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RESEARCH LETTER

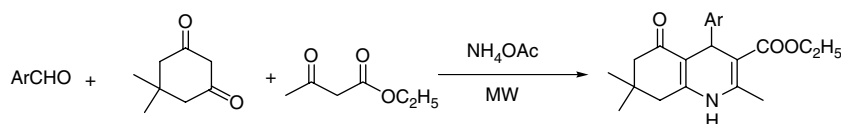
One-pot multicomponent synthesis of polyhydroquinolines under catalyst and solvent-free conditions

Sudarshan Das, Sougata Santra, Anupam Roy, Sharmistha Urinda, Adinath Majee and Alakananda Hajra*

Department of Chemistry, Visva -Bharati University, Santiniketan 731235, India

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An efficient one-pot condensation has been developed for the synthesis of polyhydroquinolines via a four component coupling reaction of aldehyde, dimedone, ethyl acetoacetate, and ammonium acetate under catalyst and solvent-free conditions. Non-hazardous experiment procedure, operational simplicity, mild reaction conditions, and the compatibility with various functional groups represent the advantages of the present method.



Keywords: Hantzsch condensation; polyhydroquinolines; microwave; catalyst and solvent-free; four-component

Introduction

1,4-Dihydropyridines exhibit a spectrum of interesting pharmacological properties such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, antidiabetic, calcium channel modulators, and hepatoprotective agents (1–4). The synthesis of these privileged heterocyclic compounds has therefore gained special attention. Available methods for synthesis of polyhydroquinoline derivatives are using conventional heating (5), refluxing in acetic acid (6), ionic liquids (7), montmorillonite K10 (8, 9), organocatalyst (10), sulfamic acid (11), nickel nanoparticle (12), and microwave (MW) irradiation in presence of glycine as a catalyst (13). Most of these methods have their own advantages, but also suffer from certain drawbacks such as use of hazardous solvents, long reaction times, low yields, and expensive catalyst. Therefore, there is a need for a simple, efficient, and cost-effective method for the synthesis of polyhydroquinoline derivatives under environmental-friendly conditions.

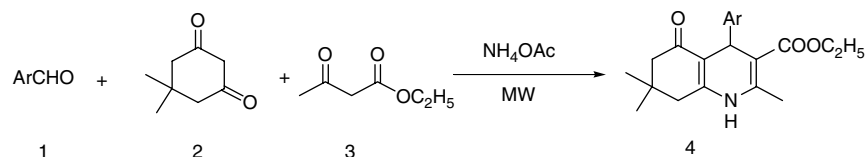
Results and discussion

As a part of our ongoing research to provide greener methodology under solvent and catalyst-free conditions (14–18), we have found that the four component reaction of aldehyde, dimedone, ethyl acetoacetate, and ammonium acetate under MW irradiation without any solvent and catalyst produced polyhydroquinoline derivatives in high yields within short reaction times (Scheme 1).

In a typical experimental procedure, a mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), and ammonium acetate (1.5 mmol) was irradiated in a microwave reactor (CEM, Discover, USA) at 90°C (250 W) for a certain period of time as required for completion (TLC) of the reaction. A wide range of structurally varied aldehydes was subjected under the present reaction conditions to get the corresponding polyhydroquinoline derivatives as summarized in Table 1.

Several functionalities such as OH, OMe, Cl, Br, F are unaffected under the present reaction conditions. Aromatic aldehydes reacted well to afford the desired products in excellent yields. However,

*Corresponding author. Email: alakananda.hajra@visva-bharati.ac.in



Scheme 1. Synthesis of polyhydroquinolines.

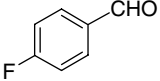
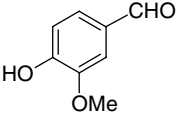
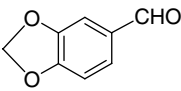
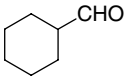
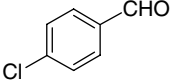
aliphatic aldehydes such as *n*-butyraldehyde, *iso*-butyraldehyde and valeraldehyde except cyclohexanecarboxaldehyde (entry 12) produced a mixture of products that are yet to be characterized. The

present procedure was also equally effective for methyl acetoacetate (entry 13). In general, the reactions were very fast. The whole operation does not involve any organic solvent. Only ethanol was

Table 1. Synthesis of polyhydroquinoline derivatives.

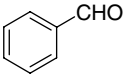
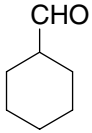
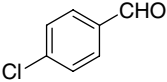
Entry	Aldehyde	Product	Time (min)	Yield ^a (%)	MP (°C)	
					Found	Reported
1		4a	3	88	201–203	202–204 (9)
2		4b	3	82	260–262	261–262 (9)
3		4c	4	82	259–261	258–260 (8)
4		4d	3	85	247–249	247–248 (8)
5		4e	6	81	207–209	207–208 (8)
6		4f	5	81	236–238	238–240 (8)
7		4g	6	78	221–223	220–222 (8)
8		4h	4	80	250–252	252–253 (9)

Table 1 (Continued)

Entry	Aldehyde	Product	Time (min)	Yield ^a (%)	MP (°C)	
					Found	Reported
9		4i	3	86	185–187	185–186 (9)
10		4j	6	81	200–202	202–204 (9)
11		4k	5	84	241–243	243–244 (8)
12		4l	3	84	215–217	–
13 ^b		4m	3	83	251–252	–

^aIsolated yields.^bThe reaction was conducted with 4-chlorobenzaldehyde, dimedone, methylacetoacetate and ammonium acetate.

Table 2. Comparison of the present protocol with recently reported methods.

Entry	Aldehyde	Present method		Reported method (12)		Reported method (13)	
		Time	Yield (%) ^a	Time	Yield (%) ^b	Time	Yield (%) ^c
1		3 min	88	1 min	95	1 min	95
2		3 min	84	–	–	–	–
3		3 min	85	2 min	90	2 min	97

^aPresent reaction conditions: 90°C, 240 W MW (without any solvent and catalyst).^bReported reaction conditions: Ni nanoparticle (10 mol%), 540 W MW.^cReported reaction conditions: Glycine (10 mol%) in acetonitrile solvent, 80°C, 180 W MW.

employed for recrystallization to provide pure compounds.

The efficiency and generality of the present protocol can be realized by comparing some of the results presented here with two recently reported methods, as shown in Table 2, which compares reaction time, yields, and reaction conditions. Thus, it is clear from Table 2 that the present protocol is more practical alternative to reported methodologies with respect to reaction conditions and general applicability.

Experimental

In a typical experimental procedure, benzaldehyde (106 mg, 1 mmol), dimedone (140 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), and ammonium acetate (115 mg, 1.5 mmol) was irradiated in a microwave reactor (CEM, Discover, USA) at 90°C (250 W) for five minutes as required to complete the reaction (TLC). After completion of reaction, the mixture was poured into crushed ice and stirred for five minutes. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (20 mL), and then recrystallized from hot ethanol to afford analytically pure product (88%, 285 mg) whose identity was established by comparison of its MP and spectroscopic data (IR, ¹H NMR) with those reported (8).

Conclusion

In conclusion, MW irradiation on a mixture of aldehyde, dimedone, ethyl acetoacetate, and ammonium acetate provides a highly efficient methodology for the synthesis of polyhydroquinoline derivatives in high yields. Operational simplicity, solvent and catalyst-free conditions, and the compatibility with various functional groups are the advantages of the present procedure. We believe that this will present a better and more practical alternative to the existing methodologies for the synthesis of polyhydroquinoline derivatives.

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