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Solvent-Free Synthesis Of 9-Arylacridine-1,8-Diones In The Melt Reaction

Corresponding Auther

Shu-Xiang Wang
College of Chemistry and Environmental Science, Hebei University, Baoding 071002, Hebei Province (P.R.CHINA)
Fax: 86-32-5079628
E-mail: orgsyn@mail.hbu.edu.cn

Co-Authors

Shao-Bo Guo, Ji-Tai Li
College of Chemistry and Environmental Science, Hebei University, Baoding 071002, Hebei Province (P.R.CHINA)

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ABSTRACT

9-Arylacridine-1,8-diones have been prepared in one-pot under solvent-free condition. It is a simple, atom efficient and environmentally friendly method. The condensations of aromatic aldehydes, ammonium acetate and 5,5-dimethyl-1,3-cyclohexane-dione (or 1,3-cyclohexanedione) in the absence of solvent at 90°C gave the title compounds in 85%-98% yields.

KEYWORDS

9-arylacridine-1-8-diones;
solvent-free;
melt reaction.

INTRODUCTION

1,4-Dihydropyridines derivatives (1,4-DHPs) possess a variety of biological activities. For example, they have been used as effective calcium channel modulators for the treatment of cardiovascular disorders[1]. 9-Arylacridine-1,8-diones related to1,4-dihydropyridines have also been found to possess coronary dilating, antifibrillary, spasmolytic and antihypertensive activities[2]. Novel 9-arylacridine -1,8-diones were prepared by the classical Hantzsch's procedure[3]. In the past, some work on these compounds has been reported[4-13]. However, the use of high temperatures, longer reaction time, organic solvents and a large amount of water media limited the application of these methods. Thus, the development of a simple, efficient and green method for the preparation of 9-arylacridine-1,8-diones is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yields.

Synthetic chemistry requires the consumption of energy and material. One of the greatest environmentally problematic aspects of organic synthetic

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chemistry is the use of solvent. The solvent has to be produced in another chemical process, which is involved in consuming energy and resources.Within the reaction the vast amount of solvent has to be heated or cooled, consuming large amount of energy, and has to be removed after completion of the reaction from the reaction mixture. The best solvent is no solvent. The solvent-free reaction has many advantages: reduced pollution, lowcost and simplicity in process and handing. These factors are especially important in industry. In recent times, a move away from the use of solvents in organic synthesis has led in some cases to improved results and more green synthetic procedures[14-16].

All of the results stated above spur us to study the possibility of synthesis of 9-arylacridine-1,8-diones in the absence of solvent. Herein, we wish to report a new method for the preparation 9-arylacridine-1,8-diones in one-pot under solvent-free condition.

EXPERIMENTAL

Melting points are uncorrected. 5,5-Dimethyl-1, 3-cyclohexanedione was purchased from Fluka and was used without further purification. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). ^{1}HNMR spectra were measured on Bruker AVANCE 400(400 MHz) spectrometer in DMSO using TMS as internal standard .

In a typical general experimental procedure, a mixture of 5,5-dimethyl-1,3-cyclohexanedione (or 1,3-cyclohexanedione) **(1)**, aromatic aldehydes **(2)** and ammonium acetate under solvent-free condition was stirred at 90°C (SCHEME 1). The reactions were almost completed in 10 min. The reaction mixtures were cooled to room temperature, transferred with a small amount 40% ethanol and then filtered. The obtained solid was washed with water (5 mL) to afford products with good yields (85%-98%).

General procedure

A dry 5mL round-bottomed flask with 5,5-dimethyl-1,3-cyclohexanedione (or 1,3-cyclohexane dione) (2.0 mmol), aromatic aldehydes (1.0 mmol) and ammonium acetate (1.0 mmol). The mixture was stirred at 90°C. The progress of the reaction was monitored by TLC. After completion of the reactions, the mixture was cooled to room temperature. The solid was transferred with a small amount 40% ethanol, and then filtered. The obtained solid was washed with water (5 mL). The crude products were purified by recrystallization from anhydrous ethanol. The authenticity of the products was established by comparing their melting points, IR, ^{1}H NMR and elemental analysis. Selected spectral data of some of the products are given below:

(3c) : IR (KBr, υ, cm^{-1}) 3444, 3201, 3069, 2955, 2869, 1643, 1607, 1482, 1366, 1223, 1144, 836; ^{1}HNMR (DMSO, δ, ppm): 0.87 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.96-2.51 (8H, m, 4×CH_3), 3.66 (3H, s, OCH_3), 4.75 (1H, s, ArCH), 6.71-7.06 (4H, m, ArH), 9.25 (1H, s, NH); Elemental analysis: Found C, 75.73; H, 7.65; N, 4.26%. Calcd for $C_{24}H_{29}NO_3$: C, 75.99; H, 7.65; N, 3.69%.

(3g) : IR (KBr, υ, cm^{-1}) 3426, 3169, 3047, 2943, 2844, 1637, 1602, 1363, 1232, 1135, 779; ^{1}HNMR (DMSO, δ, ppm): 1.78-2.52 (12H, m, 6 × CH_2), 4.92 (1H, s, ArCH), 7.05-7.15 (5H, m, ArH), 9.46 (1H, s, NH); Elemental analysis: Found(%): C, 77.56; H, 6.50; N, 5.21. Calcd for $C_{19}H_{19}NO_2$: C, 77.82; H, 6.48; N, 4.79.

(3i) : IR (KBr, υ, cm^{-1}) 3465, 3182, 3060, 2947, 2877, 1642, 1603, 1485, 1363, 1234, 1133, 826; ^{1}HNMR (DMSO, δ, ppm): 1.76-2.51 (12H, m, 6xCH_2), 3.67 (3H, s, OCH_3), 4.85 (1H, s, ArCH), 6.71-7.06 (4H, m, ArH), 9.40 (1H, s, NH); Elemental analysis: Found(%): C, 74.07; H, 6.57; N, 4.84. Calcd for $C_{20}H_{21}NO_3$: C, 74.30; H, 6.50; N, 4.33.

(3k) : IR (KBr, υ, cm^{-1}) 3444, 3204, 3066, 2946, 2876, 1640, 1604, 1363, 1234, 1134, 818. ^{1}H NMR (DMSO, δ, ppm): 1.75-1.94 (4H, m, 2xCH_2), 2.15 (3H, s, CH_3), 2.19-2.22 (4H, m, 2xCH_3), 2.49-2.55 (4H, m, 2xCH_3), 4.86 (1H, s, CH), 6.94-7.03 (4H, m, ArH), 9.41 (1H, s, NH); Elemental analysis: Found(%): C, 77.91; H, 6.89; N, 5.08. Calcd for $C_{20}H_{21}NO_2$: C, 78.18; H, 6.84; N, 4.56.

RESULTS AND DISCUSSION

The effects of the reaction conditions on yields of compound **(3)** are summarized in TABLE 1.

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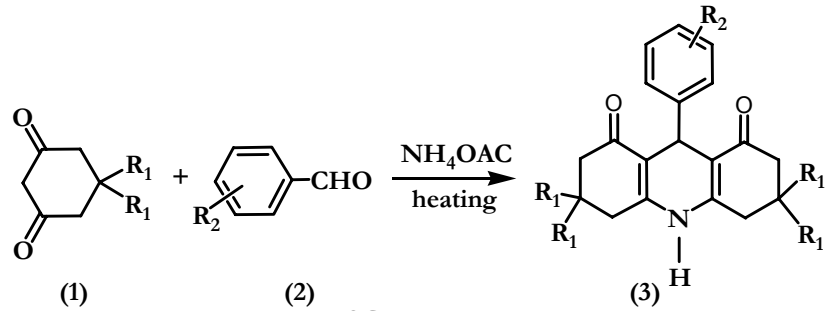

(1) (2) (3)

SCHEME 1

TABLE 1 : The effects of the reaction conditions on the yield of 9-(piperonylphenyl)- 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-hexahydroacridine-1,8-diones

Entry	Molar ratio[a]	Temperature/ °C	Time/min	Yield*/%
1	2:1:2	60	50	76
2	2:1:2	80	20	97
3	2:1:2	90	10	98
4	2:1:2	100	10	98
5	2:1:1.5	90	10	97
6	2:1:1	90	10	98

[a]Molar ratio of piperonal 5,5-dimethyl-1,3-cyclohexane-dione, 2b and ammonium acetate.
*Yields of isolated product.

Firstly, a mixture of piperonal **(2b)**, ammonium acetate and 5,5-dimethyl-1,3-cyclohexane-dione was chosen as the model reaction to detect the proper reaction temperature. When the reaction temperature is 60°C, 80°C, 90°C and 100°C, the reaction yields is 76%, 97%, 98% and 98% respectively and the reaction time is 50 min, 20 min, 10 min and 10 min respectively. The temperature of 90°C is sufficient to this model reaction. Higher the temperature did not improve the results to a greater extent. We did also the experiment with the different ratios of 5,5-dimethyl-1,3-cyclohexane-dione, **(2b)** and ammonium acetate. When the molar ratios are 2:1:2, 2:1:1.5 and 2:1:1, the reaction gave **(3b)** in 98%, 97% and 98% yields respectively. Decreasing of the amount of ammonium acetate did not reduce the results to a lower extent. This reaction can be carried out stoichiometricly.

Therefore, we chose the reaction conditions that are the reaction temperature of 90°C and a 2:1:1 ratio of reagents. And **(3a-3n)** were synthesized successfully. The main results for the synthesis of these compounds are given in TABLE 2.

The effect of electron and the nature of substituents on the aromatic ring did not show strongly obvious effects in terms of yields under this reaction conditions. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as alkyl group, alkoxyl group) were employed and reacted well to give the corresponding 9-arylacridine-1,8-diones in excellent yields. But m-nitrobenzaldehyde reacted with ammonium acetate and 5,5-dimethyl-1,3-cyclohexane-dione to give **(3g)** at 90°C for longer time (6h). When the reaction temperature was increased to 120°C, the reaction time was reduced to 2.5 h. p-Chlorobenzaldehyde reacted with ammonium acetate and 1,3-cyclohexane-dione to give **(3n)** at 90°C for 3 h. When the reaction temperature was increased to 120 °C, the reaction time was reduced to 1.5 h.

Next, we investigated the effect of substitution in 1,3-cyclohexane-dione system such as 5,5-dimethyl-1,3-cyclohexanedione. Aromatic aldehydes such as benzaldehyde and different substituted benzaldehydes react with ammonium acetate and 5,5-dimethyl-1,3-cyclohexane-dione to afford the corresponding products **(3a-3g)** in excellent yields. Similarly, in the reaction of aromatic aldehydes and ammonium acetate with 1,3- cyclohexane-dione under the same reaction conditions, **(3h-3n)** were obtained in excellent yields. But because of steric effect 5,5-dimethyl-1,3-cyclohexane-dione requires longer reaction time than 1,3-cyclohexane- dione to give the corresponding products.

Solvent-free reaction is a more effective method to prepare the title compounds than that carried out in solvents. Using ethanol as solvent, **(3i,3j,3l)** and **(3m)** have been prepared by the condensation of

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TABLE 2: Preparation of 9-arylacridine-1,8-diones under solvent-free condition

Entry	R_1	R_2	T/°C	Time/min	Yield*/%	Mp/°C	
						Found	Reported
3a	CH_3	H	90	15	85	295-296	292[4]
3b	CH_3	3,4-(OCH_2O)	90	10	98	322-324	324-326[9]
3c	CH_3	4-CH_3O	90	10	93	291-292	270-272
3d	CH_3	4-CH_3	90	15	89	325-327	>300[13]
3e	CH_3	4-(CH_3)N	90	25	94	290-292	293-294[4]
3f	CH_3	4-Cl	90	20	97	296-298	296-298[9]
3g	CH_3	3-NO_2	90	360	97	292-294	283-285[9]
	CH_3	3-NO_2	120	150	98	292-294	283-285[9]
3h	H	H	90	10	86	323-325	
3i	H	3,4-(OCH_2O)	90	10	96	305-307	307-308[6]
3j	H	4-CH_3O	90	10	96	304-306	270[6]
3k	H	4-CH_3	90	10	95	322-324	
3l	H	4-(CH_3)N	90	10	90	281-282	286-287[6]
3m	H	3-NO_2	90	15	98	285-287	280-281[6]
3n	H	4-Cl	90	180	95	298-299	298-299[6]
	H	4-Cl	120	90	95	298-299	298-299[6]

*** Yields of isolated product.**

substituted benzaldehydes in the presence of ammonium hydroxide in 78%, 80%, 82% and 82% yields respectively under refluxing for 4 h[6]. Using AcOH as solvent, **(3a)** and **(3e)** have been prepared in 74% and 42% yields respectively under refluxing for 0.5 h[4]. Using water medium, **(3d)** has been prepared in 76% yield under refluxing for 2 h[13]. And all these method use the excess of reagent containing nitrogen atom. In present process, **(3a,3d,3e,3i,3j,3l)** and **(3m)** were obtained under solvent-free conditions for 10-25 min in 85%, 89%, 94% 96%, 96% 90% and 98% yields respectively. It is noted that this reaction can be completed stoichiometricly.

In conclusion, we have described a general and highly efficient procedure for the preparation of 9-arylacridine-1,8-diones under solvent-free condition. It is possible to apply the tenets of atom utilisation to the generation of biologically interesting products. Moreover, the procedure offers several advantages including high yields, operational simplicity, stoichiometric reactions, minimal environmental impact which makes it a useful and attractive process for the synthesis of these compounds.

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