ppm) 5.57 (br s, 1 NH), 7.92 (dd, *J* = 1.8, 0.9 Hz, 1 Ar-H), 7.53 (br s, 2Ar-H), 7.22−7.19 (m, 3Ar-H), 6.73 (dd, *J* = 3.3, 1.8 Hz, 1Ar-H). MS m/z: 184 (m+).

2-Propyl-1H-benzo[d]imidazole (Table 1, entry 10):m.p. 152-154 °C, ^{1}H NMR (DMSO-d*6*, 400 MHz, δ ppm) 0.96 (t, 3 CH_3, *J* = 7.5 Hz), 1.68-1.87 (m, 2 CH_2), 3.05 (t, *J* = 7.5 Hz, 2 CH_2,), 7.20 to 7.30 (m, 2 H), 7.50 to 7.60 (m, 2 H) and 5.3 (brs, 1 H, NH). MS m/z: 160 (m+).

Conclusions

3-morpholinopropane-1-sulfonic acid was found to be mild and environmentally/user friendly organocatalyst in the synthesis of potent benzimidazoles under ultrasonic irradiation in ethanol. The present research involves the use of gracious organocatalyst which will attract attentions of scientific community because of main advantages such as (i) lack of sensitivity to moisture and oxygen, (ii) low cost and low toxicity, (iii) greater selectivity, (iv) easy to scale-up, (v) no metal contamination and (vi) readily availability. The developed economically attractive procedure may be applicable in the production of pharmaceutical and chemical intermediates.

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