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Synthesis Of Imidazole Derivatives Using Multiple Synthetic Routes And Their Catalytic Response

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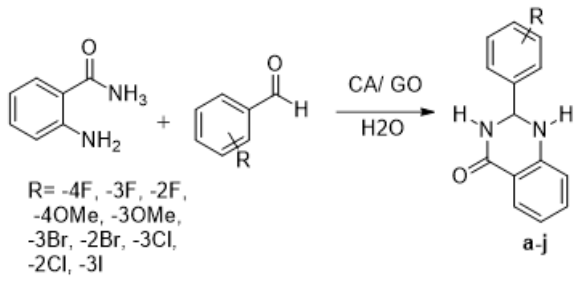
Abstract:
Synthesis of water-soluble imidazole derivatives which is attached with base sensitive fluorophore peripheral units with different organic compounds under conventional and silica supported Muffle furnace methods. Solvent free synthetic approach has more merits than the conventional method, such as non-toxic, shorter reaction time, easy workup procedure without purification process and higher yields. Synthesized substituted imidazole derivatives are acted as excellent catalytic response for the preparation of Gem-bisamides derivative under conventional approach.

Keywords: Imidazole, conventional, solid phase, optimization, Different solvent.

INTRODUCTION

Recently, carbon materials are probably the best alternative for the gene- ration of various organic compound synthesis. Because, they have extraordinary properties, for example, huge explicit surface area, high permeable structure and solid connections among carbon and hydrogen atoms. Thus, graphene oxide is a promi- sing contender for a wide assortment of synergist applications. Nitrogen-containing aromatic heterocyclic compounds, particularly imidazoles, have garnered significant attention in research and industrial chemistry in recent years, mainly due to their versatile range of biological and pharmacological activities [1]. They play a pivotal role in the synthesis of biologically active molecules [2]. They play a pivotal role in the synthesis of biologically active molecules and process [3], such as anticancer, anti-aging, anticoagulant, anti-inflammatory, antimicrobial, anti-tubercular, antidiabetic, antimalarial, antiviral drugs, and enzyme inhibitors [4,5,6]. They also act as selective plant growth regulators, fungicides, herbicides, and therapeutic agents [7]. Nowadays, green chemistry and organometallic catalysis have extended the application of imidazoles as ionic liquids and N-heterocyclic carbenes (NHCs) [8,9]. Therefore, imidazole derivatives have become more popular due to the demand for environmentally friendly methods in chemical organic synthesis. There are several approaches for the synthesis of substituted imidazoles by condensation [10], ring cyclization [11], oxidation

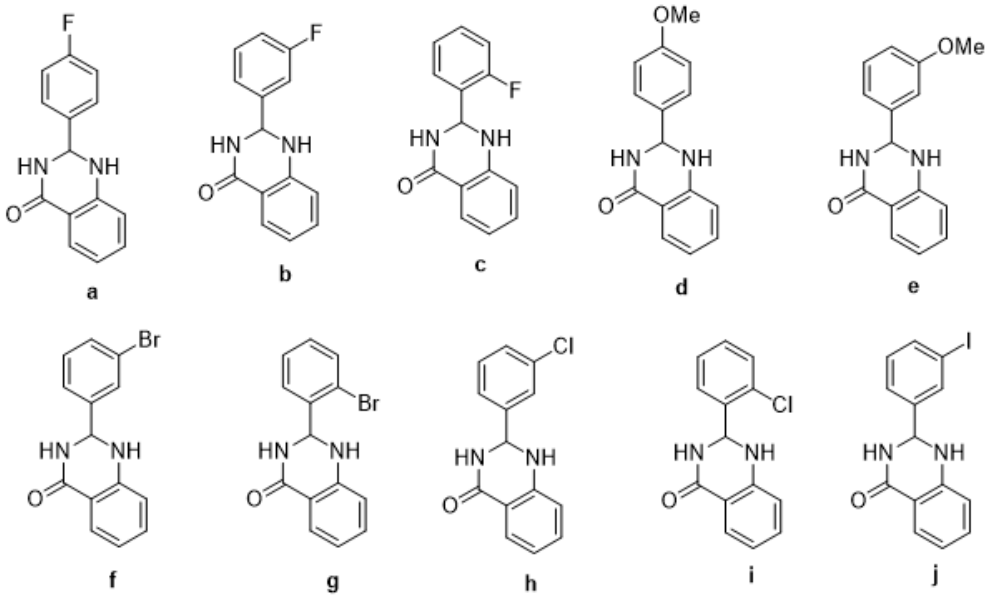
conversion [12], solid face analysis [13], flash vacuum pyrolysis [14], microreactor [15] and ionic liquid promoted technique [16]. In most cases, tri and tetra-substituted imidazoles are synthesized by three or four components of cyclo-condensation of 1,2-diketones, ammonium acetate with aldehydes, and anilines using a variety of different catalysts under efficient green method or solvent-based conditions [17]. Some of the well-known methods for the synthesis of substituted imidazoles are Van Leusen [18], Debus-Radziszewski [19], Marckwald [20], and Wallach [21] in the last few decades [22]. Continuing our interest in N-containing heterocycles [23,24,25], we propose this review, which comprehensively explores recent advancements in imidazole synthesis. We emphasize reviewing critical strategies, catalytic approaches, and sustainable methodologies based on two, three, and four components. As imidazole derivative synthesis continues to evolve, it promises scientific innovation while addressing environmental sustainability concerns in the chemical industry.



Reagent and conditions: CA: H2O/ a-j, ref, 10-75 min, 87-95%;
SSA: Muffule furnace, 100 ^{0}C, 05-35 min., 89-99%

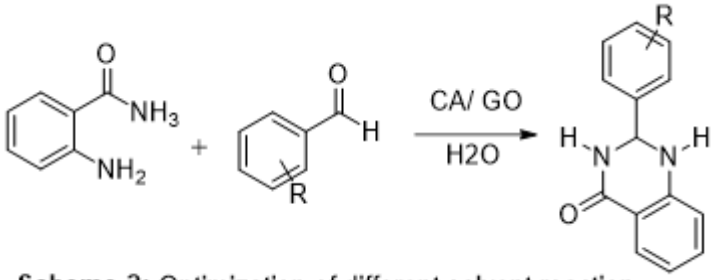
Scheme 1: One-pot synthesis of substituted gem-bisamides derivatives under multiple approach

RESULTS AND DISCUSSION Synthesis of imidazole derivatives: A mixture of organo-catalyst (5 mg), 1 mmol of 2-aminobenzamide was stirred at 30 °C for 10 min. Subsequently, corresponding substituted benzaldehydes (1.2 mmol) was added. The resulting mixture was stirred at the same temperature until the reaction was completed. Then the catalyst was separated by simple filtration. The upper organic phase with the product was concentrated under reduced pressure. The crude products were purified by column chromatography (**Scheme-I**). In present work, citrus extracted modified graphene oxide as a heterogeneous Nano catalyst was synthesized and utilized for the synthesis of imidazole derivatives under mild conditions in a short time. The graphene oxide was prepared via modified Hummers method further the citric acid was covalently bonded to graphene oxide nanosheets and then characterized by using several analytical techniques. **FTIR studies:** FT-IR spectrum of modified graphene oxide revealed characteristic peaks at 1067 (C-O), 1277 (C-O-C), 1389 (C-OH) and 1715 (C=O), while the band at 1625 cm^{-1} can be attributed to the C=C vibration of oxidized graphene sheets [11,13]. The new peaks [Fig. 1A(ii)] appeared at 3355, 1629, 1317 and 781 cm^{-1} which are corresponds to O-H streching, C-H bending, C-H streching and O-H bending, respectively. The high intensity of 1629 cm^{-1} is due to the overlap of amide C=O stretching along with O-H bending.



OPTIMIZATION OF SOLVENT

In order to identify a reliable solvent for the synthesized heterogeneous nanocatalyst catal-yzed in the imidazole derivatives synthesis, a series of solvent such as ethanol, methanol, isopropanol, acetonitrile, tetra- hydrofuran, 1,4-dioxane, toluene, ethanol:water, methanol: water and water were employed. The reaction was performed using organic solvents and the desired imidazoles with a good yield upto 77% (Table-1). To improve more benign nature of the carbocatalyst and practice greener protocols, the experi- ment was tried water as medium, the results were encouraging and excellent yield were observed up to 98% without further purification. Finally, water medium at room.



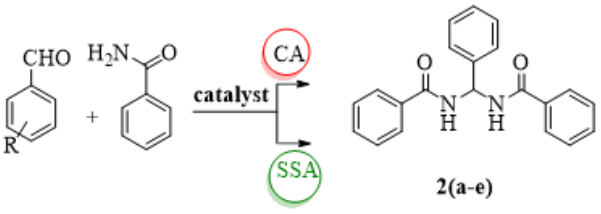
Scheme-2: Optimization of different solvent reaction

CATALYTIC ACTIVITY

Conventional and solid phase solvent free Muffle furnace methods are used to make imidazole derivatives from readily available starting materials. In the presence of various concentrations of our catalyst with/without solvent, a one-pot multicomponent reaction is tested. Substituted imidazole derivatives which outperformed the other imidazole derivatives in the terms of catalytic activity. For one-pot preparation of substituted oxazinone derivatives, the reactions are repeated with various concentrations such as 1.813×10^{-2} mmol, 3.627×10^{-2} mmol, 5.440×10^{-2} mmol, and 7.254×10^{-2} mmol to optimize the catalyst concentration of core moiety containing imidazole derivatives. As the catalyst concentration is increased from 5.440×10^{-2} mmol into 7.254×10^{-2} mmol, the proportion of yield and reaction time have not changed significantly.

S.No	Solvent	Catalyst load (Mg)	Yield (%)
1	H_2O	10	98
2	EtOH	10	77
3	EtOH: H_2O	10	73
4	MeOH: H_2O	10	57
5	MeOH	10	53
6	THF	10	52
7	Iso-Propyl alcohol	10	72
8	Toluene	10	68
9	1,4-Dioxane	10	15
10	Ethyl Acetate	10	70
11	ACN	10	68
[a] Reaction conditions: 2-Aminobenzamide (1 mmol), aldehydes (1.2 mmol), CA/GO catalyst (5 mg), solvent (5 mL), 0.5 h at room temp.;[b]All are isolated yield.			

Under a conventional/solid phase technique, various substituted oxazinone derivatives are produced; reactions are repeated with varying concentrations. $MgFe_2O_4$ and SiO_2-SO_3H catalysts were utilised to prepare benzthioxazione under microwave aided solvent free method, as shown in Tables 1-2. Reaction time and yield percentage are significant, but the catalyst is expensive, as is the base sensive catalyst. The gem-bisamides but derivatives were synthesised using 200 mg of Amberlite IRA-400 Cl catalyst, which took over 2 hours to complete. Imidazole derivatives takes 20 minutes to complete. Catalyst has potential due to its faster reaction time, higher yield without the need of solvents,and environmental friendliness. **Table1.** Derivatives are synthesised with the use of varied concentrations of Imidazole **(a-j).** T= Time in minutes; Y= percentage of yield



Reagent and conditions: CA: CH_3CN/ **(2a-e)**, ref, 10-75 min, 87-95%; SSA: Muffule furnace, 100 ^{0}C, 05-35 min., 89-99%

Scheme 3: One-pot synthesis of substituted gem-bisamides derivatives under multiple approach

CONCLUSIONS

In summary, citric acid on graphene nanosheet was synth- esized via simple chemical modification method. Efficient, imidazole derivatives were preceded over metal-free, citric acid graphene nanosheets under mild conditions. The surface analysis for a prepared heterogeneous orangocatalyst demonstrates that the graphene oxide was well functionalized with citric acid. The citric acid-grafted graphene oxide displayed a superior acidic behaviour and exhibited remarkable catalytic activity. Sustainable nature of the catalyst is very high and more stable even after few cycles.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

S.No	Catalyst	Concentration of Imidazole derivatives											
		1.8135 × 10^{-2} mmol				3.627 × 10^{-2} mmol				5.440 × 10^{-2} mmol			
		CR		MR		CR		MR		CR		MR	
		T	Y	T	Y	T	Y	T	Y	T	Y	T	Y
1	a	90	66	45	77	80	76	35	83	90	89	25	96
2	b	100	65	50	74	90	75	40	80	89	88	30	93
3	c	80	67	40	76	70	77	30	82	91	92	20	90
4	d	70	74	35	80	60	84	25	85	50	91	15	92
5	e	60	77	30	79	50	87	20	86	40	90	10	95
6	f	100	62	50	75	90	72	40	81	80	93	30	88
7	g	110	64	55	72	100	74	45	81	90	91	35	90
8	h	90	67	45	73	80	77	35	80	70	92	25	89
9	I	80	69	40	79	70	79	30	83	60	91	20	91
10	j	70	72	35	76	60	82	25	84	50	95	15	93

EXPERIMENTAL

Analytical reagent grade graphite powder, sodium nitrate, potassium permanganate, citric acid and hydrogen peroxide (30%) were purchased from Sigma-Aldrich and used without further purifications.

Synthesis of heterogeneous organ catalyst: Graphene oxide (GO) was synthesized from graphite powder using modified Hummers method [8], then citric acid modified graphene oxide was synthesized by the following procedure, 200 mg of grap- hene oxide was dispersed in 50 mL of water via sonication. To a dispersed solution, 50 mL of 10 M citric acid solution were added dropwise with constant stirring. The resultant solution was stirred at room temperature for 3 h and the obtained black precipitate was washed thoroughly and labeled as CA/GO [12].

2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (a): Yield: 95%; solid, m.p. 175-177 °C. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.20-7.27), (1Hd, 7.15-7.22), (1Ht, 6.05), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Ht, 7.47), (1Ht, 6.85), (1Hd, 7.69); ^{13}C NMR (75 MHz, DMSO) δ: 76.0, 113.6, 116.7, 117.2, 125.9, 126.7, 128.3, 132.9, 144.4, 145.6, 165. MS: m/z: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.87; H, 5.31; N, 12.44.

2-(3-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (b): Yield: 85%; solid, m.p. 165-167 °C. ^{1}H NMR (300 MHz, DMSO) δ:
(1Hd, 7.20-7.27), (1Hd, 7.15-7.22), (1Ht, 6.05), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Ht, 7.47), (1Ht, 6.85), (1Hd, 7.69); ^{13}C NMR (75 MHz, DMSO) δ: 76.3, 113.7, 116.9, 117.3, 125.5, 126.5, 128.7, 132.3, 144.7, 145.7, 165.3. MS: m/z: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.86; H, 5.30; N, 12.87.

2-(2-fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one (c): Yield: 80%; solid, m.p. 164-166 °C. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.63-7.69), (1Hm, 7.71-7.7.79), (1Hm, 7.10-7.19), (1Hd, 7.29), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.00), (1Hm, 7.47), (1Hm, 6.85), (1Hd, 7.67); ^{13}C NMR (75 MHz, DMSO) δ: 69.3, 113.4, 115.3, 116.8, 117.1, 124.1, 128.2, 128.4, 129.3, 132.7, 145.5, 159.4, 165.1. MS: m/z: 224.26; Anal. Calculated for $C_{14}H_{12}N_2O$: C, 74.91; H, 5.35; N, 12.48; Found: C, 74.85; H, 5.29; N, 12.42.

7-Bromo-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (d): Yield: 78%; solid, m.p. 164-166 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (3Hs, 3.81), (1Hd, 6.89-6.97), (1Hd, 7.45-7.54), (1Hd, 6.01), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.05), (1Hm, 7.47), (1Hm, 6.80), (1Hd, 7.67); ^{13}C NMR (75 MHz, DMSO) δ: 55.9, 76.1, 113.5, 114.1, 116.3, 117.3, 127.8, 128.1, 132.8, 136.5, 145.3, 158.1, 165.7. MS: m/z: 254.29; Anal. Calculated for $C_{15}H_{14}N_2O_2$: C, 70.78; H, 5.50; N, 11.01; Found: C, 70.74; H, 5.46; N, 10.97.

2-(3-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (e): Yield: 75%; solid, m.p. 160-162 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (3Hs, 3.75), (1Hs, 6.95), (1Hd, 6.91-6.97), (1Hd, 7.11), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.05) (1Hd, 7.69), (1Hm, 7.27), (1Hm, 7.47), (1Hm, 6.85); ^{13}C NMR (75 MHz, DMSO) δ: 55.5, 76.4, 111.1, 112.3, 113.5, 116.5 117.2, 118.2, 128.5, 129.3, 132.7, 145.5, 145.7, 160.7, 165.9. MS: m/z: 254.29; Anal. Calculated for $C_{15}H_{14}N_2O_2$: C, 70.78; H, 5.50; N, 11.01; Found: C, 70.73; H, 5.42; N, 10.92.

2-(3-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (f): Yield: 76%; solid, m.p. 169-171 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.45), (1Hd, 7.54), (1Hd, 7.37), (1Hd, 6.05), (1Hd, 6.21), (1Hd, 8.65), (1Hd, 7.01), (1Hd, 7.68), (1Hm, 7.28) (1Hm, 7.47), (1Hm, 6.78); ^{13}C NMR (75 MHz, DMSO) δ: 75.5, 113.6, 116.9, 117.3, 122.8, 124.5, 128.2, 129.1, 129.6, 130.5, 132.8, 145.7, 146.3, 165.4. MS: m/z: 303.16; Anal. Calculated for $C_{14}H_{11}BrN_2O$: C, 55.41; H, 3.62; N, 9.23; Found: C, 55.37; H, 3.58; N, 9.19.

2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1H)-one (g): Yield: 74%; solid, m.p. 159-161 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.55), (1Hd, 7.19), (1Hd, 6.05), (1Hd, 6.27), (1Hd, 8.65), (1Hd, 7.05), (1Hd, 7.69), (1Hm, 7.07), (1Hm, 7.25) (1Hm, 7.35), (1Hm, 6.79); ^{13}C NMR (75 MHz, DMSO) δ: 72.5, 111.3, 113.6, 116.7, 121.9, 127.5, 128.3, 128.9, 129.2, 132.5, 132.9, 136.3, 145.6, 165.3. MS: m/z: 303.16; Anal. Calculated for $C_{14}H_{11}BrN_2O$: C, 55.41; H, 3.62; N, 9.23; Found: C, 55.37; H, 3.58; N, 9.19.

2-(3-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (h): Yield: 88%; solid, m.p. 166-168 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.47), (1Hd, 7.39), (1Hd, 7.33), (1Hd, 6.09), (1Hd, 6.31), (1Hd, 8.65), (1Hd, 7.07), (1Hd, 7.68), (1Hm, 7.29) (1Hm, 7.47), (1Hm, 6.80); ^{13}C NMR (75 MHz, DMSO) δ: 75.9, 113.8, 116.1, 117.3, 124.1, 126.5, 126.2, 128.3, 129.3, 132.7, 134.5, 145.6, 165.4. MS: m/z: 258.71; Anal. Calculated for $C_{14}H_{11}ClN_2O$: C, 64.93; H, 4.25; N, 10.82; Found: C, 64.89; H, 4.21; N, 10.78.

2-(2-chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (i): Yield: 74%; solid, m.p. 159-161 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hd, 7.65), (1Hd, 7.24), (1Hd, 6.07), (1Hd, 6.08), (1Hd, 8.61), (1Hd, 7.05), (1Hd, 7.65), (1Hm, 7.21), (1Hm, 7.26) (1Hm, 7.41), (1Hm, 6.73); ^{13}C NMR (75 MHz, DMSO) δ: 70.5, 113.4, 116.7, 117.1, 126.5, 128.2, 128.3, 128.7, 132.6, 13.5, 132.9, 142.7, 145.3, 165.4. MS: m/z: 258.71; Anal. Calculated for $C_{14}H_{11}ClN_2O$: C, 64.93; H, 4.25; N, 10.82; Found: C, 64.87; H, 4.21; N, 10.78.

2-(3-iodophenyl)-2,3-dihydroquinazolin-4(1H)-one (j): Yield: 79%; solid, m.p. 189-191 ºC. ^{1}H NMR (300 MHz, DMSO) δ: (1Hs, 7.85), (1Hd, 7.79), (1Hd, 7.47), (1Hd, 6.05), (1Hd, 6.21), (1Hd, 8.65), (1Hd, 7.01), (1Hd, 7.68), (1Hm, 7.28) (1Hm, 7.47), (1Hm, 6.78); ^{13}C NMR (75 MHz, DMSO) δ: 75.5, 113.6, 116.9, 117.3, 122.8, 124.5, 128.2, 129.1, 129.6, 130.5, 132.8, 145.7, 146.3, 165.4. MS:

m/z: 350.16; Anal. Calculated for $C_{14}H_{11}IN_2O$: C, 47.97; H, 3.14; N, 7.99; Found: C, 47.93; H, 3.10; N, 9.15.

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