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[P-DABCO]CL/ PEG-400: AN EFFICIENT RECYCLABLE CATALYTIC SYSTEM FOR THE SYNTHESIS OF QUINOLINE DERIVATIVES

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ABSTRACT

Here in we report, synthesis of quinoline derivatives (**4a-j**) by one-pot multi-component reaction between cyanoacetic acid hydrazide , substituted aromatic aldehyde and aromatic amine using [P-DABCO]Cl /PEG-400. This reaction route carries variety of characteristics to become efficient pathway for title compound. The catalytic system for this transformation is heterogeneous, reusable, and mild with short reaction time and with quantitative yield of product. Thus, this green pathway attracts the researchers for simple and efficient transformation with simple isolation and purification of desire product.

I. INTRODUCTION

Convergent synthesis of heterocyclic compounds from relatively simple starting materials can be achieved using tandem C–C bond formations [1-2]. Such transformations are usually operated in one pot without isolation or purification of intermediates. The development of tandem reactions for efficient construction of small molecules with operational simplicity and assembly efficiency is a prime goal of combinatorial chemistry [3-4]. This has attracted significant interest in the era of development of multi-component reaction (MCR) protocols for synthesis of heterocyclic compounds. Furthermore, MCRs comply with the principles of green chemistry in terms of atom economy of steps as well as many of the stringent criteria of ideal organic synthesis.

Such reactions are effective in building highly functionalized small organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity, coupled with minimization of time, labor, cost and waste production [5-6].

Quinoline is an organic compound from heterocyclic class with double-ring structure containing a benzene ring fused with pyridine at two adjacent carbon atoms. Quinoline is also known as, benzopyridine, benzo[b]pyridine, 1-benzazine and benzazine. It is a hygroscopic, yellowish oily liquid, slightly soluble in water, soluble in alcohol, ether and many other organic solvents. Isoquinoline is a congener of quinoline and differs from quinoline in nitrogen position (at 2nd position) [7].

Quinoline alkaloids obtained from natural sources show remarkable biological activities and relatively simple structures have attracted great interest in the scientific community, especially researchers involved in the chemistry of natural products [8]. Quinoline and its congeners have also attracted the interest of synthetic organic chemists due to the need to obtain increased amounts aimed at additional biological research. Quinoline alkaloids derived from flowering plants, animals and microorganisms possessed numerous biological activities [9].

Various quinoline derivatives have been synthesized and reported for different activities. Quinoline derivatives are widely used as "parental" compounds to synthesize molecules with medical benefits, especially with anti-malarial and anti-microbial activities [10-11]. A number of quinoline and its derivatives are known to possess anticancer, antifungal, hypotensive, anti HIV, analgesics and anti-inflammatory activities [12-17]. Substitution of the group in a suitable position of a bioactive molecule is found to exert a profound pharmacological effect [18]. The quinoline nucleus has naturally stirred in many alkaloids with swaying antitumor activity, for example, camptothecin [19]. A

patent was obtained for an isolation procedure of camptothecin a quinoline analogous from Notihapodytes Foetida [20].

On the other hand, cyanoacetic acid hydrazide is well reagent known that the hydrazone group plays an important role for the antimicrobial activity [21]. It plays an important pharmacological activities like antibacterial, antifungal, anticonvulsant, anti-inflammatory, anti-malarial and anti-tubercular activities [22-27]. It is versatile and convenient intermediate for synthesis of heterocyclic compounds [28]. The beta functional nitrile moiety of the molecule is favorable unit for addition followed by cyclization or cycloaddition with numerous reagents [29]. The beta functional nitrile, cyanoacetic acid hydrazide and their analogues are important starting materials or intermediate for synthesis of nitrogen containing heterocyclic compound. The research deals with the effective use of cyanoacetic acid hydrazide in the synthesis of variety of poly functional hetrocyclic compound with biological interest. Cyanoacetic acid hydrazide can act as ambident nucleophile, as both N and C nucleophile.

These findings have oriented attention towards the combination of two bioactive scaffolds for the synthesis of some new series of functionalized quinoline derivatives that might have potent bioactivity.

Recovery of heterogeneous catalysts from the reaction mixture can be simply achieved by filtration, representing an advantage over conventional, homogeneous catalysts. Moreover, they can be reused after activation, thereby making the process economically viable. Naturally occurring clay has unique physical and chemical properties such as shape selectivity, acidic/basic nature and thermal stability. Polysterene-supported DABCO IL catasyst is a highly efficient heterogeneous catalyst that has been used for several organic transformations [30-34]. 1,4 Diazobicyclo[2.2.2] octane (DABCO), an organic amine used as various organic transformation[35] as well as supported catalyst [36].

Another aspect of green synthesis is the use of a green solvent. Liquid or low melting polymers have recently emerged as alternative green solvents with unique properties such as thermal stability, commercial availability, non-volatility, miscibility with a number of organic solvents and recyclability. Polyethylene glycols (PEGs) [37-38] are considered to be such green solvents that overcome the toxic solvent effect on the environment. Most reported methods for synthesis of quinoline derivatives suffer from various drawbacks such as long reaction time and/or application of expensive, toxic catalysts and solvents. Recently, we reported a one-pot three-component reaction of cyanoacetic acid hydrazide with substituted benzaldehyde, and aromatic amines in the presence of heterogeneous catalyst using PEG-400 as a green solvent. In the present work, to establish a quick and efficient approach for this class of compounds, we investigated the catalytic activity of [P-DABCO]Cl in synthesis of quinoline and its derivatives via tandem three-component one-pot reactions in PEG-400 as a green reaction solvent.

II. RESULTS AND DISCUSSION

The heterogeneous catalyst [P-DABCO]Cl IL (polystyrene-supported DABCO) catalyst prepared from chloromethyl polystyrene using reported method [39]

A one-pot, three-component reaction protocol for synthesis of quinoline derivatives in the presence of [P-DABCO]Cl IL as a highly efficient heterogeneous base catalyst was carried out in PEG-400 under stirring. This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost instantaneously. Highly pure product can be obtained simply by recrystallization from aqueous acetic acid (**Scheme 1**) without using any chromatographic technique.

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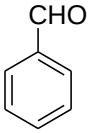
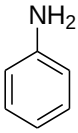
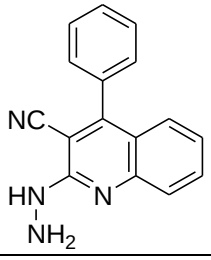
Scheme 1: Synthesis of hydrazinylquinoline-3-carbonitrile derivatives 4a-j.

Considering the importance of the green chemistry concept, the reaction was initially carried out under solvent-free and catalyst-free conditions at RT and high temperature (100°C) for 60 min. However, formation of the desired product was not observed. The increasing interest of organic chemists in the use of PEG-400 as a solvent of choice and its unique properties [35-36] attracted our attention to its use as a green solvent in the present study. Subsequent optimization experiments used PEG-400 as the solvent for reaction, which proceeded very smoothly, and solvent could be recycled as well. At the inception of this work, we studied a one-pot, three-component reaction protocol as a model with [P-DABCO]Cl IL in different solvents (**Table 1**). Our observations revealed that, amongst the various solvents, PEG-400 was the most effective, green and environmentally friendly solvent.

Table 1: Comparison of various solvents for the synthesis of hydrazinylquinoline-3-carbonitrile derivatives

Sr. No.	Solvent	Time (in Min)	Yield (%)
1	_____	120	Trace
2	Acetonitrile	120	50
3	Ethanol	100	60
4	DMF	100	60
5	PEG-400	50	>80

Table 2: Synthesis of compounds (4a-j)

Entry	R_1	R_2	Product	Yield (%)	M.P. (°C)
4a				176-178	80

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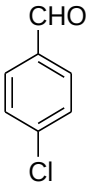
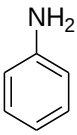
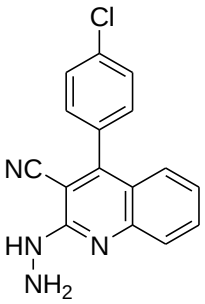
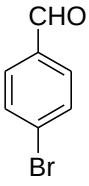
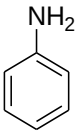
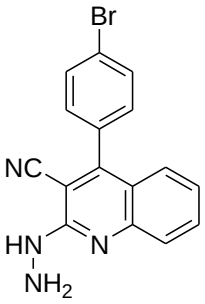
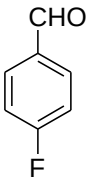
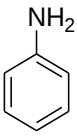
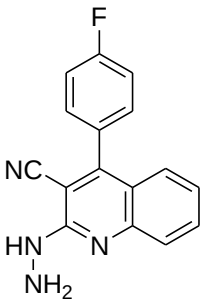
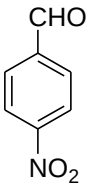
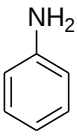
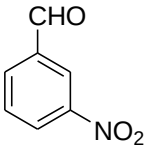
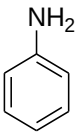
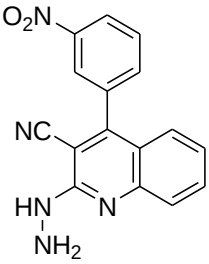
4b				190-192	82
4c				196-198	88
4d				212-214	80
4e				176-178	89
4f				188-190	90

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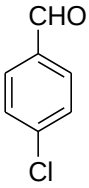
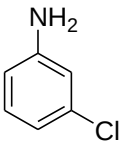
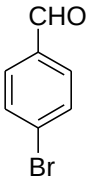
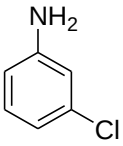
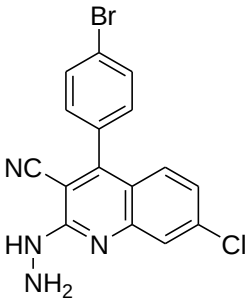
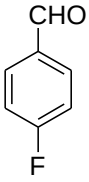
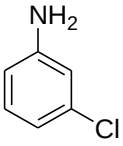
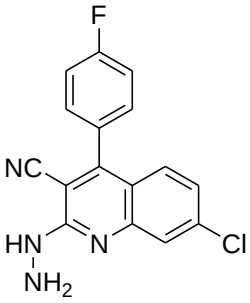
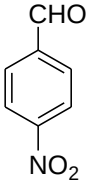
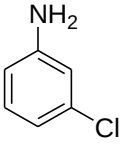
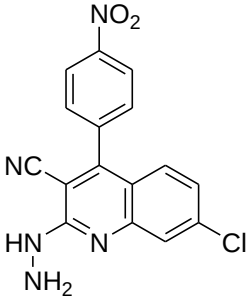
4g				202-204	84
4h				210-212	83
4i				222-224	87
4j				224-226	89

Mechanistically, the formation of the product is proposed to involve the following steps (**Fig. 1**). The reaction occurs via initial formation of 2-cyano-3-phenyl acrylohydrazide by knoevenagel condensation of cyanoacetic acid hydrazide with substituted aromatic aldehyde. Knoevenagel condensation occurs smoothly in presence of [P-DABCO]Cl. Knoevenagel product undergoes Michael addition with substituted amine followed by cyclization and aromatization gives the title product (**4a-j**).

The newly synthesized compounds were established spectroscopically. The infrared (IR) spectra of the compounds showed the presence of –N–H stretch of NH and NH_2 at 3250–3300 cm^{-1} and characteristic stretch at 2200–2300 cm^{-1}, indicating the presence of C≡N group.

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Scheme 2: possible mechanism of catalyzed mechanism

III. MATERIAL AND METHODS

Melting points were determined by open capillary method and were uncorrected. The chemicals and solvents used were of laboratory grade and purified prior to use. Completion of the reaction was monitored by thin-layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using UV chamber. IR spectra were recorded (in KBR pallets) on Shimadzu spectrophotometer.

General procedure for the synthesis of cyanoacetic acid hydrazide:
A mixture of ethyl cyanoacetate (0.01 mole) and Hydrazine hydrate (0.02 mole) in round bottom flask add dropwise with stirring at 0^0c. After completion of reaction (monitoed by TLC).The solution was poured into ice cold water (50 ml) and acidified with dil. HCl. The solid product separated out was filtered and recrystallized from aq. acetic acid as white product.

General procedure for the synthesis of 2-hydrazinyl-4-phenylquinoline-3-carbonitrile derivatives (4a-j)

An eqimolar quantity of cyanoacetic acid hydrazide , substituted aromatic aldehyde and aromatic amine was stirred in PEG-400 in presence of catalytic amount of [P-DABCO]Cl for 1 to 1.5 hrs at 50-60 °C. After completion of reaction (monitored by TLC), reaction mixture is filtered in ice cold water and neutralize by dil HCl. The formed product was filter, washes with water and recrystallized by aq acetic to obtain pure title product.

Synthesis of 2-hydrazinyl-4-phenylquinoline-3-carbonitrile (4a)

M.P. 176-178 °C; Yield, 80% ; IR (KBr, cm^{-1}): 3360-3240 cm^{-1} (N-H), 2245 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.89 (s, 2H, NH_2), 8.26 (s, 1H, NH), 7.92-7.34 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 160.2, 156.0, 150.7, 138, 129.3, 126.8, 127.4, 124.9, 117.0, 83.0; MS: 260 [M^+]; Anal. Calc. for $C_{16}H_{12}N_4$: C 73.83 (72.79), H 4.65 (4.68), N 21.52 (20.92).

Synthesis of 4 (4-chlorophenyl)2-hydrazinylquinoline-3carbonitrile (4b)

M.P. 190-192 °C; Yield, 82% ; IR (KBr, cm^{-1}): 3385-3265 cm^{-1} (N-H), 2239 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.78 (s, 2H, NH_2), 8.12 (s, 1H, NH), 7.84-7.26 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 167.2, 147.2, 153.7, 134.8, 136.2, 132.0, 129.4, 128.8, 126.9, 125.3, 123.8, 117.0, 93.1; MS: 294 [M^+]; Anal. Calc. for $C_{16}H_{11}ClN_4$: C 65.20 (65.33), H 3.76 (3.95), N 19.01 (20.06).

Synthesis of 4-(4-bromophenyl)-2-hydrazinylquinoline-3-carbonitrile (4c)

M.P. 196-198 °C; Yield, 88% ; IR (KBr, cm^{-1}): 3420-3398 cm^{-1} (N-H), 2268 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.93 (s, 2H, NH_2), 8.38 (s, 1H, NH), 7.91-7.52 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 162.8, 153.7, 147.9, 134.0, 132.2, 126.9, 125.8, 124.5, 123.6, 115.6, 114.0, 93.1; MS: 338 [M^+]; Anal. Calc. for $C_{16}H_{11}BrN_4$: C 56.66 (55.89), H 3.27 (3.75), N 16.52 (15.85).

Synthesis of 4(4-flurophenyl)-2-hydrazinylquinoline-3-carbonitrile (4d)

M.P. 212-214 °C; Yield, 80% ; IR (KBr, cm^{-1}): 3255-3362 cm^{-1} (N-H), 2251 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.62 (s, 2H, NH_2), 8.27 (s, 1H, NH), 7.78-7.22 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 168.1, 155.4, 149.5, 138.6, 134.7, 127.2, 124.8, 122.9, 120.4, 116.3, 83.8; MS: 278 [M^+]; Anal. Calc. for $C_{16}H_{11}FN_4$: C 69.06 (70.12), H 3.98 (3.12), N 20.13 (19.89).

Synthesis of 2-hydrazinyl-4(4-nitrophenyl) quinoline -3-carbonitrile (4e)

M.P. 176-178 °C; Yield, 89% ; IR (KBr, cm^{-1}): 3297-3348 cm^{-1} (N-H), 2271 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.79 (s, 2H, NH_2), 8.44 (s, 1H, NH), 7.83-7.31 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 160.8, 151.5, 145.0, 134.4, 134.7, 129.7, 128.3, 123.8, 121.4, 115.9, 80.2; MS: 305 [M^+]; Anal. Calc. for $C_{16}H_{11}N_5O_2$: C 62.95 (61.68), H 3.63 (3.11), N 22.94 (22.00).

Synthesis of 2-hydrazinyl-4(3-nitrophenyl) quinoline -3-carbonitrile (4f)

M.P. 188-190 °C; Yield, 90% ; IR (KBr, cm^{-1}): 3320-3408 cm^{-1} (N-H), 2250 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.89 (s, 2H, NH_2), 8.51 (s, 1H, NH), 7.91-7.48 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 164.4, 153.2, 147.5, 134.1, 131.7, 129.7, 126.9, 125.2, 124.9, 122.6, 120.8, 118.2, 85.9; MS: 305 [M^+]; Anal. Calc. for $C_{16}H_{11}N_5O_2$: C 62.95 (620.3), H 3.63 (3.15), N 22.94 (22.5).

Synthesis of 7 – chloro – 4 (4 – chlorophenyl)- 2 - hydrazinylquinoline-3-carbonitrile (4g)

M.P. 202-204 °C; Yield, 84% ; IR (KBr, cm^{-1}): 3270-3359 cm^{-1} (N-H), 2238 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.66 (s, 2H, NH_2), 8.42 (s, 1H, NH), 7.72-7.33 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 160.8, 155.7, 144.3, 137.6, 134.3, 130.7, 129.1, 128.4, 126.5, 124.6, 122.3, 121.7, 120.5, 116.6, 89.1; MS: 329 [M^+]; Anal. Calc. for$C_{16}H_{10}Cl_2N_4$: C 58.38 (59.23), H 3.06 (3.87), N 17.02 (17.88).

Synthesis of 4-(4-bromophenyl)-7-chloro-2-hydrazinylquinoline-3-carbonitrile (4h)

M.P. 210-212 °C; Yield, 83% ; IR (KBr, cm^{-1}): 3235-3340 cm^{-1} (N-H), 2268 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.70 (s, 2H, NH_2), 8.51 (s, 1H, NH), 7.89-7.42 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6,

TMS, δ, ppm): 168.4, 153.8, 148.4, 136.5, 132.7, 131.2, 129.9, 127.1, 126.3, 123.0, 121.8, 120.8, 119.1, 81.7; MS: 373 [M^+]; Anal. Calc. for $C_{16}H_{10}BrClN_4$: C 51.43 (51.03), H 2.70 (2.99), N 15.00 (15.69).

Synthesis of 7-chloro-4(4-flurophenyl)-2-hydrazinylquinoline-3-carbonitrile (4i)

M.P. 222-224 °C; Yield, 87% ; IR (KBr, cm^{-1}): 3290-3368 cm^{-1} (N-H), 2245 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 9.06 (s, 2H, NH_2), 8.78 (s, 1H, NH), 7.95-7.56 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 165.3, 150.7, 146.5, 138.0, 134.9, 132.1, 130.6, 128.2, 124.7, 122.6, 119.6, 118.5, 88.4; MS: 312 [M^+]; Anal. Calc. for $C_{16}H_{10}ClFN_4$: C 61.45 (60.78), H 3.22 (3.30), N 17.92 (17.09).

Synthesis of 7-chloro)-2-hydrazinyl-4-(4-nitrophenyl)quinoline-3-carbonitrile (4j)

M.P. 224-226 °C; Yield, 89% ; IR (KBr, cm^{-1}): 3235-3340 cm^{-1} (N-H), 2260 (C≡N); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 8.86 (s, 2H, NH_2), 8.59 (s, 1H, NH), 7.68-7.19 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, TMS, δ, ppm): 160.1, 151.8, 147.6, 139.1, 135.0, 133.2, 131.7, 129.3, 125.8, 123.5, 118.6, 119.6, 80.9; MS: 339 [M^+]; Anal. Calc. for $C_{16}H_{10}ClN_5O_2$: C 56.56 (55.89), H 2.97 (2.17), N 20.61 (20.97).

IV. CONCLUSION

The catalyst shows an environmentally friendly character, is inexpensive and easily prepared, and can be recycled without activation. Our protocol is a practical approach using PEG as a commercially available, low cost, recyclable, nonionic solvent. In most cases, the reaction proceeded smoothly to produce the corresponding 2-hydrazinyl-4-substituted phenylquinoline-3-carbonitrile derivatives (quinoline derivatives). The reaction was efficient, mild, clean, eco-friendly and the products were obtained in excellent yield without formation of any side product. The catalyst shows an environmentally friendly character, is inexpensive and easily obtained, and can be recycled without activation. Thus here we find an efficient catalytic system for synthesis of quinoline derivatives

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