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AN EFFICIENT SYNTHESIS OF N-SUBSTITUTED ACRIDIONE DERIVATIVES AND EXPLORED BIOEVLUATION

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ABSTRACT

The present versatile and an efficient synthesis of N-alkyl derivatives of acridine 10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione is by obtained from 9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione with substituted (bromomethyl)benzene which is also three component cyclocondensation of 1,2-dicarbonyl compounds like dimedone, bromo benzaldehyde and ammonium chloride in the presence CAN and ethanol as solvent condition. All the compounds were evaluated by advanced spectroscopic data (1H NMR, 13C NMR& LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. In the present study, ten hybridized imidazoles derivatives were synthesized via cyclo condensation and evaluated for their invitro antimicrobial activity.

KEYWORDS: Dimedone, Chlorobenzalehyde, CAN, 10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-‘hexahydroacridine-1,8(2H,5H)-dione,9-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione, Anti-bacterial activities.

1. INTRODUCTION

Multicomponent reactions were encouraged an outstanding status in synthetic organic and medicinal chemistry for their high degree of atom economy and application in the diversity oriented convergent synthesis of complex organic moiety from simple and readily available substrates in a single vessel. Acridine and its derivatives are important structural motifs

possessing antimalarial, antiviral, and antiallergic properties[1–3]; acridines act as potent drugs for antitumor activity both in vitro and in vivo against a range of murine and human tumors.[4] They are also found to act as fluorescent molecular probes for monitoring polymerization processes[5] and are used as -type semiconductors and in the electroluminescent devices. Recently fluorinated acridones are reported to possess anticancer activity.[6–9] There are a few reports in the literature on the three-component Hantzsch-type condensation of aromatic aldehydes, anilines, and dimedone via traditional heating in organic solvents[10, 11], under microwave irradiation[12], and in ionic liquids.[13] The main drawbacks of these methods are the inability to synthesize profuse quantity of acridines using substituted anilines containing electron withdrawing groups.[14] Further, the reactions are carried out in refluxing organic solvents, which require higher temperature and longer hours for completion[10, 15] and unusual breaking of C–N bond takes place under certain reaction conditions as noticed in a few cases.[16] Hence, the exploration of a simple, efficient, and green method for the synthesis of acridines using electron-deficient amines and electron-deficient aldehydes is of current interest. In continuation with our work on one-pot multicomponent reactions under sonic condition.[17–19], we, herein, report the synthesis of a series of acridines by a one-pot four-component reaction as shown in Schemes 1.

2. METHODS AND MATERIALS

2.1. Experimantal

All starting materials such as reagents, solvents and chemicals were commercial products were procured from Sigma Aldrich and were used without further purification except liquid aldehydes and benzyl bromide which were distilled before use. The melting points our desired compounds were measured on Agarwal thermometer make melting point apparatus. ^{1}HNMR and ^{13}CNMR spectra were obtained on 400 MHz and 100 MHz Bruker Avance instruments in $CDCl_3$ using TMS as a standard. The mass spectra prepared compounds were recorded using ESI-Q TOF instrument.

2.2.1.GeneralProcedure9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

A mixture of 4-chlorobenzaldehydes (1mole), dimedone (2mole) and Ammonium acetate (1.5mole) and freshly prepared catalytic amount of zinc acetate in ethanol was taken in 50mL RB flask. When the solution stands once, it becomes clear, was added and the reaction mixture was refluxed for 4 hours. The reaction was identified by TLC (465, ethyl acetate: n-

hexane) after the completion of reaction. The reaction crude was poured into 100gm crushed ice and the solution was neutralized with aqueous solution of $NaHCO_3$ and product was extracted using ethyl acetate, the combined organic layer was washed distilled water and organic layer separated. The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

Characterizationof9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

Palebrownsolid,Yields-90%.M.p-257-259^{0}C;^{1}HNMR(400Mz,$CDCl_3$)ppm:9.874(s,1H,NH), 7.641-7.297(m,4H,Ar-H),4.473(s,1H,-CH),2.088(s,2H,-CH_2),1.624(s,2H,-CH_2),1.145(s,3H, CH_3),0.974(s,3H,-CH_3);^{13}CNMR(100MHz,$CDCl_3$)ppm:196.95,148.25,142.84,132.09,128.77, 126.47,118.24,118.74,113.07,56.47,51.58,40.56,31.95.29.47,26.06.LCMS(m/z): 385.45 (M+2). Molecularformule: $C_{23}H_{31}NClO_2$; ElementalAnalaysis: CalculatedC-64.49, H-6.12, N-3.27. Obtained: C-64.41, H-6.11, N-3.36.

2.2.2.Geneneralprocedurerof10-benzyl-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6, 7,9,10-hexahydroacridine-1,8(2H,5H)-dione derivatives:

A mixture 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dioneand substituted 4-(Chloromethyl) benzene is dissolved in methylene dichloride in 50mL RB flask and slowly triethylamine added into above mixture . When the solution becomes clear, the reaction mixture was continued under refluxed condition for 5 hours. The reaction was identified with help of TLC (4:6, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into 100gm crushed ice and the solution was neutralized with aqueous solution of $NaHCO_3$ and the product was extracted with ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous Na_2SO_4 and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

1.10-benzyl-9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

Palebrownsolid;Yield-88%,M.p 265-267^{0}C.^{1}HNMR(400Mz,$CDCl_3$)ppm: 7.810-7.613 (m,2H,Ar-H),7.595-7.278(m,7H,Ar-H),4.488(s,1H,-CH-),2.245(s,2H,-CH_2-),2.077(s,,2H,-CH_2-),1.544 (s,2H,-CH_2-),0.987(s,3H,-CH_3),0.925(s,3H-CH_3).^{13}CNMR(100MHz,$CDCl_3$)

ppm:194.76, 159.17, 142.38, 133.29, 130.87, 128.74, 127.44, 126.02, 123.74, 120.45, 112.22, 50.75, 42.65, 31.23, 30.27, 28.76, 26.85 .LCMS(m/z): 476.39(M+2). Molecular formulae: $C_{30}H_{32}ClNO_2$,. Elemental Analysis: Calculated C-69.50.,H-6.22,N-2.70. Obtained: C-69.41, H-6.20, N-2.79.

2.9-(4-Chlorophenyl)-10-(4-hydroxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

Pale Yellow solid yield-91%, m.p:271-273^{0}C.^{1}HNMR(400Mz,$CDCl_3$)ppm: 9.642(s,1H,-OH), 7.887-7.715(m,2H,Ar-H), 7.588-7.292(m,4H,Ar-H), 7.245-6.914(m,4H,Ar-H), 4.495(s,1H,-CH-) 2.174(s,2H,-CH_2-),1.674(s,2H,-CH_2-),0.986(s,3H,-CH_3-),0.895(s,3H,-CH_2-).^{13}CNMR(100 MHz, $CDCl_3$)ppm:196.78, 159.79, 151.57, 142.05, 132.38, 129.44, 128.47, 128.04, 122.65, 120.48, 52.66, 41.75, 30.89, 28.09, 26.75.LCMS(m/z): 490.49(M+2). Molecular formulae: $C_{30}H_{32}NO_3Cl$. Elemental Analysis: Calculated C-67.42.,H-6.03,N-2.62. Obtained: C-67.34, H-6.01, N-2.71.

3.9-(4-Chlorophenyl)-10-(4-methoxybenzyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro acridine-1,8(2H,5H)-dione

Whitecompound;Yield-90%,.M.p-264-266^{0}C^{1}HNMR(400Mz,$CDCl_3$)ppm:7.924-7.751(m,2H,Ar-H),7.457-7.280(m,2H,Ar-H),7.245-6.849(m,4H,Ar-H),4.471(s,1H,-CH-),4.296(s,2H,-CH_2-), 3.694(s,3H,-OCH_3),1.860(s,2H,-CH_2-),1.094(s,3H,-CH_3),0.945(s,3H,-CH_3-).^{13}CNMR(100MHz, $CDCl_3$) ppm:196.58, 159.78, 152.06, 143.87, 132.14, 129.77, 129.24, 128.72, 127.60, 122.53, 110.05, 50.48, 41.72, 32.65, 30.90, 28.54, 27.62. LCMS (m/z):504.45(M+2). Molecular formulae: $C_{31}H_{34}ClNO_3$ .Elemental Analysis: Calculated C-67.88.,H-6.25,N-2.58. Obtained: C-67.83, H-6.24, N-2.65.

4.9-(4-Chlorohenyl)-3,3,6,6-tetramethyl-10-(4-methylbenzyl)-3,4,6,7,9,10-hexahydroacri dine-1,8(2H,5H)-dione

Palewhitesolid;Yield-90%,M.p-264-266^{0}C.1HNMR(400Mz,$CDCl_3$)ppm:7.823-7.712(m,2H,Ar-H),7.441-7.327(m,2H,Ar-H),7.220-6.914(m,4H,Ar-H),4.559(m,2H,-CH-),4.045(s,2H,-CH_2), 1.884(s,2H,-OCH_2),1.652(s,2H,-CH_2),0.984(s,3H,-CH3-),0.905(s,3H,-CH_3).^{13}CNMR (100MHz, $CDCl_3$)ppm: 195.87, 160.08, 142.75, 133.14, 131.55, 129.47, 128.91, 128.42, 110.35, 50.19, 41.37, 39.26, 31.56, 28.67, 27.08. LCMS (m/z): 459.27(M+2). Molecular formulae: $C_{31}H_{34}NClO_2$. Elemental Analysis: Calculated C-69.92.,H-6.44,N-2.63. Obtained: C-69.86, H-6.42, N-2.71.

5.9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-10-(4-nitrobenzyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione

Darkred solid; Yield-87%,M.p-268-270^{0}C.^{1}HNMR(400Mz,$CDCl_3$)δppm: 8.168-8.024(m,2H,Ar-H), 7.892.-7.702(m,4H,Ar-H), 7.426-7.298 (m,2H,Ar-H), 4.574(s,2H,-CH_2-), 4.175(s,2H,-CH_2-), 1.967(s,2H,-CH_2-),1.680(s,2H,-CH_2-),0.982(s,3H,-CH_3-),0.915(s,3H,-CH_3-).^{13}CNMR (100MHz, $CDCl_3$)ppm: 197.88, 161.74, 142.76, 140.12, 137.68, 129.56, 128.75, 128.07, 127.72, 128.05, 122.78, 113.96, 53.65, 43.30, 40.16, 31.37, 28.09, 27.14 .LCMS(m/z): 520.25(M+2). Molecular formulae: $C_{30}H_{31}N_3O_4$ Cl .Elemental Analysis: Calculated C-63.95.,H-5.35,N-4.97. Obtained: C-63.88, H-5.34, N-5.05.

3. BIOLOGICAL ACTIVITY

3.1. Anti- Bacterial Activity

In vitro anti-bacterial activities of newly tested compounds are screened against four pathogenic bacteria strains. The results of the bacterial activity were examined for the compounds. The gram negative bacteria were examined Escherichia Coli Pseudomonas aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compound's a solvent the streptomycin 10 µglml discs were used as a standard. The rest of the compounds were found to be moderate active against the tested micro- organism.

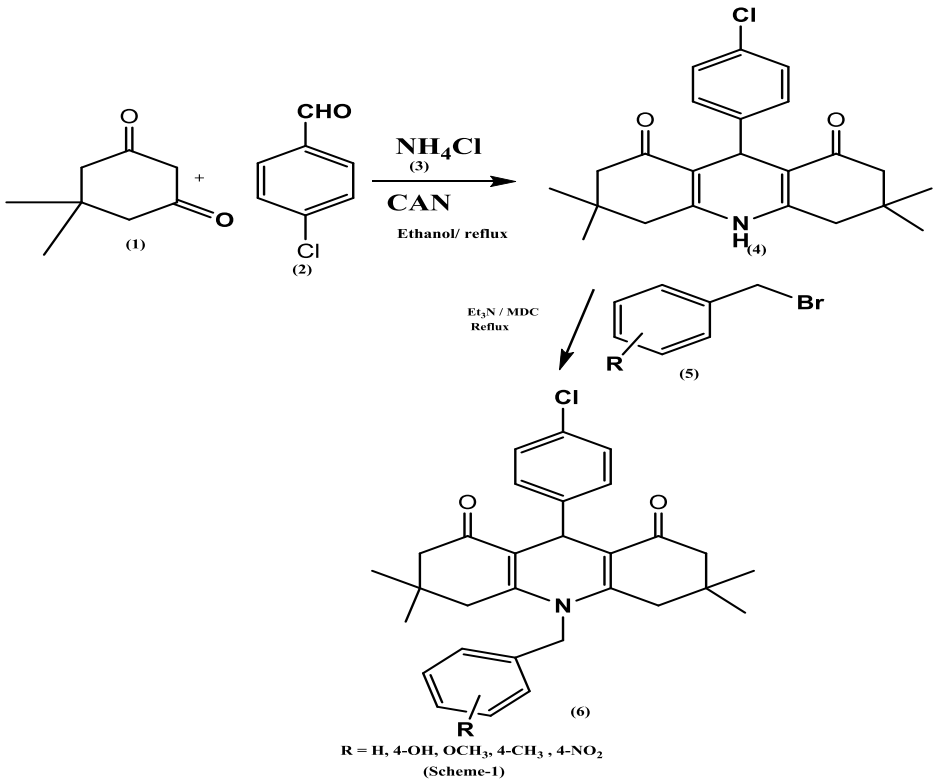
4. RESULT AND DISCUSSION

4.1. CHEMISTRY

To a mixture of 3-nitro benzaldehyde (2mmol), dimedone (4mmol) and ammonium chloride (3mmol) and CAN (4mmol) was added in 50ml round bottom flask and was stirred at 70^{o}C. This reaction is considered as model reaction. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was cooled to room temperature and water (5 ml) was added, solid separated was filtered and product was obtained. It was characterized by IR, ^{1}H NMR, ^{13}C-NMR and mass.

All newly synthesized compounds can be synthesized under at 70^{0}C condition. These desired derivatives were obtained. The scope and advantages of these catalysts can be used to accelerate the rate of reaction and reaction is completed maximum two hours. The rate of reaction enhanced by using these catalysts is CAN. We were used different substituted benzyl bromide either electron releasing group of benzyl bromide as well as electron attracting group of benzyl bromide. The main and exact aim of this method is cost

effectiveness of catalyst, easy work-up and purification of products by non-chromatographic methods, good to excellent yields and very short time reactions.



(Scheme-1)

4.2. BIOLOGICAL ACTIVITY

All the titled compounds were examined by anti- bacterial activity. The electron withdrawing group of compounds and electron releasing group compounds exhibited various potent activities. Therefore, electron withdrawing group of compounds exhibited low biological potent activity compared with electron releasing groups. The compound which possess electron donating group showed well to excellent activity as shown in **Table-I.**

Table-I: Antibacterial activity screening activity synthesized scaffold.

Entry	Anti-Bacterial Activity			
	S.aureus	E.coli	S. typhi	B.substill
4a	04	08	09	10
4b	14	13	15	18
4c	20	20	16	18
4d	19	20	21	19
4e	20	21	20	21
4f	11	09	07	09
Streptomycin	25	25	22	22
Ketoconazole	NA	NA	NA	NA
DMSO	---	----	---	---

5. CONCLUSION

The reaction condition carried at 70^0C condition for all the required titled analogous. The yields of the titled compounds were obtained from 85-91%. This compound possesses electron releasing group acquired highest yield than that of the compound possesses electron attracting group. The rates of the reaction of the titled derivatives are enhanced by using catalyst CAN. All the derivatives are examined by anti- microbial activity against gram (+Ve), gram(-Ve) and fungal. Otherwise the compounds having electron releasing group which showed excellent potent active than that of the electron attracting group**.**

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