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Facile and Efficient Synthesis of Acridinediones from Primary Amino Alcohols Via Three-component Condensation Reactions Assisted by Microwave Irradiation

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Abstract. On microwave irradiation of three component reaction of dimedone, appropriate aromatic aldehydes and amino alcohols in a stiochiometrical ratio 2:1:1 for few minutes afforded the formation of a solid fused three membered ring of the corresponding of 3,6,6-tetramethyl-,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives in an excellent yield (80 – 91.3%). The structure of all products has been characterised by X-ray crystal structural analyses, ^{13}C-NMR, ^{1}H-NMR, IR and Mass spectrum analyses.

Keywords: One pot, microwave irradiation, three component reactions, amino alcohols, β-diketone, and acridinediones.

1. Introduction

Microwave irradiation can be used as a facile and general method for the construction of a wide variety of acridine derivatives. The reaction involves a three component condensation (with potential for combinatorial work) being carried out with almost excellent yields by microwave irradiation and considerably shortened reaction time. A major concern to overcome such problems in organic synthesis has considered the use of microwave (MW) irradiation as a source of energy.

One-pot multicomponent coupling reactions (MCRs), where several organic moieties are coupled in one step, for carbon-carbon and carbon–heteroatom bond formation is an attractive synthetic strategy for the synthesis of small–molecule libraries with several degrees of structural diversities [1-10] ,

Creation of new products in a single step via one-pot multicomponent coupling reactions (MCRs) technique has considered as a highly economic method among the multi-component reactions especially if we use microwave method [11-15]. They provide an efficient and useful synthetic method of diverse and complex compounds, as well as small and drug-like heterocycles [16-19]. In a higher product yield than classical chemistry [20-25]. The importance of these processes is underscored by the large number of publications [26].

Acridine derivatives have a wide spectrum of biological activities as antibacterial, antimalarial, anticancer and mutagenic properties,acridine systems have attracted considerable attention due to their potential pharmacological activity, there are many industrial applications for acridine and his derivative Which are class of compounds well known for a long time since the 19th century where they were first used as pigments and dyes [27-29]. Acridinium cations substituted at the endocyclic N atom find numerous applications in immunological assays as well as in chemical, biochemical and environmental analyses [30].in the last years acridine systems have attracted considerable attention due to their potential pharmacological

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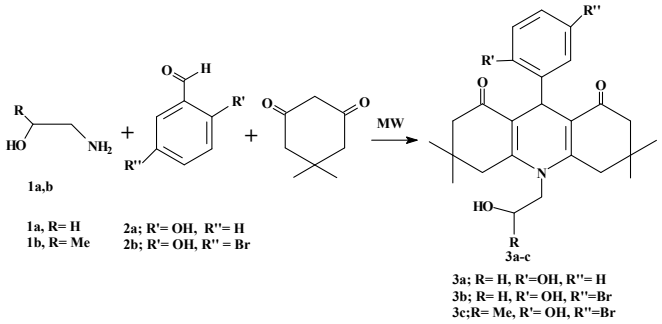
activity, acridine and its hydro derivatives have high and more biological activities like anti-malerial [31,32], antitumor [33], antileishmanial activities [34], DNA-binding and DNA photo-damaging ability [35], antimicrobial activity [36,37], potassium channel blockers [38]. in this case and These findings give us activations us to prepare some new acridine derivatives. There's no any one try to use amino alcohols for synthesis tetrahydroacridin-1,8-diones through microwave irradiation, the most reported using aromatic amines as main substrate to get the acridino nitrogen atom.

Chemical and pharmaceutical industries are facing constraints regarding the environmental aspects and saving energy. A major concern to overcome such problems in organic synthesis has considered the use of microwave (MW) irradiation as a source of energy. In this study we use an excellent synthetic method for new decahydro acridine-1,8-dione derivatives 3a-c through three component condensation reactions by microwave technique . The employed amino alcohols 1a, b exhibits an excellent substrate for synthesis of acredindiones under our reaction conditions.



scheme 1

Crystals of 3a-c were grown in diluted ethanolic solutions, and their respective structures were determined by X-ray crystallography (Figures 1, 2 and 3). The structures confirmed the stereochemical assignment of the acridinedione derivatives 3a-c and identified as 10-(2-hydroxyethyl)-9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-,2,3,4,5,6,7,8,9,10- decahydroacridine-1,8-dione (3a), 9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxyethyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (3b) and 9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (3c) respectively.

2. Discussions

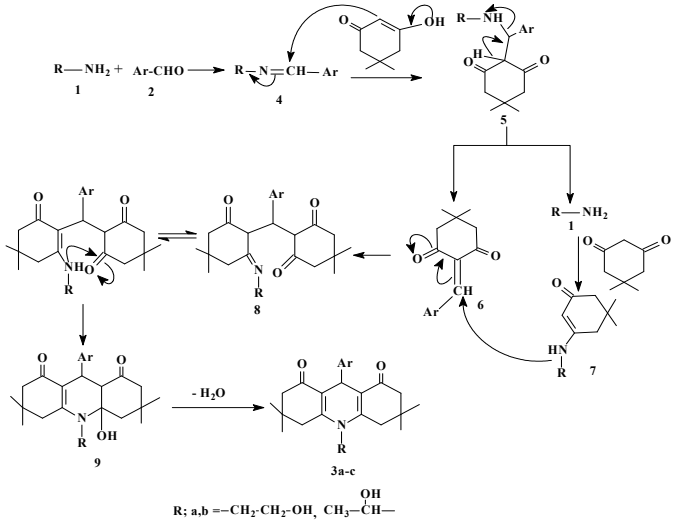
On microwave irradiation of an ethanolic solution of a mixture of dimedone, appropriate aromatic aldehydes and amino alcohols (Scheme 1) in a stiochiometrical ratio 2:1:1 for 10 minute followed by evaporation of the solvent under vacuum afforded the formation of the solid fused three membered ring of acridinedione derivatives 3a-c in an excellent yield (80% -92%) see scheme 1.

The X-ray crystal structure analysis of 3a-c was carried out (see figures 1,2 and 3 in experimental section). It clearly demonstrates the three fused hydro acredindione structures along with the aromatic and alcoholic chain substituent. The x-ray studies of the single crystals of 3a-c showed that the three fused rings of acridenedione moiety are not planar and are stabilized by intra- and intermolecular O-H…O, C-H…O and C-H…Br hydrogen bonds40,42. Some of crystal data and some of selected bond length have been recorded (see experimental section).

The IR spectra showed characteristic absorptions between 33401-3410cm-1 and at 3339-3369cm-1 for the phenolic and alcoholic hydroxyl group respectively. Absorptions between 2957– 3010cm-1 were assigned for the aromatic substituent while absorptions between 2886- 2666cm-1 were attributed to asymmetric and symmetric aliphatic stretch. The cyclic carbonyl group was remarked at a strong stretch absorption between 1704 and 1716cm-1. The mass specta of 3a-c, exhibited the correct molecular ion peaks at 488 (100%) and 490 (100%) for the bromo isomers of 3b and 502 (100%) and 505 (100%) for isomers of 3c. 1H-NMR spectra of 3a-c remarked a chemical shift betweens δ = 10 and 9.8ppm for phenolic OH group while alcoholic OH group was observed at chemical shift between 5.4 and 5.1ppm. Aromatic signals were observed at 6.8- 7.6ppm. Signal at δ= 3.8- 4.5 were assigned for proton at C2 and C7 respectively while peaks at 2.8 -3.5 for protons at C4 and C5 were observed. Ethyl protons were assigned at chemical shifts

between 2.6 and 3.0ppm for 3a & 3b and between 2.6 and 2.5-2.9ppm for 3c. A multiple peaks were observed at 1 -1.5ppm in 3a-c attributed to the methyl groups of dimedone and that one of isopropanol. 13C-NMR of 3a-c showed a characteristic peak at δc 198ppm for carbonyl group and 155-157ppm for aromatic substituent. The chemical shift of C=C in pyridyl ring was appeared clearly as two peaks at 129 and 130ppm. C alcoholic was appeared between 68 and 62 ppm. Two peaks at 49 and 51ppm were attributed to two carbon atoms at C2 andC7 while a single peak at 40ppm was assigned for two carbon atoms of C3 and C6. Multiple peaks of the four methyl carbons of dimedone were observed at 20 ppm for 3a-c while one single peak was appeared at 10ppm and attributed for the methyl carbon atom of isopropanol chain in 3c.

Formation of the hydro acridinediones 3a-c may be rationalized by an initial formation of the imine 4 from the condensation of the aromatic aldehydes 2 with the appropriate amino alcohol 1 (see Scheme 2). On attacking of the enol form of dimedone to the imine 4 could afford the formation of adduct 5 which in turn underwent an internal arrangement to release the aminoalcohols 1 and arylidenes 6. The released aminoalcohols 1 could react with another molecule of dimedone to give the amino enone 7 which in turn could attack through its nucleophilic amino group into the electrophilic carbon atom of the former arylidene 6 to obtain the new imine 8. The unstable imine 8 could rearrange into the relatively stable structure of the hydroxy hydroacredindiones 9 which ultimately could stabilized easily into the title structure of hydro acridindiones 3a-c by elimination of a molecule of water (Scheme 2).



3. Experimental

Mp's were determined using open glass capillaries on a Gallenkamp digital melting point apparatus and are uncorrected. The IR spectra were recorded with Varian 3600 FT-IR instrument using potassium bromide pellets. The 1H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were measured in DMSO-d6 using a Firm Bruker AV300 system with TMS as an internal standard. Chemical shifts are expressed as d [ppm], s for singlet, m for multiplet and b for broad. Mass spectra have been obtained with Varian MAT CH-7 instrument in EPSRC National Centre Swansea, United kingdum, using electron impact ionization (70 eV). X-ray analyses have been determined by X-ray Bruker Smart Apex II in X ray analyses unit, Baku University, Baku State, Azerbaijan. For microwave irradiation a Kenstar (OM-20ESP, 2450 MHz) domestic microwave oven was used. All of the compounds in this study exhibited satisfactory, mass, ^{1}H-NMR and ^{13}C-NMR spectra.

3.1. Materials

Starting materials: Benzaldehyde, 2-hydroxybenzaldehyde, 4-bromo-2-hydroxybenzaldehyde, 5,5-dimethylcyclohexane-1,3-dione (dimedone) and 2-amino ethanol were used as received from chemical suppliers (Aldrich). 1-Amino propan-2-ol was prepared according to literature [40]. All employed solvents have been distilled and dried.

General procedure for preparation of 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione 3a-c:

In a small beaker, a solution of 0.01 mole of aromatic aldehyde **2** was added to a solution of 0.01 moles of amino alcohols **1** in ethanol and irradiated for 1 minute. Then, a solution of 0.02 mole of dimedone (5,5-dimethyl-1,3-cyclohexanedione) was added. The reaction mixture was continued to be irradiated under microwave oven (300W) for 10 minute, the products allowed to cool down to room temperature. A yellow precipitate of the N-alcohol derivatives of 3,3,6,6-tetramethyl-9-aryl-1,2,3,4,5,6,7,8,9,10- decahydroacridine-1,8-diones **3a-c** was obtained in an excellent yield (~90%). All products were crystallized from ethanol and showed one spot on TLC by using a mixture of isopropanol : heptane (3:1) as an eluent (Rf =0.95). See table 1.

Table 1: Yield and melting points of products of acridinediones obtained under microwave irradiation:

Compound	Mp (^{0}C).	solvent	Yield %
(3a)	189	ethanol	80
(3b)	199	ethanol	87
(3c)	235	ethanol	91.3

10-(2-hydroxyethyl)-9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione: 3a

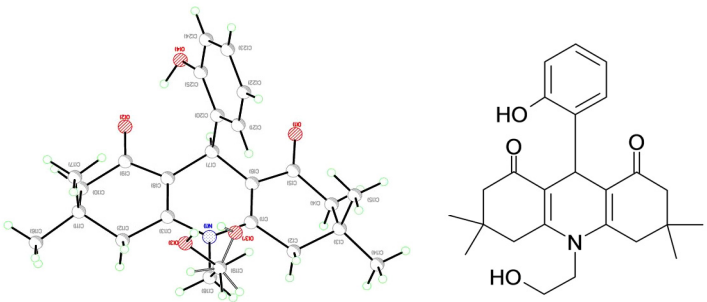


Fig.1: X-ray image of compound **3a**

For crystal data and structure refinement of **3a**, please refer to our previous work [41].

Yield (80.7%), mp 189ºC ; IR: cm^{-1} 3441(OH, Phenolic and alcoholic), 3031(Ar), 2857, 2886 (CH aliphatic), 1716 (C=O), 1622 (C=C); ^{1}H-NMR: δ 10.0 (s,1H, OH phenolic), 7.2-7.6 (t, 4H, Ar), 5.7(d, 1H,C9), 5.2 (s. OH alcoholic), 4.5(m, 2H, at C-2), 4.3(m, 2H at C7), 3.4 (m, 2H at C4), 3.0 (m, 2H at C-5), 2.5(m, 4H of ethyl group), 1.3-1.6(m, 12H, of 4 methyl groups); ^{13}C-NMR: δ_c 198 (C=O at C-1, C-8), 155 (C=C Ar), 128,129 (C=C, in acredine fused rings), 115, 62(C-O alcoholic), 50, 48 (2$CH_{2\,a}$ at C2 and C7), 40 (quaternary carbon at C3 and C6), 35 (CH_2-$CH_2$of ethanol) and 18-20 (C of 4 Me groups).

9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxyethyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione: 3b

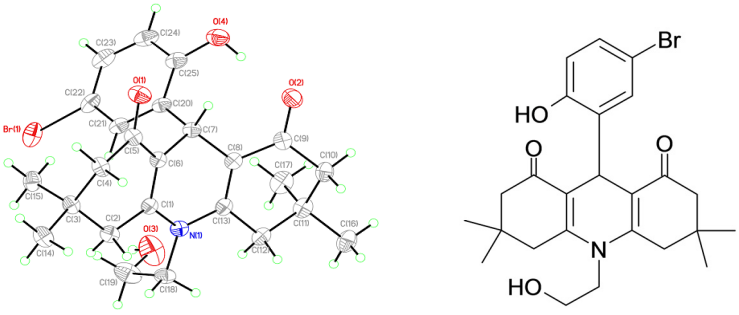


Fig. 2: X-ray image of compound **3b**

3.2. Crystal data and structure refinement of 3b

Empirical formula $C_{25}H_{30}Br\ N\ O_4$; Formula weight 488.41; Independent reflections 5137 [R(int) = 0.0714]; Temperature 296(2) K; Completeness to theta = 27.00° and 99.7 % ; Wavelength 0.71073 Å; Max. and min. transmission 0.8427 and 0.6185; Space group P2(1)/n; Density (calculated) 1.374 Mg/m^3; Absorption coefficient 1.772 mm-1; Crystal size 0.30 x 0.20 x 0.10 mm^3.

3.3. Selected bond length [Å] and angels [°] in 3b

O(1)-C(5) 1.220(3), O(2)-C(9) 1.244(4), C(5)-C(6) 1.453(4), C(8)-C(9) 1.423(5), C(1)-C(6) 1.355(4) 1.355(4), C(8)-C(13) 1.345(4), N(1)-C(1) 1.398(3), N(1)-C(13) 1.393(4), O(4)-H(4C) 0.8200, 1.895(4); O(1)-C(5)-C(6) 120.6(3), O(2)-C(9)-C(8) 122.1(3), C(1)-C(6)-C(5) 120.7(3), C(13)-C(8)-C(9) 120.8(3), C(6)-C(1)-N(1) 119.2(3), C(8)-C(13)-N(1) 120.2(3), C(13)-N(1)-C(1) 119.8(2), C(9)-C(8)-C(7) 118.7(2), C(5)-C(6)-C(7) 117.7(2), C(6)-C(7)-C(8) 108.4(2).

For crystal data and structure refinement of **3a**, please refer to our previous work [39].

Yield (61.8%), mp 199ºC; Recrystalised from ethanol; IR: cm^{-1} 3410, 3339 (OH Phenolic and OH alcoholic respectively), 2957 (Ar), 2886 (Aliph), 1704 (C=O), 1595 (C=C), 625 (C-Br); ^{1}HNMR: δ 9.8 (s,1H, OH phenolic), 7.2(s, 1H, Ar), 7.1(d, 2H, Ar), 6.6(d, 1H,C9), 5.1(s. OH alcoholic), 4.15(t, 2H, at C-2), 3.85(t, 2H at C7), 3.0 (d, 2H at C4), 2.7(d, 2H at C-5), 2.3(m, 4H of ethyl group), 1-1.1(m, 12H, of 4 methyl groups); ^{13}C NMR: d 197,198 (C=O, C-1, C-8), 155, 135 and 131 (C=C Ar), 111, 112 (C=C, in acridine fused rings), 120 (C-N), 64(C-Br), 50 (C-OH), 20, 28, 30 and 32 (C-C of CH,3CH_2 and 5CH_3); M^+ isotopes 488 (100), 489 (30), 490(100), 491(30).

9-(5-bromo-2-hydroxyphenyl)-10-(2-hydroxypropyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione: 3c

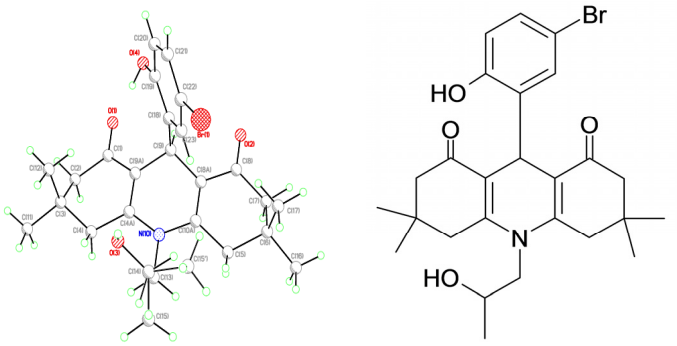


Fig. 3: X-ray image of compound **3c**

3.4. Crystal data and structure refinement of 3c

Empirical formula $C_{26}H_{32}Br\ N\ O_4$, formula weight 502.44, Independent reflections 6209 [R(int) = 0.0663], Temperature 296(2) K, Completeness to theta = 28.50° and 98.3 % , Wavelength 0.71073 Å, Max. And min. transmission 0.729 and 0.632, Space group P 21/n, Density (calculated) 1.342 Mg/m^3, Absorption coefficient 1.684 mm-1, Crystal size 0.30 x 0.20 x 0.20 mm^3.

3.5. Selected bond length [Å] and angels [°] in 3c

O(1)-C(1) 1.237(5), O(2)-C(8) 1.223(4), C(1)-C(9A) 1.443(5), C(8)-C(8A) 1.467(4), C(4A)-C(9A) 1.361(5), C(8A)-C(10A) 1.345(4), C(4A)-N(10) 1.386(4), N(10)-C(10A) 1.398(4), O(4)-C(19) 1.351(5), Br(1)-C(22) 1.890(4); O(1)-C(1)-C(9A) 121.5(3), O(2)-C(8)-C(8A) 120.8(3), C(4A)-C(9A)-C(1) 120.4(3), C(10A)-C(8A)-C(8) 121.0(3), C(9A)-C(4A)-N(10) 119.9(3), C(8A)-C(10A)-N(10) 119.6(3), C(4A)-N(10)-C(10A) 119.9(3), C(8)-C(8A)-C(9) 117.2(3), C(1)-C(9A)-C(9) 119.3(3), C(8A)-C(9)-C(9A) 108.0(3).

Yield (62.1%), mp 235ºC; Recrystalised from ethanol; IR: cm^{-1} 3401, 3369 (OH, phenolic and alcoholic), 2957 (Ar), 2871, 2666 (Aliph), 1 626 (C=O), 1594 (C=C), 667 (C-Br) ; ^{1}HNMR: δ 9.9 (s,1H, OH phenolic), 7.3(s, 1H, Ar), 7.2(d, 2H, Ar), 5.1(s, 1H, alcoholic), 4.8(s, 1H, at C-9), 3.9(s, 4H, 2CH_2 of C-2, C-7), 3.2 (s, 4H, 2CH_2 at C-4, C-5) 2.8-2.9(d, 2H, CH_2 of propyl group), 2.5-2.7(m, 1H, CH of propyl group), 0.9-1.2(m,

15H, $5CH_3$); ^{13}C NMR: 198 (C=O), 153 and 130 (C=C 62(C-Br), 49 (C-OH), 40,22 and 18 (C-C of $CH,3CH_2$ and $5CH_3$); MS m/z (%): M^+ isotopes 502(100), 503(30), 504(100), 505(30).

4. Conclusion

In summary, we use new methodology for synthesis of the new acridine derivatives **3a-c** from simple common chemicals by using the economical technique of three-component condensation reactions to give the product in good to excellent isolated yields, and decreasing the time of formation from 5 hour to 10 minute.

Supporting Information: X-ray data of compounds **3b,c** are available if required.

5. Acknowledgment

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