Current Chemistry Letters 9 (2020) 71–78

Contents lists available at GrowingScience

Current Chemistry Letters

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Microwave-promoted three-component Hantzsch synthesis of acridinediones under green conditions

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C H R O N I C L E

Article history:
Received January 2, 2017
Received in revised form
March 1, 2017
Accepted April 21, 2017
Available online
July 27, 2019

Keywords:
Acridinediones
Arylaldehydes
Dimedone
Hantzsch synthesis
Microwave

A B S T R A C T

In this study, a green and practical approach towards Hantzsch dihydropyridine synthesis of acridine-1,8-diones is introduced. Via the mentioned protocol, the one-pot condensation reaction of structurally diverse aromatic aldehydes, dimedone and NH4OAc was promoted by microwave radiation at solvent and catalyst-free conditions. Consequently, acridinedione products were produced in 81–97% yields within 3–8 min. The current protocol represents the prominent advantages in terms of the using a simple synthetic procedure, short reaction times, mild reaction conditions, high yield of the products as well as omission of hazardous and cost-effective organic solvents/reagents.

1. Introduction

Multi-component reactions (MCRs) have been widely utilized as an efficient synthetic protocol towards preparation of numerous organic and pharmacological materials.[1] This method bring an economical and environmental-friendly approach via the one-pot condensation reaction of three or more components in a one-step to produce new compounds containing the starting materials in their skeletal arrangement.[2]

Acridinediones are one of the important class of nitrogen heterocyclic compounds involving the ring of 1,4-dihydropyridine (1,4-DHP). These materials are considered as effective pharmaceutical agents and active intermediates in organic and medical chemistry.[3,4] Furthermore, acridinedione derivatives have a wide range of biological activities such as anti-microbial,[5-7] anti-fungal,[8] anti-bacterial,[9] anti-tumor,[10] anti-cancer,[11] anti-glaucoma,[12] anti-malarial,[13-15] DNA binding properties[16] and inhibitors of carbonic anhydrase.[17] 1,4-DHPs are also utilized as electroluminescence materials and can be used in laser dyes because of their strong fluorescent activities.[18,19] In this context, the multi-component Hantzsch synthesis of 1,4-dihydropyridines has been widely utilized as an efficient synthetic procedure for preparation of acridinediones through the one-pot condensation reaction of aldehydes, β-diketones and various nitrogen containing compounds such as urea, methyl amine, ammonium acetate, aniline or other appropriately primary amines.[20,21] Because of the great conveniences of acridinediones, therefore, the immense interest has been devoted to the synthesis of these materials using

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doi: 10.5267/j.ccl.2019.8.001

heterogeneous or homogeneous catalyst systems.[22-41] Although most of the reported methods exhibit the useful synthetic advantages, however they generally suffer from shortcomings in terms of using expensive and hazardous solvents/reagents, the prolonged reaction times, undesirable yields, harsh reaction conditions and tedious work-up procedures. Therefore, the development and introduction of a green and practical approach which eliminate utilizing cost-effective solvents/catalysts from the medium of reactions, based on the principles of green chemistry, is more demanded.

Nowadays, the useful utility of microwave radiation in organic synthesis has attracted the considerable interest of numerous scientists. Via this synthetic method, the amazing acceleration, selectivity (chemo-, regio- and stereo-) and high yield as well as the purity of products under mild conditions are accessible. The influence of microwave radiation is derived from the combination of thermal effect (arising from the heating, superheating or hot spots) and the selective absorption of radiation by polar substances. This type of promotion is not usually accessible by classical heating and the polarizing radiation involving non-thermal effects.[42-44] In this area, the existence of numerous reports in literature shows the importance of microwave radiation towards synthesis of various materials[45-52] as well as 1,4-dihydropyridines[53-57] in dry or solution media.

Aligned to the outlined strategies and continuation of our research program towards synthesis of acridinediones using the magnetic layered double hydroxide,[58] herein, we wish to report a simple and efficient procedure for the titled transformation under solvent and catalyst-free conditions. The reactions were carried out through the three-component condensation reaction of aromatic aldehydes, dimedone and NH_4OAc under microwave radiation to afford the products in high to excellent yields (Figure 1).

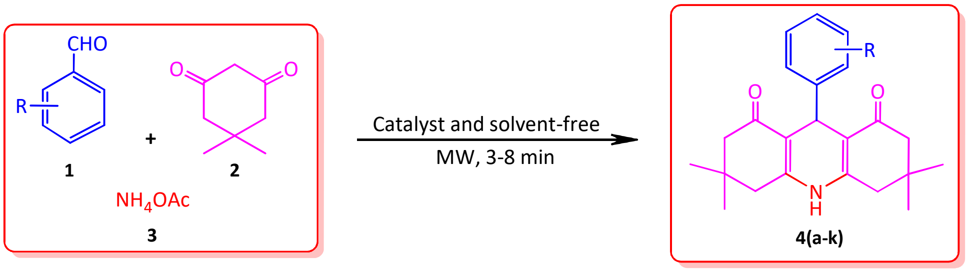


Figure 1. Synthesis of acridinediones promoted by microwave radiation

2. Results and Discussion

The study was started by performing the Hantzsch synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-acridine-1,8(2*H*,5*H*)-dione **4a** through the three-component reaction of benzaldehyde (**1**, 1 mmol), dimedone (**2**, 2 mmol), and ammonium acetate (**3**, 1.5 mmol) under various conditions involving the change of reaction-solvent, temperature as well as radiation of microwave at 500 and 700 W power energy. The results of these investigations were summarized in Table 1. The table shows that progress of the titled reaction inside the solvents (H_2O, MeOH, EtOH and THF) even at reflux was not noteworthy. Further examinations resulted that the influence of microwave radiation for synthesis of acridinedione **4a** was more satisfactory. Examining of the power amplitude for radiation of microwave resulted that using the energy of 700 W was the requirement for completion of the condensation reaction within 5 min. Therefore, the condition mentioned in entry 8 (Table 1) was selected as the optimum reaction conditions.

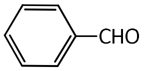
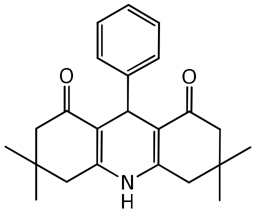
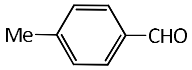
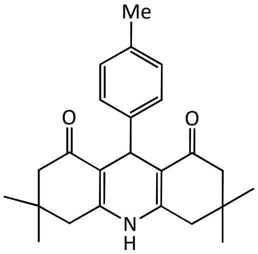
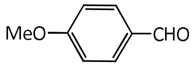
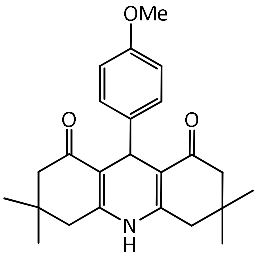
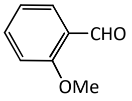
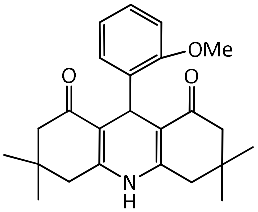
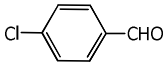
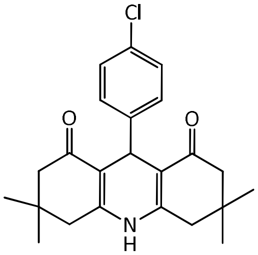
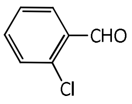
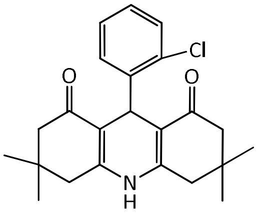
Table 1. Optimization experiments for synthesis of acridinedione **4a**[*]

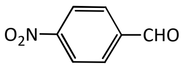
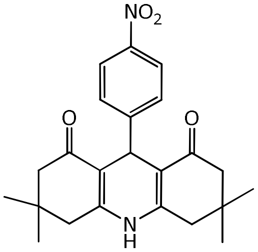
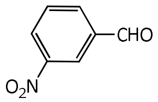
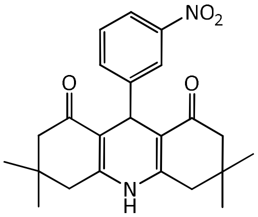
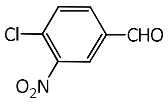
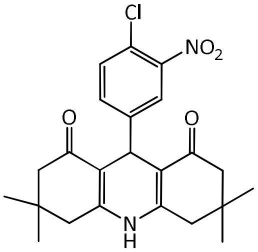
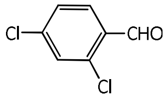
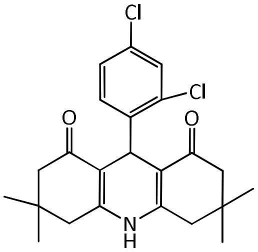
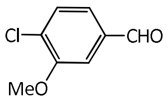
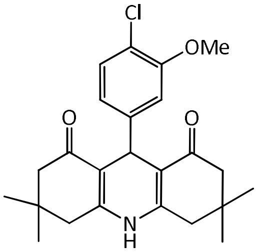
Entry	Solvent (2 mL)	Temperature (°C)	Microwave (Watt)	Time (min)	Conversion (%)
1	H_2O	Reflux	–	240	0
2	MeOH	Reflux	–	120	5
3	EtOH	Reflux	–	120	5
4	THF	Reflux	–	100	8
5	Solvent-free	r.t.	–	120	0
6	Solvent-free	80	–	120	15
7	Solvent-free	–	500	10	95
8	Solvent-free	–	700	5	100

[*] All reactions were carried out with the molar ratio of 1:2:1.5 for benzaldehyde, dimedone and NH_4OAc, respectively.

The utility of catalyst and solvent-free synthesis of acridinedione **4a** by microwave radiation was further investigated by the three-component condensation reaction of structurally diverse aromatic aldehydes, dimedone and ammonium acetate at the optimized reaction conditions. The results of these investigations were illustrated in Table 2. Investigation of the results exhibited that all reactions were carried out successfully with 5–8 min to afford the products in high to excellent yields. Moreover, it is notable that the influence of electron-withdrawing and releasing functionalities of the aromatic rings on the rate of condensation reactions was negligible.

Table 2. Microwave-assisted synthesis of acridinediones under catalyst and solvent-free conditions[a]

Entry	Substrate	Product	Time (min)	Yield (%)[b]	Mp (°C)		Ref.
					Found	Reported	
1		 **4a**	5	95	273–275	277–278	40
2		 **4b**	7	86	>300	>300	36
3		 **4c**	3	81	278–280	299–301	37
4		 **4d**	4	97	>300	>300	41
5		 **4e**	6	91	298–300	295–297	38
6		 **4f**	8	91	298–300	290–292	36

7			**4g**	3	81	271–273	268–270	36
8			**4h**	5	91	295–297	298–300	36
9			**4i**	6	86	275–277	–	–
10			**4j**	8	91	>300	–	–
11			**4k**	6	81	297–299	300	36

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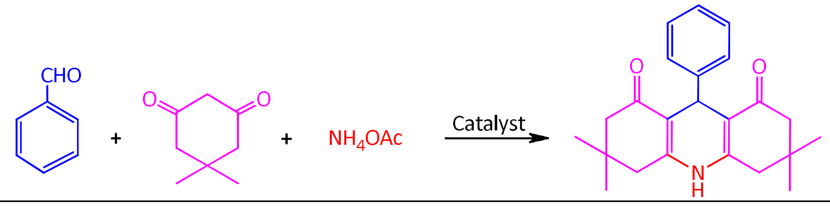
[a] All reactions were carried out with aromatic aldehyde (1 mmol), dimedone (2 mmol) and NH_4OAc (1.5 mmol) under solvent and catalyst free conditions using microwave irradiation (700 W). [b] Yields refer to isolated pure products.

Suitability of this synthetic protocol was also highlighted by comparison of the obtained result for synthesis of acridinedione **4a** with current protocol and the previously reported systems (Table 3). A case study shows that in terms of high yield, short reaction time, the elimination for using hazardous and expensive organic solvents/promoters, the present system shows the prominent advantages in comparison to the previously reported works.

Although the exact mechanism of this synthetic protocol is not clear, however, a depicted mechanism (Fig. 2) explains the role of microwave radiation and condensation pathways of the reactants leading to the synthesis of acridinedione materials. The mechanism shows that through the Knoevenagel condensation of activated arylaldehyde (**I**) with dimedone, the benzylidene diketone (**II**) was produced. At the next, the Michael reaction of second molecule of dimedone with the activated benzylidene diketone (**III**) affords the bisdimedone intermediate (**IV**). Finally through the intramolecular reaction of the prepared imino product (**V**) and ring closing step, the final acridinedione (**VI**) was produced.

Table 3. Comparison of the synthesis of acridinedione **4a** with different protocols



Entry	Catalytic system	Reaction conditions	Yield (%)	Ref.
1	Catalyst-free	Solvent-free, 5 min, microwave	95	*
2	Betainium ionic liquid	EtOH, 180 min, 80 °C	90	36
3	KH_2PO_4	$EtOH/H_2O$, 300 min, 120 °C	94	37
4	Fe_3O_4@SiO_2-MoO_3H	Solvent-free, 25 min, 90 °C	92	38
5	Cellulose sulfuric acid	Solvent-free, 300 min, 100 °C	80	39
6	[CMIM][CF_3COO]	$EtOH/H_2O$, 80 min, 80 °C	87	41
7	Fe_3O_4@SiO_2@Ni-Zn-Fe LDH	Solvent-free, 25 min, 70-80 °C	94	58

[*] Present system

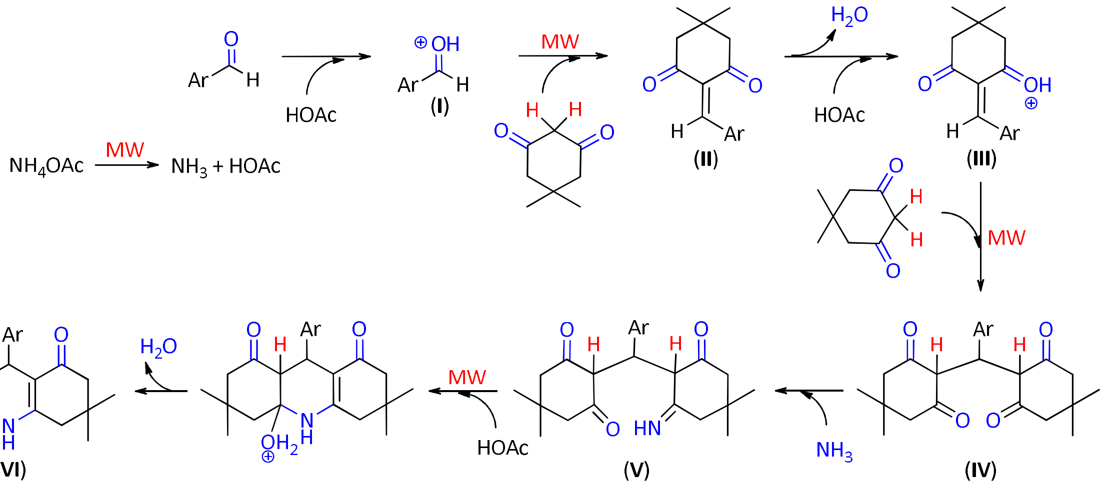


Fig. 2. A plausible mechanism for microwave-assisted synthesis of acridinediones

3. Experimental

3.1. Materials and methods

All chemicals and solvents were purchased from commercial sources and they were used without further purification. ^1H, ^{13}C NMR and FT-IR spectra were recorded on Bruker Avance (300 MHz) and Thermo Nicolet Nexus 670 instruments, respectively. The products were characterized by their spectra and compared with the reported data in the literature. All yields refer to isolated pure products. Thin layer chromatography (TLC) was used for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminum sheet. Melting points were measured in open capillary tubes with Electrothermal 9100 melting point apparatus and were uncorrected. A domestic microwave oven was used for irradiation of microwave.

3.2. A typical procedure for three-component condensation reaction of benzaldehyde, dimedone and ammonium acetate

In a small test tube, a mixture of benzaldehyde (0.106 g, 1 mmol), dimedone (0.280 g, 2 mmol) and NH_4OAc (0.115 g, 1.5 mmol) at room temperature was prepared. The mixture was then irradiated by microwave (700 W) for 5 min under solvent and catalyst-free conditions. After completion of the reaction (monitored by TLC, *n*-hexane/ethyl acetate: 4/2), the mixture was cooled to the room temperature and the crude product was recrystallized from hot ethanol to afford the pure 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10-hexahydro-acridine-1,8(2*H*,5*H*)-dione **4a** in 95% yield (Table 2, entry 1).

4. Conclusions

In this study, an easy and efficient method for microwave-promoted synthesis of acridinedione materials via the three-component condensation reaction of structurally diverse arylaldehydes (1 mmol), dimedone (2 mmol) and NH_4OAc (1.5 mmol) was introduced. All reactions were carried out under solvent and catalyst-free conditions under microwave radiation (700 W) giving the products in 81–97% yields within 3–8 min. The present method represents the significant advantages in terms of short reaction times, high yield of products, easy work-up procedure as well as the benefits-deletion of utilizing expensive and hazardous organic solvents and promoters.

Acknowledgements

The authors gratefully acknowledge the financial support of this work by the research council of Urmia University.

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