



An efficient and eco-friendly preparation of N-substituted acridine-1,8-dione derivatives using triethylamine as catalyst in ethanol medium

Abdelkader Brahimi^{1,2,*}, Boumadiene Benlahreche³, Abdelghani Elmahdaoui Rebhi⁴, Mokhtar Boualem Lahrech⁵

¹Faculty of Science and Technology, University of ZIANE Achour, Djelfa, Algeria.

²Laboratory of Organic Chemistry and Natural Substance, Faculty of Exact Sciences and informatics, University of Ziane Achour, Djelfa, Algeria.

* Corresponding Author Email: abdelkader.brahimi@unv-djalfa.dz - ORCID: 0000-0002-5247-1150

³Laboratory of Organic Chemistry and Natural Substance, Faculty of Exact Sciences and informatics, University of Ziane Achour, Djelfa, Algeria.

Email: boumadien2e@gmail.com - ORCID: 0000-0002-5247-3350

⁴Laboratory of Organic Chemistry and Natural Substance, Faculty of Exact Sciences and informatics, University of Ziane Achour, Djelfa, Algeria.

Email: aldeghan2i@gmail.com - ORCID: 0000-0002-5247-8950

⁵Laboratory of Organic Chemistry and Natural Substance, Faculty of Exact Sciences and informatics, University of Ziane Achour, Djelfa, Algeria.

Email: mokhta2r@gmail.com - ORCID: 0000-0002-5247-9750

Article Info:

DOI: 10.22399/ijcesen.4300

Received: 25 April 2025

Revised: 05 November 2025

Accepted: 07 November 2025

Keywords

1,8-dioxo-decahydroacridines

Aniline

Aromatic aldehyde

One-pot multicomponent reactions

Triethylamine

Abstract:

This work presents a straightforward, efficient, and environmentally benign method for synthesizing N-substituted acridine-1,8-dione derivatives (4a-h). The synthesis is achieved via a one-pot, three-component condensation of an aromatic aldehyde, dimedone, and p-toluidine. The protocol employs ethanol as a green solvent and triethylamine (TEA) as a simple, effective catalyst. This approach offers significant advantages over conventional methods, including operational simplicity and mild reaction conditions. The reaction proceeds efficiently, affording the target products in excellent yields of 86–91%. A key practical benefit is the simple work-up; pure products are easily isolated by filtration and recrystallization, eliminating the need for complex chromatography. This method, characterized by its high yields, minimal environmental impact, and practicality, provides a robust and scalable route to the biologically significant acridine-dione core.

1. Introduction

Acridine and its derivatives constitute an important class of heterocyclic compounds with a wide range of potential biological and pharmacological activities, including anticancer,^{1,2} antiviral, antimalarial, antiallergic, ^{3,4} antibacterial and antimicrobial, ⁵ anti-inflammatory, ^{6,7} antidiabetic, ⁸ mutagenic, ⁹ and in vitro and in vivo antitumor activity against various tumors in mice and humans. ¹⁰ Acridine and its derivatives also have applications in industry and dye production. They possess excellent photophysical properties, ¹¹ making them ideal candidates for use as laser dyes.¹² Acridine and its derivatives are used as photosensitizers ¹³ and as photoinitiators in

polymerization reactions. ¹⁴ These molecules can exist in neutral, protonated, or deprotonated forms.

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Several methods have been reported for the synthesis of substituted acridines, including multicomponent condensation (MCR) of various aromatic aldehydes, cyclic ketones, and nitrogen reactants such as ammonium hydroxide, ¹⁶ ammonium bicarbonate, ¹⁷ ammonium acetate, basic alumina catalyst, ¹⁸ hydroxylamine, ¹⁹ and various anilines,²⁰ in hazardous/non-hazardous solvents using microwave heating and conventional reflux methods.

Previously, A.Djemoui et al. ²¹ reported the synthesis of various acridine-1,8-diones using the three-component reaction of ammonium acetate with aldehydes and 1,3-dicarbonyls. The reaction

was refluxed in ethanol with the use of triethylamine (TEA) as an effective catalyst. Under these conditions, the reaction proceeded in a regioselective manner to form the title compounds in high yields. Continuing the research, we performed the reaction using p-toluidine as a nitrogen source with aromatic aldehydes and dimedone refluxed in ethanol with the use of triethylamine (TEA) as an effective catalyst for formed a series of N-substituted acridine-1,8-diones (4a-h) (Scheme 1) in good to excellent yields.

2. Experimental Materials

All chemicals were obtained from Sigma Aldrich and were used without further purification. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm or iodine vapor for a few seconds. The melting point in °C was determined in open capillaries using a Stuart MPS-10 melting point electrothermal apparatus. The ¹H and ¹³C NMR spectra were acquired on a Bruker AQS-AVANCE spectrometer (400 MHz) at 25 °C using DMSO-d₆ as solvent. The chemical shifts (δ) are indicated in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, = 0.00 ppm).

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

To a mixture of dimedone (2 eq), aromatic aldehyde 2a-h (1 eq), and the p-toluidine 3 (1 mmol) 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). All the products were fully characterized on the basis of their melting-points and spectral data (¹H NMR and ¹³C NMR).

9-Phenyl-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4a):

yellow solid, (yield 89%), m.p: 263-265°C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.82 (s, 6H, 2×CH₃), 0.90 (s, 6H, 2×CH₃), 2.10–2.32 (m, 8H, 4×CH₂), 2.38 (s, 3H, CH₃), 5.22 (s, 1H, CH), 7.03–7.33 (m, 5H, Ar-H), 7.54 (d, J = 8.0 Hz, 2H, Ar-H), 7.82 (d, J = 8.0 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm) : 21.6, 27.1, 29.8, 32.6, 34.1, 42.1, 50.2, 109.7, 113.6, 128.8, 128.9, 129.5, 131.1, 132.0, 132.1, 136.1, 140.1, 150.7, 151.7, 196.1 C=O.

9-(4-Methylphenyl)-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4b): yellow solid, (yield 88%), m.p: 295-297°C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.89 (s, 6H, 2×CH₃),

1.03 (s, 6H, 2×CH₃), 2.12–2.24 (m, 8H, 4×CH₂), 2.29 (s, 3H, CH₃), 2.42 (s, 3H, CH₃), 5.23 (s, 1H, CH), 7.10–7.28 (m, 4H, Ar-H), 7.49 (d, J = 8.4 Hz, 2H, Ar-H), 7.69 (d, J = 8.4 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 20.8, 27.4, 29.3, 32.5, 33.6, 40.7, 50.6, 108.8, 114.8, 126.9, 128.1, 129.1, 130.5, 132.4, 132.6, 136.1, 140.1, 150.4, 151.3, 195.5 C=O.

9-(4-Cyanophenyl)-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4c):

yellow solid, (yield 87%), m.p: 274-276°C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.83 (s, 6H, 2×CH₃), 0.96 (s, 6H, 2×CH₃), 2.06–2.24 (m, 8H, 4×CH₂), 2.34 (s, 3H, CH₃), 5.25 (s, 1H, CH), 7.10–7.35 (m, 4H, Ar-H), 7.57 (d, J = 8.2 Hz, 2H, Ar-H), 7.88 (d, J = 8.2 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 22.1, 26.4, 29.2, 32.0, 33.3, 41.3, 50.6, 110.4, 113.2, 119.4, 128.3, 128.7, 129.6, 132.0, 132.1, 136.4, 140.4, 151.0, 152.3, 195.1 C=O.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4d):

yellow solid, (yield 88%), m.p: 284-286°C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.91 (s, 6H, 2×CH₃), 1.00 (s, 6H, 2×CH₃), 2.13–2.27 (m, 8H, 4×CH₂), 2.33 (s, 3H, CH₃), 3.58 (s, 3H, OCH₃), 5.18 (s, 1H, CH), 7.13–7.33 (m, 4H, Ar-H), 7.47 (d, J = 8.2 Hz, 2H, Ar-H), 7.91 (d, J = 8.2 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 21.1, 26.2, 29.4, 32.3, 33.5, 41.5, 50.6, 108.7, 114.6, 127.7, 129.1, 129.6, 131.1, 132.3, 132.6, 136.2, 139.4, 151.0, 152.1, 195.0 C=O.

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4e):

yellow solid, (yield 90%), m.p: >300°C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.84 (s, 6H, 2×CH₃), 0.96 (s, 6H, 2×CH₃), 2.01–2.18 (m, 8H, 4×CH₂), 2.33 (s, 3H, CH₃), 5.20 (s, 1H, CH), 7.15–7.24 (m, 4H, Ar-H), 7.55 (d, J = 8.0 Hz, 2H, Ar-H), 7.80 (d, J = 8.0 Hz, 2H, Ar-H), 9.63 (s, 1H, OH); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 20.6, 26.5, 30.1, 32.1, 33.3, 41.5, 50.4, 109.3, 113.1, 128.5, 129.2, 129.6, 131.2, 131.8, 132.3, 136.4, 139.4, 150.6, 151.9, 194.2 C=O.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-10-p-tolylhexahydroacridine-1,8-dione (4f):

yellow solid, (yield 86%), m.p: >300 °C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.84 (s, 6H, 2×CH₃), 1.05 (s, 6H, 2×CH₃), 2.00–2.19 (m, 8H, 4×CH₂), 2.36 (s, 3H, CH₃), 5.24 (s, 1H, CH), 7.11–7.24 (m, 4H, Ar-H), 7.52 (d, J = 8.0 Hz, 2H, Ar-H), 7.75 (d, J = 8.0 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 21.2, 26.3, 29.4, 32.3, 33.4, 41.4, 50.3,

109.4, 113.3, 128.1, 128.4, 129.2, 130.3, 132.0, 132.6, 136.5, 139.5, 149.8, 151.4, 194.6 C=O.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (4g): yellow solid, (yield 91%), m.p: 274-276 °C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.87 (s, 6H, 2×CH₃), 1.01 (s, 6H, 2×CH₃), 2.01–2.29 (m, 8H, 4×CH₂), 2.34 (s, 3H, CH₃), 5.25 (s, 1H, CH), 7.09–7.21 (m, 4H, Ar-H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H), 7.78 (d, J = 8.1 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 21.1, 26.1, 29.2, 32.7, 33.9, 42.1, 50.4, 109.1, 113.4, 128.4, 128.6, 129.6, 130.4, 132.4, 132.8, 136.3, 140.1, 151.0, 152.1, 194.0 C=O.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-10-p-tolyl-hexahydroacridine-1,8-dione (4h): yellow solid, (yield 90%), m.p: >300 °C; ¹H NMR (400 MHz, DMSO-d₆, δ in ppm): 0.89 (s, 6H, 2×CH₃), 0.99 (s, 6H, 2×CH₃), 2.02–2.14 (m, 8H, 4×CH₂), 2.30 (s, 3H, CH₃), 5.21 (s, 1H, CH), 7.14–7.34 (m, 4H, Ar-H), 7.48 (d, J = 8.2 Hz, 2H, Ar-H), 7.78 (d, J = 8.2 Hz, 2H, Ar-H); ¹³C NMR (100MHz, DMSO-d₆, δ in ppm): 21.5, 27.0, 30.3, 32.4, 34.1, 41.3, 51.0, 109.5, 113.5, 128.2, 128.5, 129.2, 130.4, 131.8, 132.1, 136.1, 141.4, 150.5, 151.5, 194.2 C=O.

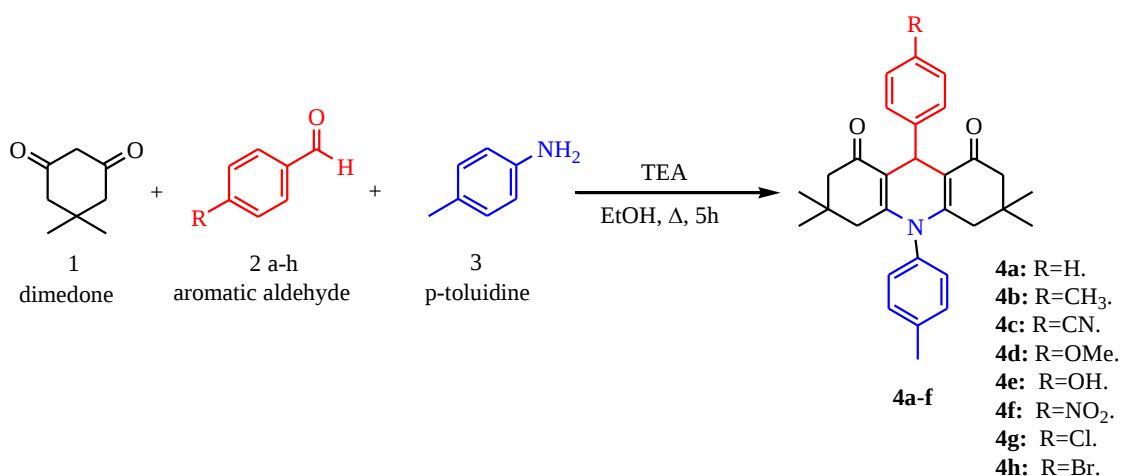


Figure 1. One-pot three compounds reaction for synthesis of N-substituted acridine-1,8-diones derivatives (4a-h) using triethylamine (TEA).

Table 1. One-pot synthesis of 1,8-dioxo-decahydroacridines derivatives (4a-f) catalyst by triethylamine (TEA).

Compounds	R	Yield* (%)		M.P. (°C)	
		Exp**	(Lit.)	Exp**	(Lit.)
4a	H	89	89 [22]	263-265	266-268 [22]
4b	CH ₃	88	85 [22]	295-297	296-298 [22]
4c	CN	87	- -	274-276	- -
4d	OCH ₃	88	81 [22]	284-286	282-285 [22]
4e	NO ₂	86	- -	>300	- -
4f	OH	90	83 [22]	>300	352-354 [22]
4g	Cl	91	83 [22]	269-271	273-276 [22]
4h	Br	90	- -	>300	- -

(*) Isolated yield of product using triethylamine (TEA). The structure of products are determined by NMR and all spectral data are in good agreement with those of literature.

(**) Exp.: Experimental value (Lit.: literature value).

3. Results and Discussion

In this work, we have found that the combination of dimedone 1 with aromatic aldehydes 2a-h and the p-

toluidine 3 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 to excellent 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.

A mechanism, shown in (Scheme 2), is proposed to explain the role of the triethylamine catalyst (TEA) in the synthesis of 1,8-dioxo-decahydroacridines

derivatives 4a-h. The mechanism we propose for this transformation is based on the in-situ formation of enaminone B derived from dimedone and p-toluidine, the adduct of Knoevenagel A derived from dimedone 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.

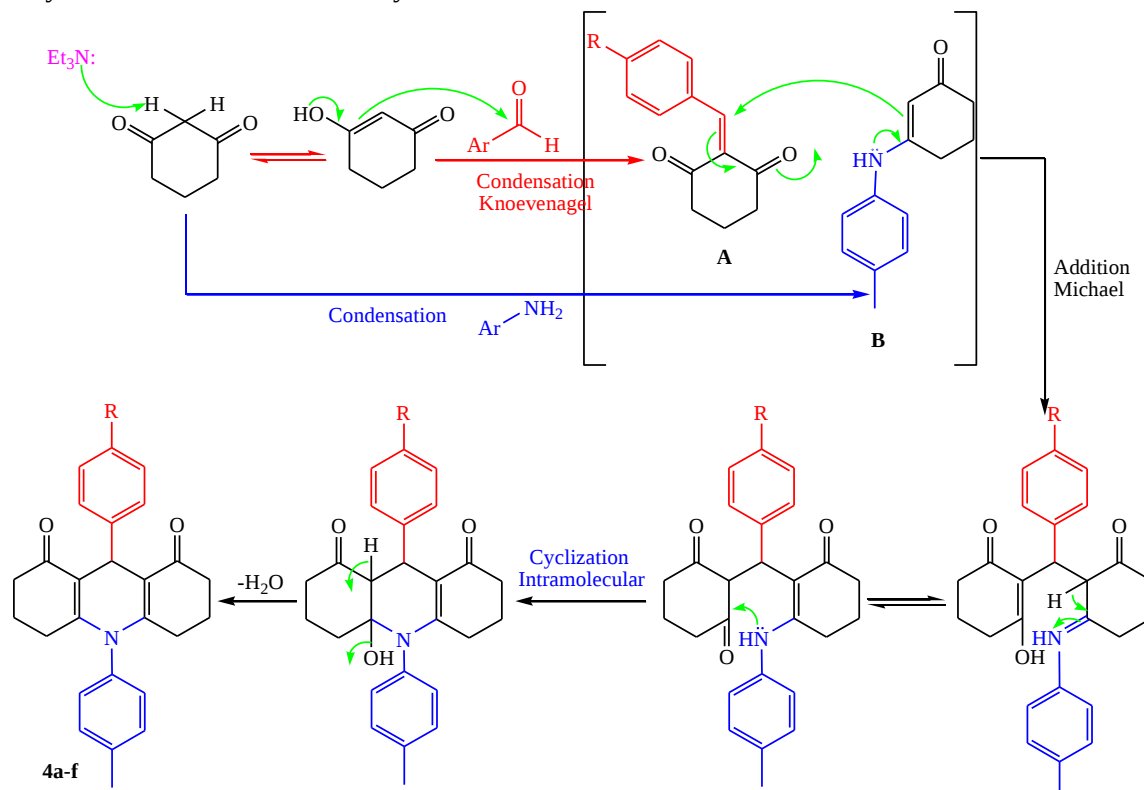


Figure 2. Proposed mechanism of the synthesis of N-substituted acridine-1,8-diones derivatives 4a-h using triethylamine (TEA).

4. Conclusions

In conclusion, the one-pot three-component reaction of dimedone 1 with aromatic aldehyde 2a-h and p-toluidine 3, in the presence of a catalytic amount of triethylamine in ethanol as solvent, constitutes an extremely efficient and chemoselective method for the synthesis of N-substituted acridine-1,8-diones derivatives 4a-h. The promising points for the presented protocols are efficiency, good to excellent yields, cleaner reaction profile, simplicity, lowcost, and compliance with the green chemistry protocols.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

- **Acknowledgement:** The authors acknowledge the University of Ziane Achour of Djelfa and Scientific Research in Algeria.
- **Author contributions:** The authors declare that they have equal right on this paper.
- **Funding information:** The authors declare that there is no funding to be acknowledged.
- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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