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Note

One-pot multicomponent synthesis of some novel acridines

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Acridine derivatives **1b-5b** have been synthesized from dimedone, 1,3-cyclohexanedione, cyclohexanone and phenols by reacting each with vinyl acetate in 2% sodium hydroxide followed by treatment with ammonia.

Keywords: Acridines, dimedone, phenols, multi-component reaction, vinyl acetate

Acridines are interesting heteroaromatic structures that are much sought after targets because of their broad biological properties. Their activities against bacteria[1,2], parasites[2], and tumors[3] depend mainly on the nature and position of substituents on the acridine nucleus. Recently some, bis- and tetra- acridines have shown *in vitro* anti-parasitic activity against *Leishmania infantum*[4]. The potential of these compounds in the fight against cancer was noted as early as 1920. Since then, a large number of molecules have been tested as antitumor agents, a recent target being their telomerase and topoisomerase inhibition activity[2].

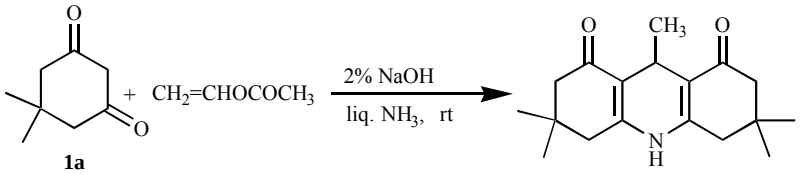
Acridine derivatives have also been used as pigments and dyes. The synthesis, electrochemistry and photo physical properties of acridine-1,8-dione dyes are particularly well explored[5,6]. Some methods are reported for the synthesis of acridine-1,8-diones from dimedone and aldehydes by traditional heating in organic solvents[7] or in water[8] or by irradiating under microwaves[9].

In recent years, the one-pot multicomponent condensation reactions have received significant attention[10] since two or more steps in the synthetic sequence can be carried out without the isolation of intermediates. This leads to reduction of time and energy and constitutes overall an economical way of developing new pharmaceutically important compounds[11]. We report herein a one-pot multicomponent synthesis of the titled compounds using vinyl acetate and liquor ammonia as the reagents.

Results and Discussion

Vinyl acetate was added drop wise to a stirred solution of dimedone **1a** in 2% sodium hydroxide at room temperature. After 1 hr, 5 mL of liquor ammonia was added and the stirring was continued for further 2 hr. A brown colour solid precipitated out, which was filtered and purified by column chromatography to give a pale yellow solid **1b**. IR spectrum of **1b** exhibited a strong band at 1585 cm^{-1} ascribable to carbonyl group and a brand band in the region 3330-3453 cm^{-1}due to NH group. The ^1H NMR spectrum revealed a fine doublet at δ 0.79-0.81 and doublet at δ 0.99-1.02 accountable to C_9-methyl group and C_3- and C_6-methyl groups respectively. A multiplet at δ 2.05-2.37 for C_2-, C_4-, C_5-, and C_7-methylene protons, a quartet at δ 3.70 for C_9-H and a singlet at δ 9.04 for NH proton were also found. The elemental analysis of **1b** corroborated the proposed molecular formula $C_{18}H_{25}NO_2$. The mass spectrum illustrated the molecular ion peak at *m/z* 287 (M^+) along with fragment ion peaks at 272, 216, 147, and 117. All the above spectral data supported the compound **1b** to be 3,3,6,6,9-pentamethyl-l,8-dioxo-decahydroacridine[6] (**Scheme I**). To study the generality of this process, several examples of poly functionalized acridines such as 9-methyl-1,8-dioxo-decahydroacridine **2b**, 9-methyl-1,8-dihydroxy-9,10-dihydroacridine **3b**, 9-methyl-1,3,6,8-tetrahydroxy-9,10-dihydroacridine **4b** and 9-methyldecahydro-acridine **5b** have been prepared from 1,3-cyclo-hexanedione **2a**, resorcinol **3a**, phloroglucinol **4a** and cyclohexanone **5a** respectively. The results are summarized in **Table I**. The structures of all the compounds were confirmed by their analytical and spectral data (**Table II**).

We propose the possible mechanism (**Scheme II**) to account for the reaction. One molecule of dimedone **1** was first condensed with vinyl acetate to afford **6.** Then the active methylene group of another molecule of dimedone was reacted with **6** by conjugative addition reaction to give the intermediate **7**. The intermediate **7** was attacked by ammonia on the hydroxyl group and gave the intermediate **8**. The intermediate **8** was cyclised by the nucleophilic attack



1a **1b**

Scheme I

Table I — Physical data of compounds **1b-5b**

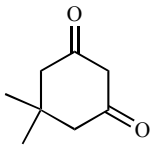
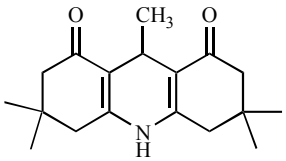
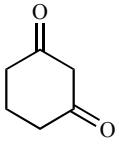
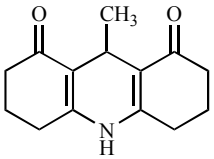
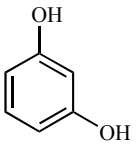
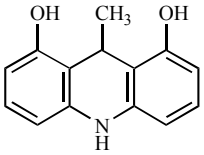
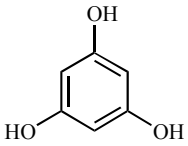
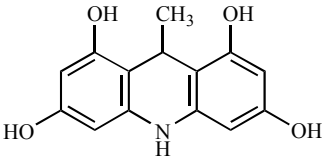
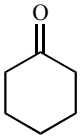
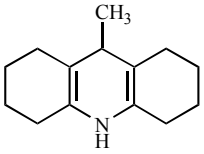
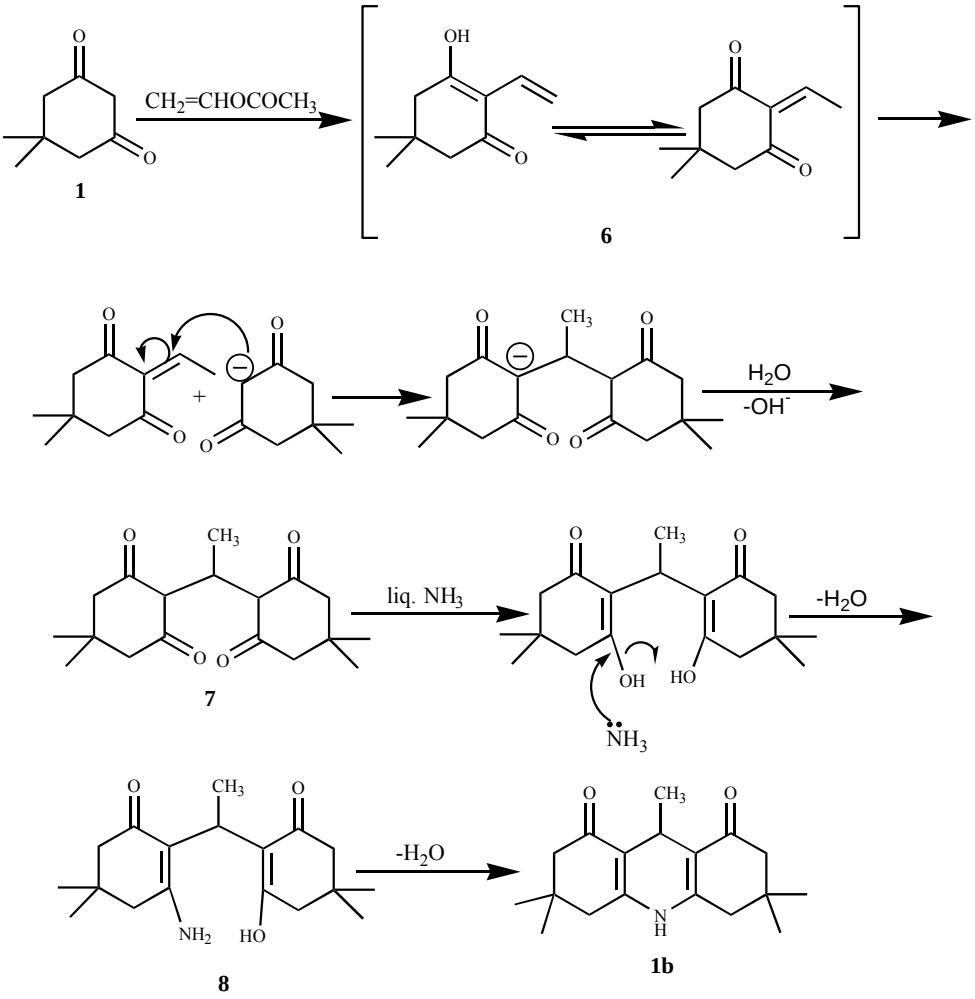
Compd	Substrate **a**	Product **b**	Yield (%)	m.p. °C
1			65	240-42
2			86	290-92
3			68	>300
4			84	>300
5			79	>300

Table II — Characterization data of compounds **1b-5b**

Compd	IR (KBr) (ν_{max}, cm^{-1})	^{1}H NMR (DMSO-d_6) (δ ppm)	Found (Calcd) C	H	N	MS (70 eV) $M^{+\cdot}$ (*m/z*)
1b	1585 (C=O) 3330-3453 (NH)	0.79-0.81 (d, 3H, C_9-CH_3), 0.99-1.02 (d, 12H, C_3- & C_6-CH_3), 2.05-2.37 (m, 8H, C_2-, C_4-, C_5 & C_7-H), 3.70 (q, 1H, C_9-H), 9.04 (s, 1H, NH)	75.30, (75.26)	8.76, (8.78)	4.86 (4.87)	287
2b	1613 (C=O) 3200-3350 (NH)	1.02 (d, 3H, C_9-CH_3), 2.02 (m, 4H, C_3- & C_6-H), 2.22 (t, 4H, C_2- & C_7-H), 2.55 (t, 4H, C_4- & C_5-H), 3.71 (q, 1H, C_9-H), 9.12 (s, 1H, NH)	72.70, (72.72)	7.39, (7.41)	6.03 (6.06)	231
3b	3100-3400 (NH, OH)	1.73 (d, 3H, C_9-CH_3), 4.73 (q, 1H, C_9-H), 6.68-8.36 (m, 6H, Ar-H), 9.73 (s, 1H, NH), 11.92 (bs, 2H, OH)	74.01, (74.01)	5.76, (5.77)	6.12 (6.16)	227
4b	3200-3440 (NH, OH)	1.60 (d, 3H, C_9-CH_3), 4.80 (q, 1H, C_9-H) 6.68-7.97 (m, 4H, Ar-H,), 9.32 (s, 1H, NH), 10.92 (bs, 2H, OH), 11.38 (bs, 2H, OH)	64.86, (64.86)	5.07, (5.06)	5.40 (5.41)	259
5b	3100-3250 (NH)	0.90 (d, 3H, C_9-CH_3), 1.75-2.26 (m, 12H, C_1-, C_2-, C_3-, C_6-, C_7- & C_8-H), 2.56 (t, 4H, C_4- & C_5-H), 3.70 (q, 1H, C_9-H), 9.11 (s, 1H, NH)	82.76, (82.75)	1.03, (1.04)	6.85 (6.89)	203

Mechanism :



Scheme II

of NH_2 group on another hydroxyl group and gave the product **1b**.

In conclusion, we have developed a simple and efficient one-pot multicomponent synthetic methodology for some acridine derivatives at room temperature.

Experimental Section

Melting points were recorded on Boetieus microheating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AMX-400 (400 MHz) spectrometer, using TMS as an internal reference, and mass spectra were recorded at 70 eV on a Jeol JMS-D-300 instrument.

General procedure for the preparation of acridines, 1b-5b

The substrate **a** (**1a-5a**, 0.001 mole) was stirred at room temperature in 25 mL of 2% sodium hydroxide. To this alkaline solution, 5 mL of vinyl acetate was added drop wise. After 1 hr, 5 mL of liquor ammonia was added and continued the stirring for 2 hr. The precipitated solid was filtered and washed with water. The crude compound was purified by column chromatography [Silica gel, pet. ether and ethyl acetate (3:1)] (**Tables I** and **II**).

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