Catalyst-free, Knoevenagel–Michael Addition Reaction of Dimedone under Microwave Irradiation: An Efficient One-pot Synthesis of Polyhydroquinoline Derivatives

M. Saha, T. S. Luireingam, T. Merry, and A. K. Pal*

Department of Chemistry, North Eastern Hill University, Mawlai Campus, Shillong 793022, India
*E-mail: amartya_pal22@yahoo.com

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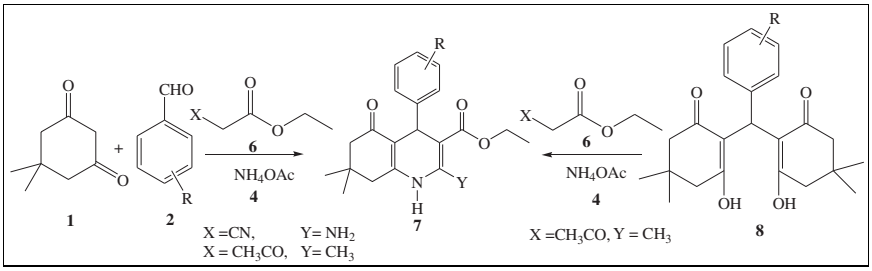

Present investigation reports a concise and efficient protocol for the synthesis of polyhydroquinoline derivatives through coupling of four different components viz. aromatic aldehydes, dimedone, ethyl acetoacetate or ethyl cyanoacetate, and ammonium acetate. The same phenomenon can be observed using arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones), ethyl acetoacetate, and ammonium acetate in one pot under microwave irradiation. The key advantages of the given protocol include short reaction time, high yields, and simple work-up and purification procedure. The present method also allows us to synthesize highly functionalized title compounds from simple and readily available starting materials.

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INTRODUCTION

Design of highly efficient chemical reaction sequence that provide structurally complex molecules and diversity with a minimum number of synthetic steps to assemble compounds with increasing properties is a major challenge of modern drug discovery [1]. Recently, multicomponent reactions have emerged as a highly valuable synthetic tool in modern drug discovery. The atom economy and convergent character, the simplicity of one-pot procedure, the possible structural variation, and the very large number of accessible compounds are among the described advantages of multicomponent reaction [2]. Thus, they are perfectly amenable to automation for combinatorial synthesis [3].

Many chemical processes require a large amount of energy from heating, which can have considerable adverse effects on the environment. Therefore, microwave technology is becoming increasingly attractive as an alternative energy source to assist organic reactions under milder conditions [4]. Microwave irradiation is a powerful tool for reducing reaction time and increasing desire product yields, thus producing many efficient organic reactions [5,6].

Polydroquinolines are an important group of nitrogen heterocycles that have attracted much attention because of their diverse therapeutic and pharmacological properties, such as calcium channel blockers, vasodilator, antiatherosclerotic, bronchodilator, antitumor, geroprotective, antidiabetic activity, and hepatoprotective [7,8]. Furthermore, recent studies have revealed several other medicinal applications that include neuroprotectant and platelet anti-aggregratory activity, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as a chemosensitizer in tumor therapy [9].

Therefore, several methods have been developed for the preparation of polyhydroquinoline derivatives by using various catalysts, including molecular iodine [10], ionic liquid [11], rare earth metal triflates [12], $HClO_4$–SiO_2 [13], HY-zeolites [14], TMSCl–NaI [15], ceric ammonium nitrate [16], grinding technique [17], ultrasound [18], montmorillonite K 10 [19], *p*-TSA [20], polymer [21,22], hetrapolyacid [23], heterogeneous catalyst [24], L-proline [25], nickel nanoparticles [26], and $ZrCl_4$ [27] . Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction time, unsatisfactory yields, high cost, harsh reaction conditions, the use of volatile organic solvents, stoichiometric amounts of catalyst, and also environmentally toxic catalysts. Moreover, there are relatively limited number of reports on the synthesis of polyhydroquinoline derivatives as compared with simple 4-substituted 1, 4-dihydropyridine molecules. Herein, for the first time, we report the synthesis of polyhydroquinoline derivatives without using any catalyst or base under microwave irradiation.

RESULT AND DISCUSSION

In continuation of our research work in the development of highly expedient methodologies for the synthesis of

biologically important heterocyclic compounds [28], we report here the synthesis of polyhydroquinoline from the Knoevenagel condensation of various aromatic aldehydes, β-keto/cyano esters, ammonium acetate, and dimedone in a protic solvent under microwave irradiation in the absence of any added catalyst. In fact, we concentrated our study on the effect of solvents, on this condensation process. The reaction was carried out in various aprotic, protic, polar, and nonpolar solvents. Impressive result was achieved in polar protic solvent such as ethanol.

The reaction of dimedone **1** (1.42 mmol), benzaldehyde **2a** (1.42 mmol), ethyl acetoacetate **3** (1.42 mmol), and ammonium acetate **4** (2.85 mmol) in ethanol (2 mL) under microwave irradiation has been considered as a model reaction. We have also studied the effect of different microwave power setting and temperature variation on this conversion. It was observed that the best result was obtained at 80 W and 50°C. After optimizing the condition, the generality of this method was examined by the reaction of several substituted aromatic aldehydes, ammonium acetate, ethyl acetoacetate or ethyl cyanoacetate, and dimedone in ethanol under microwave irradiation; (Schemes 1, 2) the results are shown in Tables 1 and 2. It is noteworthy to mention that various aromatic aldehydes containing electron-donating to electron-withdrawing functional groups at the different position in the aromatic ring did not show any remarkable effect on this conversion because desired products were obtained in high yields in relatively short reaction time (Tables 1 and 2).

In the literature, Atul Kumar *et al*. [29] have reported the synthesis of polyhydroquinolines from arylmethylene bis (3-hydroxy-2-cyclohexene-1-ones) **8**. Compounds **8a–j** were prepared by the condensation of dimedone **1** and aryl aldehydes (**2a–j**) in presence of EDDA (30 mol%) in THF under refluxing condition [30]. Encouraged by our initial results, we extended the scope of our present protocol for the condensation of arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) **8a–j** (Scheme 3) with ethyl acetoacetate and ammonium acetate in ethanol under microwave irradiation, and it was afforded polyhydroquinolines **5a–j** in good to excellent yields (Table 3). The mechanism for the formation of polyhydroquinolines **5a–j** from arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) **8a–j** is still uncertain. All the products were analytically pure, and structures were determined by the spectral methods (IR, NMR, mass) and the physical data (mp) with those in literature [25–27,31].

CONCLUSION

In conclusion, we hereby propose a simple and efficient method for the synthesis of polyhydrquinoline derivatives with excellent yields via microwave-assisted one-pot reaction. Reaction time was considerably reduced, and product yields were increased under microwave irradiation. The proposed methodology does not require any expensive catalyst or base, thus proved to be economically efficient.

Scheme 1. Synthesis of polyhydroquinoline derivatives using ethyl acetoacetate.

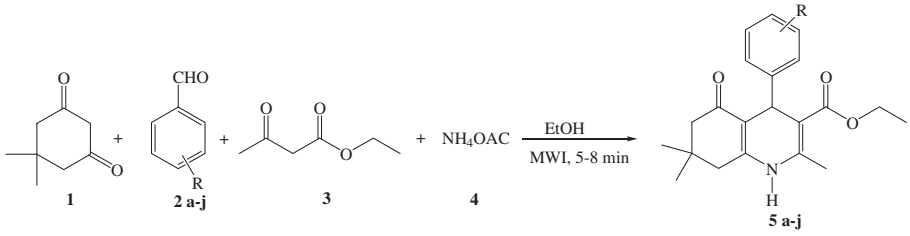

Table 1

Synthesis of polyhydroqunoline derivatives **5a–j**.

Entry	**2a–j**	Aryl aldehydes	Time (min)	Product	Yield (%)[a]
1	**2a**	Benzaldehyde	6	**5a**	88
2	**2b**	4-Nitrobenzaldehyde	5	**5b**	92
3	**2c**	4-Flurobenzaldehyde	5	**5c**	91
4	**2d**	4-Chlorobenzaldehyde	5	**5d**	89
5	**2e**	4-Methylbenzaldehyde	7	**5e**	86
6	**2f**	4-Bromobenzaldehyde	5	**5f**	90
7	**2g**	Para aminodimethylabenzaldehyde	8	**5g**	87
8	**2h**	3-Chlorobenzaldehyde	6	**5h**	88
9	**2i**	3-Flurobenzaldehyde	6	**5i**	86
10	**2j**	4-Methoxybenzaldehyde	6	**5j**	89

[a]Isolated yields.

Scheme 2. Synthesis of polyhydroquinoline derivatives using ethyl cyanoacetate.

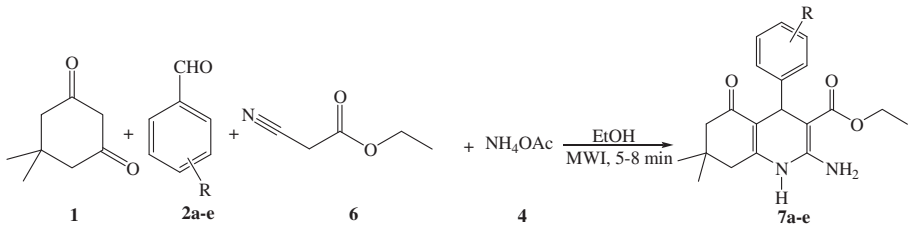

Table 2

Synthesis of polyhydroquinoline derivatives **7a-e**.

Entry	**2a–e**	Aryl aldehyde	Time (min)	Product	Yield (%)[a]
1	**2a**	Benzaldehyde	5	**7a**	91
2	**2b**	4-Methylbenzaldehyde	7	**7b**	89
3	**2c**	4-Nitrobenzaldehyde	5	**7c**	92
4	**2d**	4-Chlorobenzaldehyde	5	**7d**	91
5	**2e**	4-Bromobenzaldehyde	5	**7e**	90

[a]Isolated yields.

Scheme 3. Synthesis of polyhydroquinoline derivatives from arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones).

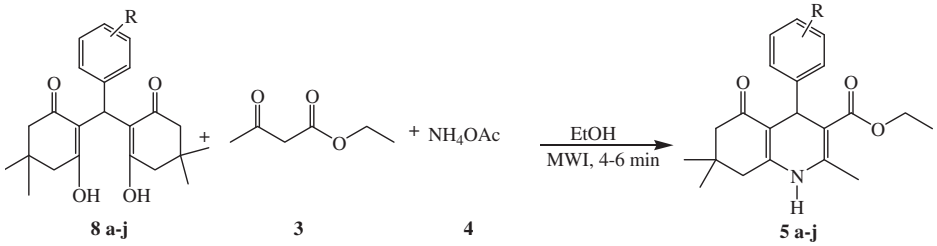

Table 3

Synthesis of polyhydroquinoline derivatives **5a–j** from **8a–j**.

Entry	**8a–j**	Aryl aldehydes	Time (min)	Product	Yield (%)[a]
1	**8a**	Benzaldehyde	4	**5a**	90
2	**8b**	4-Nitrobenzaldehyde	5	**5b**	91
3	**8c**	4-Flurobenzaldehyde	4	**5c**	89
4	**8d**	4-Chlorobenzaldehyde	6	**5d**	90
5	**8e**	4-Methylbenzaldehyde	4	**5e**	88
6	**8f**	4-Bromobenzaldehyde	4	**5f**	90
7	**8g**	Para aminodimethylabenzaldehyde	5	**5g**	86
8	**8h**	3-Chlorobenzaldehyde	4	**5h**	89
9	**8i**	3-Flurobenzaldehyde	4	**5i**	90
10	**8j**	4-Methoxybenzaldehyde	4	**5j**	90

[a]Isolated yields.

EXPERIMENTAL

All the experiments were carried out in MATTHEWS, NC-MADE IN USA, MODEL-DISCOVER-S, MODEL NO-NP-1009, microwave digester in closed vessel. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Spectrum BX FTIR, Perkin Elmer (Rodgau, Germany) (υ_{max} in cm^{-1}) on KBr disks [1]. H NMR and [13] C NMR (400 MHz and 100 MHz, respectively) spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ (chemical shifts in δ with TMS as internal standard). Mass spectra were recorded on Waters ZQ-4000 (Milford, USA). CHN were recorded on CHN-OS analyzer (Perkin Elmer 2400, Series II). Silica gel G (E-mark, India) was used for TLC. Hexane refers to the fraction boiling between 60 and 80°C.

General procedure for the synthesis of polyhydroquinoline derivatives (5a–j) and (7a–e) from dimedone. A mixture of dimedone (**1**) 200 mg (1.42 mmol), aromatic aldehydes (**2**) (1.42 mmol), ethyl acetoacetate (**3**) 0.17 mL (1.42 mmol) or ethyl cyanoacetate (**6**) 0.15 mL (1.42 mmol), ammonium acetate (**4**) 219 mg (2.85 mmol), and ethanol (2 mL) was subjected to microwave irradiation for the mentioned time, cited in Tables 1 and 2 at 80 W and 50°C. The reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and poured into crushed ice and filtered. The crude products were purified by silica gel (60–120 mesh) column chromatography using hexane and ethyl acetate (7:3) as an eluent, and the products were recrystallized from ethanol.

General procedure for the synthesis of polyhydroquinoline derivatives (5a–j) from arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) (8a–j). A mixture of arylmethylene bis (3-hydroxy-2-cyclohexene-1-ones) (**8a–j**) (0.12 mmol) ethyl acetoacetae (**3**) 0.01 mL (0.12 mmol), and ammonium acetate (**4**) 19.0 mg (0.24 mmol) in ethanol (2 mL) was subjected to microwave irradiation for 4–6 min at 80 W and temp 50°C. After complete conversion, as shown by TLC, the reaction mass was cooled to room temperature. Then, it was poured into crushed ice and filtered. The crude products were purified by silica gel (60–120 mesh) column chromatography by using hexane and ethyl acetate as an eluent,(7:3), which were further recrystallized from ethanol.

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