

Synergetic Catalytic Bleaching Earth Clay and PEG-400 for Rapid Synthesis of Polyhydroquinoline Derivatives and Their 2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Activity

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ABSTRACT Polyhydroquinoline derivatives have been efficiently synthesized *via* one-pot condensation of ethyl acetoacetate, dimedone, NH₄OAc, and the substituted aromatic aldehyde using cost-effective synergetic catalytic system basic bleaching earth clay and PEG-400. The highlight of present protocol includes catalyst recyclability, excellent yield, shorter reaction time, and use of green catalyst and solvent. Synthesized derivatives were also screened for their antioxidant activity was evaluated by 2,2-diphenyl-1-picrylhydrazyl radical scavenging assay methods.

KEYWORDS Bleaching earth clay, PEG-400, Polyhydroquinoline, Aldehydes, 2,2-Diphenyl-1-picrylhydrazyl.

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INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and pharmaceutical chemistry.^[1] The protocols of MCRs provide more benefits over conventional syntheses in terms of operational simplicity, high degree of atom economy, excellent yields, and wide substrate scope to synthesize biologically relevant scaffolds.^[2]

Polyhydroquinoline analogues are one of the important nitrogen-containing heterocycles due to their promising medicinal applications such as anti-hypertensive, antitubercular, anticancer, broncho-dilating, neuro-related, and antidiabetic activity.^[3-9] These compounds were synthesized in general by conventional methodologies using heat/reflux in presence of organic solvents.^[10-15] In addition, some processes include microwave, polymers, ionic liquids, and solid supports.^[16-25] Most of these methods suffer from one or other disadvantages such as drastic reaction conditions,

long reaction times, need of special apparatus, and the use of hazardous solvent. Thus, the development of new alternative route avoiding the use of toxic catalysts and hazardous solvents to polyhydroquinoline/*Hantzsch* pyridine derivatives is still desirable. Design of eco-friendly methodologies resulting in efficient syntheses of desired heterocycles is the need of the hour of sustainable chemical industry.^[26]

Due to discrete shape and selectivity along with thermal stability, natural clay holds key place in the field of solid phase catalysis. Bleaching earth clay has been explored in several organic transformations due to its non-toxic nature, reuse and recyclability.^[27-30] Until now, there is no literature report of utilization of fuller earth as a catalyst in the Hantzsch condensation. In addition, polyethylene glycol (PEG-400 promoted reactions^[31-34] have been reported in large numbers owing to its low vapor pressure, nontoxic, operational simplicity, and solvating ability allowing to act it as a suitable phase transfer catalyst.

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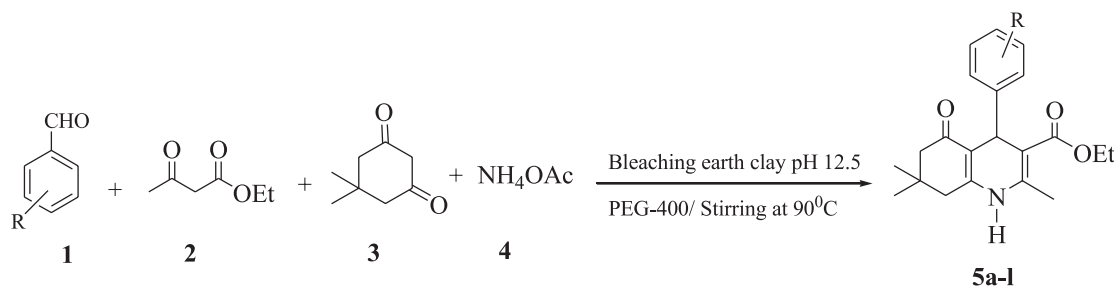
In continuation of our efforts in exploring novel synthetic protocols for the construction of pharmacologically relevant heterocycles,^[35-38] we, herein, report a one-pot method that allows a four-component coupling reaction of substituted aldehydes (**1**), dimedone (**2**), ethyl acetoacetate (**3**) and NH₄OAc (**4**) affording corresponding pure polyhydroquinoline derivatives, in good to excellent yields, using (PEG-400) as green reaction solvent and bleaching earth clay (pH 12.5) as catalyst medium (Scheme 1).

RESULTS AND DISCUSSION

The effect of various reaction parameters, such as effect of solvent/catalyst, temperature, and reaction condition, was evaluated to optimize the reaction [Table 1]. The product was not formed under neat condition at higher temperature [Table 1, Entry 1]. Then, individual screening of some basic catalyst such as triethylamine, piperidine, morpholine, and also PEG-200, 400, 600 as solvent was studied for the same model reaction, but none of these catalysts and solvents gave satisfactory yield [Table 1, Entries 2-4 and 6-8]. We also tried the reaction using bleaching earth clay

catalyst as a heterogeneous catalyst to achieve the good yield [Table 1, Entry 5]. The effect of bleaching earth clay catalyst along with PEG-200, 400 and 600 solvent systems at room temperature and higher temperature was also studied [Table 1, Entries 9-12]. The overall findings of this experiment was that the combination of PEG-400 with bleaching earth clay catalyst at 90°C gives the best results in terms of yield and time as shown in [Table 1, Entry 12 and Scheme 2] but the replacement of PEG-400 by universal solvent water with bleaching earth clay did not furnish the desired product in high percentage yield [Table 1, Entry 13]. Next, we tested polar protic solvent such as methanol, ethanol also the reaction conducted in polar aprotic solvents, such as acetonitrile, dichloromethane with bleaching earth catalyst at 90°C, were found to be resulted in lower product yield under above condition [Table 1, Entries 14-17].

The tolerance of various aldehydes with functional groups NO₂, OMe, Cl, and F under the standard optimized reaction condition was examined [Table 2, Entries 1-12]. Moreover, the reactions were clean with excellent yields without side product formation.



R=H**1a,5a**; R=4-OMe**1b,5b**; R=4-Cl**1c,5c**; R=4-Me**1d,5d**; R=3-NO₂**1e,5e**; R=4-NO₂**1f,5f**;
R=4-Br**1g,5g**; R=4-F**1h,5h**; R=4-OH**1i,5i**; R=3,4-OMe**1j,5j**; R=3-OMe,4-OH**1k,5k**; R=2,4-Cl**1l,5l**

Scheme 1: Synthesis of polyhydroquinoline derivatives

Table 1: Optimization of reaction conditions^a

| Entry | Solvent/catalyst | Temp (°C) | Time (min) | Yield ^b (%) |
|-------|-----------------------------------|--------------|------------|------------------------|
| 1 | Neat | 90 | 300 | No reaction |
| 2 | Et ₃ N | RT/90 | 300 | No reaction/10 |
| 3 | Piperidine | RT/90 | 300 | No reaction/15 |
| 4 | Morpholine | RT/90 | 300 | 15 |
| 5 | Bleaching earth clay | RT/90 | 100 | 40 |
| 6 | PEG-200 | 90 | 100 | 25 |
| 7 | PEG-400 | 90 | 100 | 30 |
| 8 | PEG-600 | 90 | 100 | 40 |
| 9 | PEG-200/Bleaching earth clay | 90 | 100 | 70 |
| 10 | PEG-400/Bleaching earth clay | 90 | 60 | 75 |
| 11 | PEG-600/Bleaching earth clay | 90 | 45 | 70 |
| 12 | PEG-400/Bleaching earth clay | 50/70/90/100 | 45 | 70/80/95/95 |
| 13 | Water/Bleaching earth clay | 90 | 45 | 20 |
| 14 | DCM/Bleaching earth clay | 90 | 45 | 30 |
| 15 | MeOH/Bleaching earth clay | 90 | 45 | 40 |
| 16 | EtOH/Bleaching earth clay | 90 | 45 | 40 |
| 17 | Acetonitrile/Bleaching earth clay | 90 | 45 | 40 |

^aAldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol), isolated yields

The principles of green chemistry tells us that organic reactions are more superior if they produce good product yield within shorter reaction time and using safer techniques. Along with these conditions another important fact is about reusability of the catalyst which gives us information that how longer our catalyst is active. Therefore, the possibility of recycling the catalyst was then examined for the same model reaction. After completion of the reaction, following the usual work-up, it can be recycled for four times. There was no significant decrease in the activity for the first three runs but after third run, it started decreasing, may be due to blockage of pores in bleaching earth clay. The results of recycling are summarized in the form of a bar chart as shown in [Figure 1].

ANTIOXIDANT STUDIES

The basic mechanism of the reducing activity assay is the reduction of Fe^{3+} of $\text{K}_3\text{Fe}(\text{CN})_6$ to Fe^{2+} by antioxidants.^[39] The fall in extinction of $\text{K}_3\text{Fe}(\text{CN})_6$ at 420 nm against appropriate blank for the selected compounds (SC) gives its reducing potential. The sample SC of 500 ml solution (1 mM in 0.5% v/v dimethyl sulfoxide) with 3 ml of 1 mM potassium ferricyanide solution and after 10 min; the absorbance was recorded at 420 nm. Quercetin (1 mM) was used as a standard reducing agent.

1 mM solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) and individual SCs in absolute ethanol were mixed

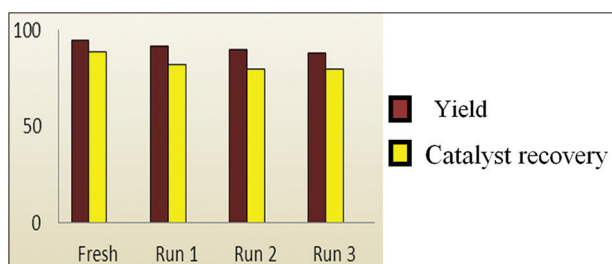


Figure 1: Reuse and recovery of bleaching earth clay and its effect on yield

Table 2: Synthesis of polyhydroquinoline derivatives

| Entry | Product | Time (min) | Yield (%) | Melting point (°C) | |
|-------|---------|------------|-----------|--------------------|------------------------|
| | | | | Observed | Reported ²⁵ |
| 1a | 5a | 2.00 | 92 | 202–204 | 203–204 |
| 1b | 5b | 1.00 | 90 | 260–261 | 257–259 |
| 1c | 5c | 1.00 | 94 | 245–246 | 245–246 |
| 1d | 5d | 1.50 | 91 | 260–261 | 260–261 |
| 1e | 5e | 1.20 | 98 | 178–179 | 177–178 |
| 1f | 5f | 1.00 | 94 | 241–243 | 242–244 |
| 1g | 5g | 2.00 | 90 | 253–255 | 253–255 |
| 1h | 5h | 2.00 | 89 | 185–186 | 184–186 |
| 1i | 5i | 1.00 | 94 | 232–234 | 232–234 |
| 1j | 5j | 2.50 | 91 | 200–201 | 198–199 |
| 1k | 5k | 1.20 | 90 | 210–212 | 210–212 |
| 1l | 5l | 1.00 | 94 | 241–243 | 241–243 |

to carry out the DPPH radical scavenging activity.^[40] Using Quercetin (1 mM) as a standard compound, the samples were observed at 517 nm, spectrophotometrically after 10 min. The results of DPPH scavenging activity and reducing ability are briefed in Table 3.

In view of the percent DPPH, radical scavenging activity and reducing activity of polyhydroquinoline derivatives the potent activity was observed only when the phenyl ring contains hydroxyl or methoxy group at 4-position [Table 3, Entries 2, 9, 10, 11]. However, the presence of electron withdrawing group did not show any reducing activity [Table 3, Entries 3, 7, 8, 12].

EXPERIMENTAL SECTION

Typical procedure for the synthesis of polyhydroquinoline derivatives (5a-5l)

A mixture of benzaldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol), bleaching earth clay (pH 12.5) (5 mol%), and dissolved in PEG-400 as a reaction solvent (2 mL). The mixture was stirred for 5 min at room temperature and then temperature raised to 90°C for stipulated time period. After completion of the reaction (checked by TLC), the crude mixture was worked up in ice cold water (100 mL). The precipitate obtained was filtered by extraction from the reaction mixture with ethyl acetate, dilution with H_2O (20 mL) and then removal of the solvent. The crude yellow products were purified further by recrystallization from hot ethanol or by passing the crude product through a pad of silica gel (10–15% ethyl acetate in hexane) to give the corresponding pure product.

Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3 carboxylate (5a)

Yellow solid; m.p. 202–204°C; FT-IR (KBr): ν_{max} 3274, 3073, 2960, 1698, 1604, 1491, 1380, 1282, 698 cm^{-1} ; ^1H

Table 3: Antioxidant activity of polyhydroquinoline derivatives

| Entry | Compound | %DPPH Radical scavenging activity | % Reducing activity |
|---------|-----------|-----------------------------------|---------------------|
| 1 | 5a | 1.9 | 2.0 |
| 2 | 5b | 18.2 | 3.2 |
| 3 | 5c | 19.7 | NR |
| 4 | 5d | 20.0 | 3.0 |
| 5 | 5e | 17.0 | NR |
| 6 | 5f | 18.2 | NR |
| 7 | 5g | 18.7 | NR |
| 8 | 5h | 19.3 | NR |
| 9 | 5i | 20.2 | 3.2 |
| 10 | 5j | 20.8 | 3.7 |
| 11 | 5k | 21.6 | 3.5 |
| 12 | 5l | 16.3 | NR |
| control | Quercetin | 76.3 | 68.2 |

Result shown are the mean values of $n = 2$. NR: No reaction under experimental conditions

NMR (300 MHz, CDCl₃): δ 7.33–7.10 (m, 5H), 6.26 (s, 1H), 5.06 (s, 1H), 4.04 (q, *J* = 7.11 Hz, 2H), 2.36 (s, 3H), 2.32–2.06 (m, 4H), 1.21 (t, *J* = 7.11 Hz, 3H), 1.07 (s, 3H), 0.91 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 195.6, 167.4, 148.3, 147.1, 128.1, 127.9, 126.2, 106.0, 59.7, 50.8, 41.2, 36.6, 32.6, 29.5, 27.3, 19.4, 14.1; HRMS(ESI) *m/z* [M+H]⁺: calcd. for C₂₁H₂₆NO₃: 340.1913, found: 340.1912.

All compounds are known and were identified by comparison of their spectral data and physical properties with those of the authentic samples [Table 2].

CONCLUSION

The present study is a cost-effective and green protocol for the preparation of polyhydroquinoline derivatives by reacting various substituted aldehydes with dimedone, ethyl acetoacetate, ammonium acetate using bleaching earth clay and PEG-400. In this present work, single use of catalyst or solvent is not effective to produce good yield of xanthene derivative but when together used, their synergetic effect has been observed on the reaction in the form of reduced reaction times, higher yields, recovery, and reusability. Synthesized derivatives were also screened for their antioxidant activity.

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SUPPORTING INFORMATION

For spectral data of other compounds, please see Supporting Information.

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