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ONE-POT THREE-COMPONENT SYNTHESIS OF SOME NEW N-SUBSTITUTED ACRIDINE-1,8-DIONE DERIVATIVES

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ABSTRACT

This study presents, a series of new N-substituted acridine-1,8-diones derivatives **4a-h** has been successfully synthesized by one-pot three compounds reaction of 1,3-cyclohexadione, with hydrazones as the nitrogen source and aromatic aldehyde derivatives with the use of triethylamine (TEA) as an efficient catalyst. All these new compounds synthesized were characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR.

KEYWORDS

Acridine-1,8-diones, hydrazone, aromatic aldehyde, one-pot multicomponent reactions.

INTRODUCTION

Many N-heterocyclic compounds are reported to date and since they have been recognized as key building blocks due to their interesting structural properties in pharmaceutical and medicinal applications, there is an increasing demand for the design and synthesis of new heterocyclic compounds with required therapeutic properties.[i] Among them, acridine and its derivatives constitute an important class of heterocyclic compounds that possess a wide spectrum of potential biological and pharmacological activities such as anticancer,[ii,iii] antiviral, antimalarial and antiallergic,[iv,v] antibacterial and antimicrobial,[vi] anti-inflammatory,[vii,viii] antidiabetic,[ix] mutagenic [x] and antitumor in vitro and in vivo against various murine and human tumors.[xi] Acridine and its derivatives have also found applications in industries and the production of dyes. They have excellent photophysical properties,[xii] making them ideal candidates for use as laser dyes.[xiii] Acridine and its derivatives are used as photosensitizers [xiv] and as photoinitiators in polymerization reactions.[xv] These molecules can exist in neutral,

protonated or deprotonated forms.[xvi]

There are many methods reported for the synthesis of substituted acridines, including multicomponent condensation (MCR) of various aromatic aldehydes, cyclic diketones, and nitrogen reagents such as ammonium hydroxide,[xvii] ammonium bicarbonate,[xviii] ammonium acetate and basic alumina catalyst, [xix] hydroxylamine, [xx] ethyl glycinate hydrochloride [xxi] and various anilines,[xxii] in hazardous/non-hazardous solvents using microwave heating methods, reflux traditional.

The present work is part of the synthesis of novel compounds N-substituted acridine-1,8-diones derivatives (4a-h) via a one-pot multicomponent reaction of 1,3-cyclohexadione (1), an aromatic aldehyde (2a-e) and hydrazones (3a–b) refluxed in ethanol with triethylamine (TEA) as the effective catalyst.

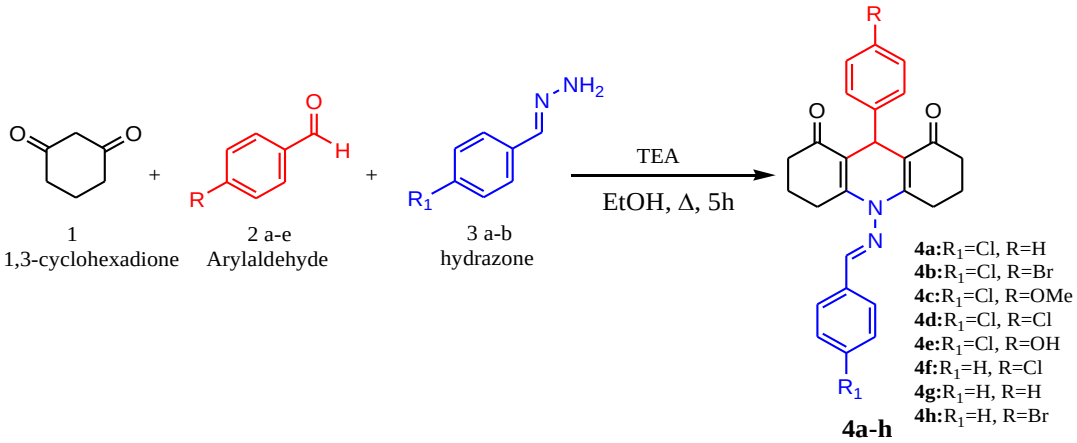
EXPERIMENTAL

Materials

All chemicals were obtained from Sigma Aldrich and were used without further purification. Thin layer chromatography (TLC) was done on silica gel TLC aluminium plates (E. Merck Kieselgel 60 F-254) and were visualized by exposure to UV-light at 254 nm or iodine vapor for few seconds. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AQS-AVANCE spectrometer (400 MHz) at 25°C using DMSO-d_6 as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm). Melting point in °C was determined in open capillaries using Electrothermal melting point apparatus Stuart MPS-10. FT-IR spectra were recorded on a Bruker ATR spectrophotometer and the values are expressed in cm^{-1}.

General procedure for the synthesis of N-substituted acridine-1,8-diones derivatives (4a-h)

To a mixture of 1,3-cyclohexanedione (2 eq), arylaldehyde **2a-e** (1 eq), and the hydrazones **3a-b** (1 eq) in ethanol (30 ml), triethylamine (2 eq) was added, the reaction mixture was heated under reflux for the 5h. The progress of reaction is monitored by TLC. After completion of the reaction left to cool, and the separated solid was filtered off, dried, and recrystallized from ethanol to afford compound **4a-h** (Scheme 1).



Scheme 1. One-pot synthesis of N-substituted acridine-1,8-diones derivatives (4a-h) .

RESULTS AND DISCUSSION

In this work, we have found that the combination of 1,3-cyclohexanedione **1** with aromatic aldehydes **2a-e** and the appropriate hydrazones **3a-b**; (1-benzylidenehydrazine or 4-chlorobenz-

ylidenehydrazine) leads to the formation of N-substituted acridine-1,8-diones derivatives **4a-h** (scheme 1).

In general, N-substituted acridine-1,8-dione derivatives **4a-h** compounds were obtained in good yields when mixtures of three starting components and two equivalents of triethylamine were refluxed in ethanol for 5 hours (table1). The desired products precipitate on cooling of the reaction mixture and filtration gives an analytically pure material.

Table 2. One-pot synthesis of N-substituted acridine-1,8-diones derivatives (4a-h).

Compounds	**R_1**	**R**	**Yield (%)**	**mp(°C)**
4a	Cl	H	83	242-244
4b	Cl	Br	87	248-250
4c	Cl	OMe	81	255-257
4d	Cl	Cl	89	244-246
4e	Cl	OH	84	240-242
4f	H	Cl	85	241-243
4g	H	H	83	230-231
4h	H	Br	82	247-249

Characterization

FT-IR spectroscopic analysis

The IR spectra of compounds **4a–h** show characteristic bands at 2940-3056cm^{-1}, 1681-1719 cm^{-1}, 1552-1600 cm^{-1} and 1464-1521 cm^{-1} which can be attributed respectively to =C-H, C=O, C=N, C=C. The infrared spectrum of compound **4e** has a band of absorption of the order of 3295 cm^{-1} due to OH stretching (linked to intermolecular hydrogen).

^{1}H-NMR spectroscopic analysis

In ^{1}H NMR, the spectra of all the compounds synthesized show signals at 1.68-2.68 ppm were assigned for the CH_2 protons. A singlet at 4.56-5.16 ppm for aliphatic CH. Aromatic protons resonate in the region of 6.75-7.94 ppm. The azo-methine signal (-CH=N) appears at 8.52-8.76 ppm in all compounds **4a-h**. In addition, the ^{1}H-NMR spectrum of **4e** reveals the presence of a singlet at 9.01 ppm corresponding to the hydroxyl group O-H, and the ^{1}H-NMR spectrum of **4c** reveals the presence of a singlet at 3.31 ppm corresponding to the O-Me methoxy group.

All spectral data from FTIR, ^{1}H-NMR and ^{13}C-NMR confirmed the structure of the N-substituted acridine-1,8-diones derivatives (4a-h).

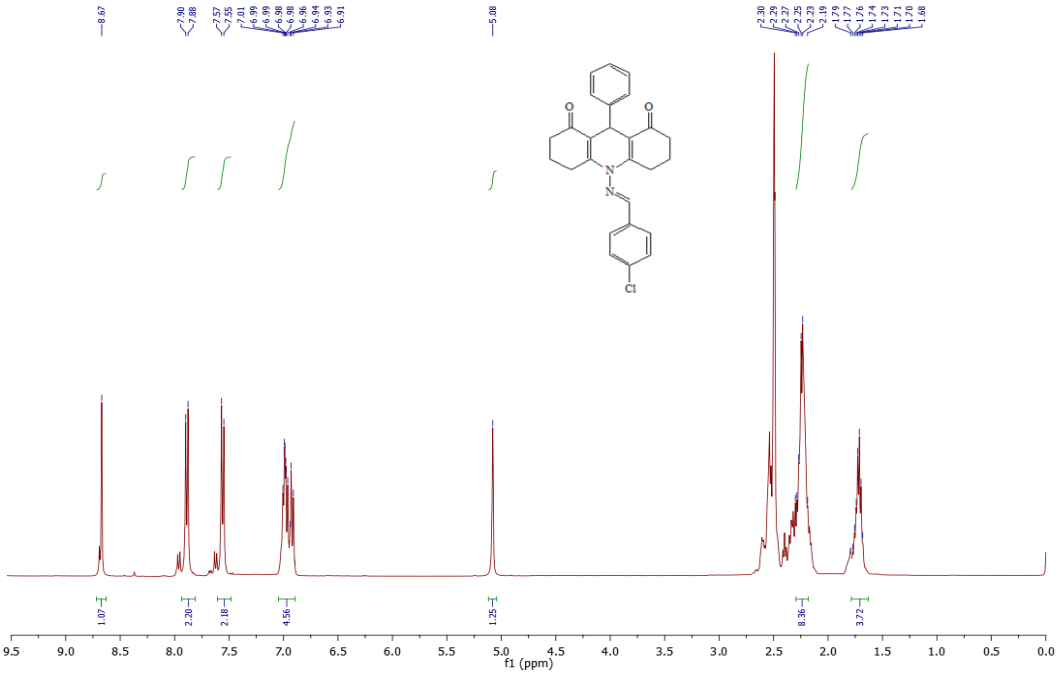


Fig 1. The ^{1}H NMR spectrum of compound **4a** in DMSO-d_6 solvent.

Spectroscopic Data

Data for 10-(4-chlorobenzylideneamino)-9-phenyl-3,4,6,7-tetrahydroacridine 1,8(2H,5H, 9H, 10H)-dione (**4a**) : Yellow powder (yield 83%), m.p. 242-244 °C; FT-IR (νmax in cm-1): 3056 (aromatic C-H), 1684 (C=O), 1554 (C=N),1465 (aromatic C=C), 989 (N-N), 687 (C-Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.67 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.01 – 6.91 (m, 5H), 5.08 (s, 1H), 2.30 – 2.19 (m, 8H), 1.79 – 1.68(m, 4H) ; 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.74, 26.07, 27.79, 37.17, 115.66, 124.60, 126.27, 127.23, 128.87, 129.50, 130.44, 133.16, 136.50, 150.16, 160.62, 196.42(C=O)

Data for 10-(4-chlorobenzylideneamino)-9-(4-bromophenyl)-3,4,6,7-tetrahydroacridine -1,8 (2H , 5H, 9H,10H)-dione (**4b**) : Yellow powder (yield 87%), m.p. 248-250 °C; FT-IR (νmax in cm-1): 3054(aromatic C-H), 1682 (C=O), 1552 (C=N),1464 (aromatic C=C), 988 (N-N), 743 (C-Br), 686 (C-Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.67 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.56 (d, J= 8.5 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 17.1 Hz, 2H), 4.57 (s, 1H), 2.44 – 2.40 (m, 4H), 2.14 – 2.09 (m, 4H), 1.89 – 1.84 (m, 4H) ; 13C NMR(100MHz, DMSO-d6, δ in ppm) :20.84, 29.09, 32.62, 37.19, 101.42, 115.86, 127.55, 127.67, 130.45, 130.74, 133.17, 136.50, 143.93, 144.66, 160.63, 195.75(C=O).

Data for 10-(4-chlorobenzylideneamino)-9-(4-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8 (2H,5H,9H,10H)-dione (**4c**): Yellow powder (yield 81%), m.p. 255-257°C; FT-IR (νmax in cm-1): 2941(aromatic C-H), 1718 (C=O), 1598 (C=N),1505 (aromatic C=C), 1248 (C-O), 1023 (N-N), 616 (C-Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.65 (s, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 5.16 (s, 1H), 3.31 (s, 3H), 2.31 – 2.23 (m, 8H), 1.89 – 1.84 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.35, 29.09, 33.47, 37.13, 57.70, 100.43, 115.82, 127.55, 127.67, 130.15, 130.74, 134.49, 137.96, 141.76, 157.02, 159.98, 198.60(C=O).

Data for 10-(4-chlorobenzylideneamino)-9-(4-chlorophenyl)-3,4,6,7-tetrahydroacridine-1,8(2

H,5H ,9H,10H)-dione (**4d**) : Yellow powder (yield 89%), m.p. 244-246 °C; FT-IR (νmax in cm-1): 2943(aromatic C-H), 1718 (C=O), 1599 (C=N),1505 (aromatic C=C), 1023 (N-N), 616 (C-
Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.68 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 7.9 Hz, 2H), 4.63 (s, 1H), 2.26 – 2.19 (m, 8H), 1.76 – 1.68 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.74, 26.06, 27.79, 37.18, 115.65, 124.60, 127.22, 128.88, 129.51, 130.45, 130.81, 133.17, 136.50, 150.16, 160.62, 196.41(C=O).

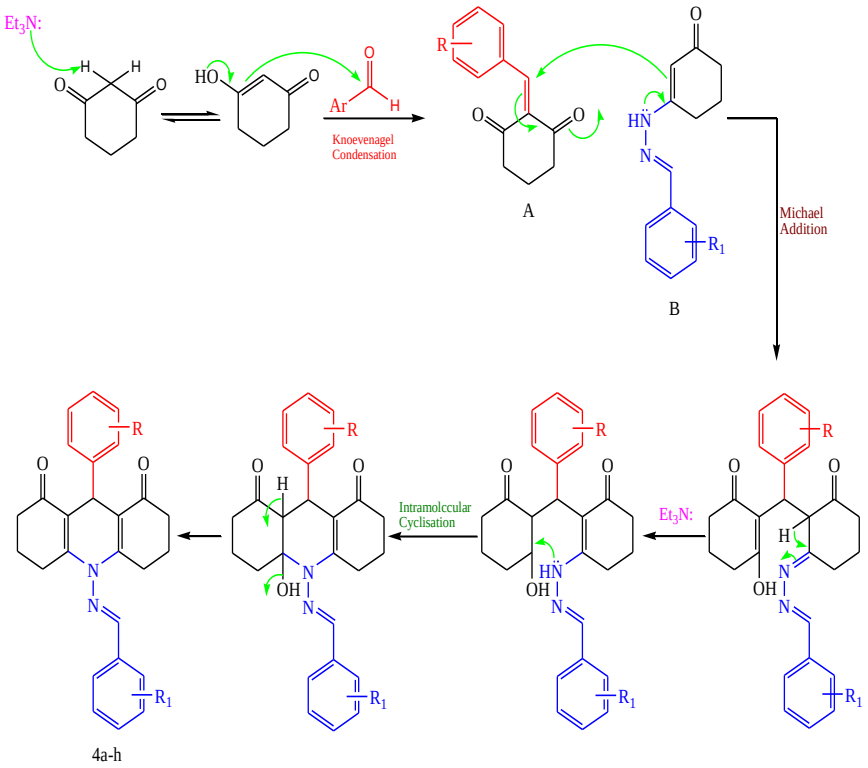
Data for 10-(4-chlorobenzylideneamino)-9-(4-hydroxyphenyl)-3,4,6,7-tetrahydroacridine-1,8 (2H, 5H, 9H, 10H)-dione (**4e**) : Yellow powder (yield 84%), m.p. 240-242 °C; FT-IR (νmax in cm-1): 3295 (OH), 3030 (aromatic C-H), 1694 (C=O), 1598 (C=N),1521 (aromatic C=C), 1021 (N-N), 685 (C-Cl);1H NMR(400 MHz, DMSO-d6, δ in ppm): 9.01 (s, 1H, -OH), 8.71 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 7.9 Hz, 2H), 4.56 (s, 1H), 2.45 – 2.41 (m, 4H), 2.12 – 2.09 (m, 4H), 1.89 – 1.84 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.99, 28.94, 32.22, 37.18, 101,55, 115.65, 128.88, 129.51, 130.18, 130.81, 134.10, 136.50, 144.65, 156.82, 160.62, 197.14(C=O).

Data for 10-(benzylideneamino)-9-(4-chlorophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9 H,10H)-dione (**4f**) : Yellow powder (yield 85%), m.p. 241-243 °C; FT-IR (νmax in cm-1): 2940 (aromatic C-H), 1719 (C=O), 1598 (C=N),1488 (aromatic C=C), 1024 (N-N), 617 (C-Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.76 (s, 1H), 7.21 – 7.17 (m, 5H), 7.01 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.80 (s, 1H), 2.45 – 2.40 (m, 4H), 2.11 – 2.07 (m, 4H) 1.89 – 1.86 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):20.18, 29.09, 32.62, 37.13, 100.43, 127.55, 127.67, 128.18, 128.78, 129.85, 130.15, 130.74, 143.93, 144.66, 159.24, 195.76(C=O).

Data for 10-(benzylideneamino)-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2H, 5H,9H, 10H) dione (**4g**) : Yellow powder (yield 83%), m.p. 230-231°C; FT-IR (νmax in cm-1): 3049 (aromatic C-H), 1718 (C=O), 1600 (C=N),1491 (aromatic C=C), 1031 (N-N); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.65(s, 1H), 7.25 – 7.20 (m, 10H), 5.16 (s, 1H), 2.68 – 2.60 (m, 8H), 1.99 – 1.93 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.33, 26.96, 31.13, 36.88, 114.16, 115.65, 128.30, 128.46, 129.51, 130.33, 130.69, 131.22, 144.01, 144.41, 153.48, 196.61(C=O).

Data for 10-(benzylideneamino)-9-(4-bromophenyl)-3,4,6,7-tetrahydroacridine-1,8 (2H,5H,9H,10H) -dione (**4h**) : Yellow powder (yield 82%), m.p. 247-249°C; FT-IR (νmax in cm-1): 3054 (aromatic C-H), 1681 (C=O), 1552 (C=N),1464 (aromatic C=C), 987 (N-N), 742 (C-Br); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.52 (s, 1H), 7.21 – 7.17 (m, 5H), 7.06 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 17.1 Hz, 2H), 4.72 (s, 1H), 2.45 – 2.40 (m, 4H), 2.11 – 2.07 (m, 4H) 1.89 – 1.86 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.84, 29.09, 35.48, 37.13, 100.43, 115.82, 127.55, 127.67, 130.15,130.45, 130.74, 133.17, 143.93, 144.66, 160.63, 196.15(C=O).

The reaction mechanism for the synthesis of N-substituted acridine-1,8-diones derivatives **4a-h** is shown in (Scheme 2). The mechanism we propose for this transformation is based on the in situ formation of enaminone **B** derived from 1,3-cyclohexanedione and hydrazone, the adduct of Knoevenagel **A** derived from 1,3-cyclohexanedione and an aromatic aldehyde, followed by cyclization of intermediates **A** and **B**, followed by removal of a water molecule to give the products **4a-h**.



Scheme2. Proposed mechanism for synthesis of compound N-substituted acridine-1,8-diones derivatives (4a-h).

CONCLUSION

In conclusion, the use of hydrazones (1-benzylidenehydrazine or 4-chlorobenzylidenehydrazine) in a three-component reaction with a mixture of 1,3-cyclohexadione and aromatic aldehydes under the conditions of triethylamine in ethanol. Lead to the formation of N-substituted acridine-1, 8-diones derivatives **4a-h** in high yields.

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