An Efficient One-pot Synthesis of *N*-Carboxymethylacridine-1,8-dione Derivatives under Microwave Irradiation

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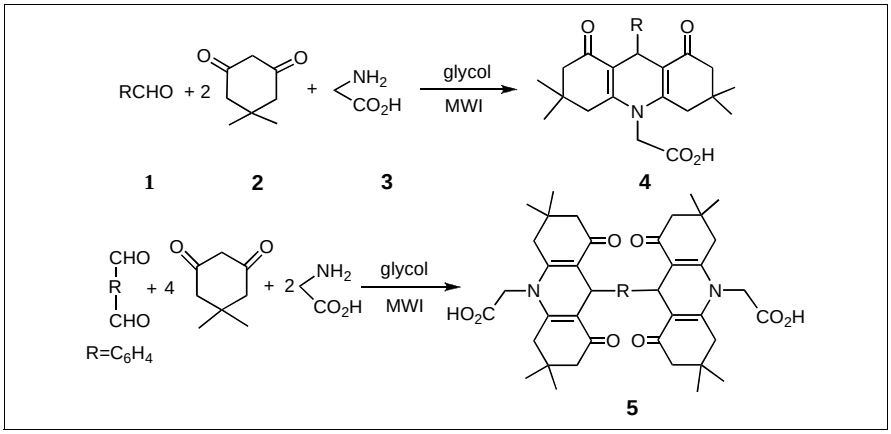

A series of *N*-carboxymethylacridine-1,8-dione derivatives were synthesized by one-pot reaction of aldehyde, dimedone and glycine in glycol under microwave irradiation without catalyst with excellent yields (78-92%) and short reaction time (4-8min). And the reaction was not only suitable for aromatic monoaldehyde, but also aromatic dialdehyde.

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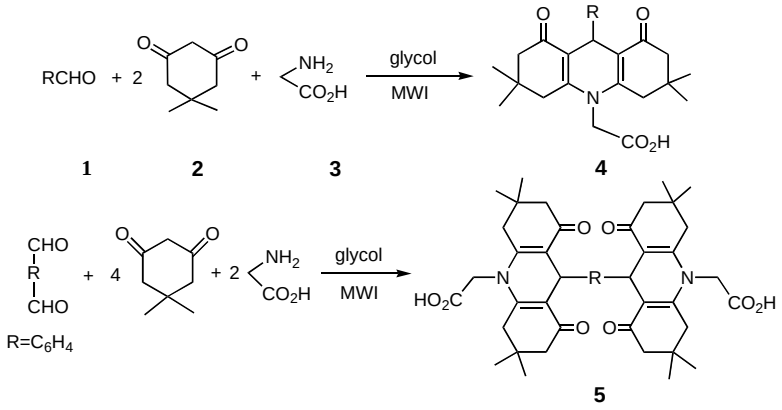
Introduction.

Acridinediones have been identified as antimalaria [1] and antitumor agents [2]. Decahydroacridine-1,8-dione derivatives have been reported to have high fluorescence efficiency and can be used as fluorescent molecular probes for monitoring of polymerization process [3]. Furthermore, the acridinedione dyes have already been reported as a class of laser dyes operating in the blue-green region [4]. They are also receiving much attention due to their likeness in properties with those of 1,4-dihydropyridines [5]. As a consequence, the interest of organic chemists in the synthesis or structure modifications of acridinedione derivatives remains high.

Shanmuguasundaramn *et al.* first synthesized two *N*-carboxymethylacridine-1,8-dione derivatives under traditional heating condition [6]. However, the reaction underwent two steps. The target compounds were refluxed in acetic acid for 2 hours and chromatographed over a column of silica and eluted with chloroform. This method involved long reaction time, complicated procedures, lower yields, and the use of a large quantity of poisonous and volatile reagents. It goes without saying

Scheme 1



that the most efficient and environmentally friendly synthesis of functionalized organic compounds would be one-pot reaction from commercially available and simple starting materials.

Multi-component reactions (MCRs) by virtue of their convergence, productivity, and ease of execution and generally higher yields of products have attracted considerable attention from the point of view of combinatorial chemistry [7]. The efficiency of microwave irradiation (MWI) in promoting organic reaction and the success of its application in heterocyclic synthesis [8] triggered us to apply it to one-pot multi-component reactions.

In our previous study [9], we have introduced hydroxyl to the nitrogen of decahydroacridine-1,8-dione under microwave irradiation. Through intensive research, we have successfully introduced carboxymethyl to the nitrogen of decahydroacridine-1,8-dione. Herein, we reported an efficient, high-yielding and simplified synthesis of *N*-carboxymethylacridine-1,8-dione derivatives **4** under MWI by employing one-pot condensation of aldehydes **1**, dimedone **2** and glycine **3** in glycol (Scheme 1).

Results and Discussion.

Initially, we explored the synthesis of **4c** by 4-cholorophenyl aldehyde **1c**, **2** and **3** in glacial acetic acid in 1:2:1.25 molar ratios at 98 °C with mechanical stirring. Unfortunately, the main product was **6** (70%) even if the reaction time was extended to 8 h. Therefore, we used glycol as solvent in stead of acetic acid. The result showed that the solvent was favourable, when **1c** reacted with **2**, **3** for 6 hours at 98 ℃ in glycol, the goal product **4c** was isolated in 70% yield. But the reaction time and yield were still not perfect.

In order to shorten the reaction time and increase the yield, the microwave technology was applied in the reaction. Compared with the traditional heating methodology, the reaction time was shortened to 4 min from 6 hours and the yields were sharply increased to 86% from 70% for synthesizing **4c**. It is obvious that the microwave accelerates the reaction and improves the reaction yield.

When aliphatic aldehyde was used as starting material instead of aromatic aldehyde, we did not obtain the target product **4** but rather intermediate product **8** (60%). In addition, we discovered that the solvent played an important role in the process. When **1c** reacted with **2**, **3** in glacial acetic acid, product **6** was obtained. While ethanol was used as the solvent, the main product was **7** (Scheme 2).

The results (Table 1) showed that the protocol could be applied to different aldehydes including aromatic aldehyde and dialdehyde with excellent yields (78-92%). The new procedure was simple to operate and the workup was just simple filtration. All the target products were characterized by IR, ^{1}H NMR and elemental analysis. Furthermore, the structure of **4c** was established by an X-ray crystallographic analysis [10] (Figure 1).

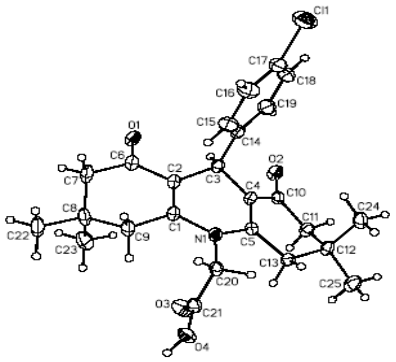


Figure 1. The structure of **4c**.

This reaction may occur via a reaction sequence of condensation, addition, cyclization and elimination (Scheme 3). At first, the condensation between aldehyde and dimedone gave 2-aryllidene-5,5-dimethyl-1,3-cyclohexanedione **9** and simultaneously dimedone reacted with glycine forming **8**. Then, Michael addition between **9** and **8** furnished the intermediate **10**, which isomerized to **11**. After that, intermolecular cyclization of **11** gave **12**, which upon dehydration gave **4**. We have also synthesized the goal products by the reaction of **8**, aldehyde and dimedone.

Scheme 2

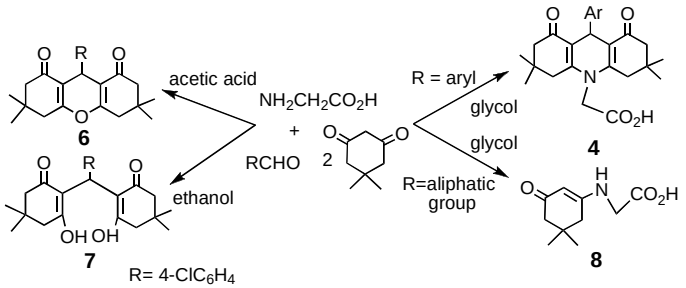
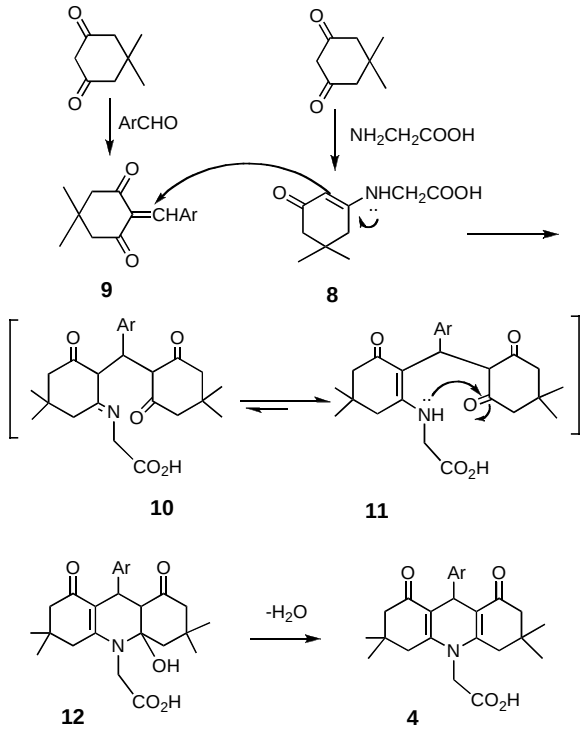


Table 1

Synthesis of **4** and **5** under microwave irradiation

Entry	R	Time (min)	Yield (%)	Mp (°C)
4a	4-FC_6H_4	6	91	241-242
4b	3-$NO_2C_6H_4$	6	85	227-228
4c	4-ClC_6H_4	4	86	300-302
4d	3,4-$Cl_2C_6H_3$	6	79	214-216
4e	2,4-$Cl_2C_6H_3$	6	78	288-289
4f	3,4-$(OCH_3)_2C_6H_3$	6	85	225-226
4g	3-OCH_3-4-OHC_6H_3	4	88	186-188
4h	C_6H_5	6	80	163-165
5a	1,4-$(CHO)_2$	7	92	273-239
5b	1,3-$(CHO)_2$	8	89	254-256

Scheme 3



In conclusion, we disclosed an efficient one-pot and microwave-assisted reaction by aldehyde, dimedone and glycine, thus realizing the introduction of carboxymethyl on the nitrogen of decahydroacridine-1,8-dione derivatives. The two step synthesis was shortened to one step efficiently. Particularly valuable features of this method included excellent yields of the products, short reaction time, environmental friendliness and ease of workup. Great efforts are underway to clarify the bioactivity of these new compounds and the results will be reported in due course.

Acknowledgments.

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EXPERIMENTAL

Microwave irradiation was carried out with a modified commercial microwave oven (2450 MHz, 650W) under atmospheric pressure. Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. Elemental analyses were determined by using a Perkin-Elmer 240c elemental analysis instrument.

General Procedure for the Synthesis of **4** and **5**.

Method A: A solution of the appropriate aldehyde (2 mmol), dimedone (4 mmol), glycine (2.5 mmol) and in glycol (0.25 mL) was irradiated for 4-8 min with power 220 W. The reaction mixture was cooled to room temperature, then poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH (**4a-4h**).

Method B: The mixture of dimedone (2 mmol) and glycine (2.5 mmol) in glycol (0.25 mL) was irradiated for 6 min with power 220 W. Then aldehyde and dimedone were added into this system, and reacted for 7-8 min with power 220 W. The reaction mixture was cooled to room temperature, then poured into water (50 mL), filtered to give the crude product, which was further purified by recrystallization from EtOH(**5a , 5b**).

2-(9-(4-Fluorophenyl)-1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4a**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3458, 1609, 1560 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 13.35 (s, 1H, COOH), 7.25-6.93 (m, 4H, ArH), 4.99 (s, 1H, CH), 4.61 (s, 2H, CH_2), 2.67-2.05 (m, 8H, $4CH_2$), 0.99 (s, 6H, $2CH_3$), 0.88 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{25}H_{28}FNO_4$: C, 70.57; H, 6.63; N, 3.29; Found C, 70.54; H, 6.51; N, 3.11.

2-(1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4b**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3450, 1616, 1569 cm^{-1}; ^{1}H

nmr (DMSO-d_6): δ 13.40 (s, 1H, COOH), 8.14 (s, 1H, ArH), 8.20 (dd, 1H, J_1=9.6 Hz, J_2=1.2 Hz, ArH), 7.85 (d, 1H, *J*=7.6 Hz, ArH), 7.46 (d, 1H, *J*=7.6 Hz, ArH), 8.14-7.45 (m, 4H, ArH), 5.10 (s, H, CH), 4.66 (s, 2H, CH_2), 2.52-2.10 (m, 8H, $4CH_2$), 1.00 (s, 6H, $2CH_3$), 0.88 (s, 6H,$2CH_3$).

Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19; Found C, 66.52; H, 6.08; N, 6.25.

2-(9-(4-Chlorophenyl)-1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4c**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3421, 1643, 1602 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.36 (s, 1H, COOH), 7.36 (d, 2H, *J*=8.0 Hz, ArH), 7.06 (d, 2H, *J*=8.0 Hz, ArH), 4.98 (s, H, CH), 4.62 (s, 2H, CH_2), 2.80-2.05 (m, 8H, $4CH_2$), 1.00 (s, 6H, $2CH_3$), 0.89 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{25}H_{28}ClNO_4$: C, 67.94; H, 6.39; N, 3.17; Found C, 68.09; H, 6.43; N, 3.02.

2-(9-(3,4-Dichlorophenyl)-1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4d**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3421, 1662, 1619 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.35 (s, 1H, COOH), 7.31(d, 1H, *J*= 8.4 Hz, ArH), 7.29 (s, 1H, ArH), 7.12(d, 1H, *J*= 8.0 Hz, ArH), 5.16 (s, H, CH), 4.64 (s, 2H, CH_2), 2.57-1.98 (m, 8H, $4CH_2$),1.01 (s, 6H, $2CH_3$), 0.86 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{25}H_{27}C_{l2}NO_4$: C, 63.03; H, 5.71; N, 2.94; Found C, 63.15; H, 5.68; N, 3.11.

2-(9-(2,4-Chlorophenyl)-1,2,3,4,5,6,7,8-octahydro-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4e**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3500, 1623, 1570 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.35 (s, 1H, COOH), 7.24(d, 1H, *J*= 8.4 Hz, ArH), 7.20 (s, 1H, ArH), 7.10 (d, 1H, *J*= 8.0 Hz, ArH), 5.16 (s, H, CH), 4.65 (s, 2H, CH_2), 2.52-2.02 (m, 8H, $4CH_2$), 1.00 (s, 6H, $2CH_3$), 0.86 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{25}H_{27}Cl_2NO_4$: C, 63.03; H, 5.71; N, 2.94; Found C, 63.21; H, 5.56; N, 2.73.

2-(1,2,3,4,5,6,7,8-Octahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4f**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3303, 1655, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.30 (s, 1H, COOH), 6.81(s, 1H, ArH), 6.76 (d, 1H, *J*= 8.4 Hz, ArH), 6.72 (d, 1H, *J*= 8.0 Hz, ArH), 4.95 (s, H, CH), 4.61 (s, 2H, CH_2), 3.66 (s, 3H,OCH_3), 3.64 (s, 3H, OCH_3) 2.62-2.04 (m, 8H, $4CH_2$), 1.04 (s, 6H, $2CH_3$), 0.89 (s, 6H, 2CH3).

Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00; Found: C, 69.58; H, 7.02; N, 2.86.

2-(1,2,3,4,5,6,7,8-Octahydro-9-(4-hdroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxoacridine-10(9*H*)-yl)acetic acid (**4g**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3480, 1632, 1593 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.31 (s, 1H, COOH), 8.55 (s, 1H, OH), 6.76 (s, 1H, ArH), 6.60 (d, 1H, *J*=8.0 Hz, ArH), 6.52 (d, 1H, *J*=8.0 Hz, ArH), 4.91 (s, H, CH), 4.43 (s, 2H, CH_2), 3.66 (s, 3H, OCH_3), 2.59-2.04 (m, 8H, $4CH_2$), 1.08 (s, 6H, $2CH_3$), 1.06 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09; Found C, 69.01; H, 6.78; N, 2.89.

2-(1,2,3,4,5,6,7,8-Octahydro-3,3,6,6-tetramethyl-1,8-dioxo-9-phenylacridine-10(9*H*)-yl)acetic acid (**4h**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3446, 2960, 1734, 1634 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.29 (s, 1H, COOH), 7.20-7.01 (m, 5H, ArH), 4.99 (s, H, CH), 4.60 (s, 2H, CH_2), 2.67-2.03 (m, 8H, $4CH_2$), 1.01 (s, 6H, $2CH_3$), 0.94 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44; Found C, 73.82; H, 7.14; N, 3.22.

1,4-Bis(3,3,6,6-tetramethyl-10-carboxymethyl-decahydroacridine-1, 8-dione-yl) -benzene (**5a**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3446, 1633, 1571 cm^{-1}. ^1H nmr (DMSO-d_6): δ 13.28 (s, 2H, 2COOH), 6.94-6.77 (m, 4H, ArH), 4.90 (s, 2H, 2CH), 4.57 (s, 4H, $2CH_2$), 2.67-2.00 (m, 16H, $8CH_2$), 0.94(s, 12H, $4CH_3$), 0.84 (s, 12H, $4CH_3$).

Anal. Calcd for $C_{44}H_{52}N_2O_8$: C, 71.72; H, 7.11; N, 3.80; Found C, 71.85; H, 7.02; N, 3.64.

1,3-bis(3,3,6,6-Tetramethyl-10-carboxymethyl-decahydroacridine-1, 8-dione-yl)- benzene (**5b**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3446, 1660, 1626 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13.30 (s, 2H, 2COOH), 7.08-6.94 (m, 4H, ArH), 4.97 (s, 2H, 2CH), 4.48 (s, 4H, $2CH_2$), 2.59-2.00 (m, 16H, $8CH_2$), 1.04 (s, 12H, $4CH_3$), 0.89 (s, 12H, $4CH_3$).

Anal. Calcd for $C_{44}H_{52}N_2O_8$: C, 71.72; H, 7.11; N, 3.80; Found C, 71.89; H, 7.23; N, 3.63.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-(*1H*)-xanthene-1,8(*2H*)-dione (**6**).

This compound was obtained according to above general procedure; ir (potassium bromide): 2980, 1680, 1660, 1620 cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.26 (s, 4H, ArH), 4.64 (s, 1H, CH), 4.48 (s, 4H, $2CH_2$), 2.14-2.03 (m, 8H, $4CH_2$), 1.10 (s, 6H, $2CH_3$), 0.98 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{23}H_{25}ClO_3$: C, 71.77; H, 6.54; Found C, 71.92; H, 6.32.

2,2'-(4-Chlorophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one(**7**).

White acerose solid, m.p. 135-136 °C (lit. [11] 134-135 °C).

[(5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)amino]acetic acid (**8**).

This compound was obtained according to above general procedure; ir (potassium bromide): 3336, 2961,1716 cm^{-1}; ^1H nmr (DMSO-d_6): δ 12.79 (s, 1H, COOH), 7.15 (s, 1H, NH), 4.68 (s, 1H, CH), 3.76 (d, 2H, *J*=6.0 Hz CH_2), 2.23 (s, 2H, CH_2), 1.97 (s, 2H, CH_2), 0.98 (s, 6H, $2CH_3$).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10; Found C, 61.02; H, 7.64; N, 7.08.

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[10] The sing-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens *P4* diffractometer (graphite monochromator, *MoKa* radiation λ=0.71073 Å). Crystal data for **4c**: Empirical formula $C_{25}H_{28}ClNO_4$, light-yellow, crystal dimension 0.25×0.18×0.15 mm, monoclinic, space group *P21/c*, *a* =12.655(3), *b* =16.582(3), *c* =11.500(3)Å, =90°, β =107.708(6)°, =90°, *V* =2298.9(9)Å^3, *Mr* =441.93, *Z* =4, *Dc* =1.277Mg/m^3 , λ =0.71073Å, μ(*Mok*α) =0.0197 mm^{-1}, *F(000)* =936, *S* =1.124, R_1 = 0.0770, wR_2 = 0.1508.

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