Research Article

MILD AND EFFICIENT ONE-POT SYNTHESIS OF SOME NOVEL ACRIDINE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AGENTS

Shankaraiah G. Konda[a*], Bhaskar S. Dawane[b]
[a] Department of Chemistry, K. J. Somaiya College of Arts, Commerce and Science, Kopargaon-423601 (M.S) India.
[b] School of chemical sciences, Swami Ramanand Teerth Marathwada University Nanded-431606 (M.S) India.
***Corresponding author's E-mail:** kondasg@rediffmail.com

Accepted on: 21-07-2011; **Finalized on:** 30-06-2012.

ABSTRACT

A simple and efficient method is described for the synthesis of some novel acridine derivatives 3 by the one-pot condensation of sartalone 1, substituted aldehyde 2, and liquor ammonia in alkaline poly ethylene glycol (PEG-400) as green reaction solvent at mild temperature. The structures of the products were confirmed on the basis spectral and analytical data. These newly synthesized compounds were evaluated for *in vitro* antibacterial activity. Most of the compounds showed potent activity.

Keywords: Polyethylene glycol (PEG-400), sartolone, substituted aldehydes, acridine derivatives, antibacterial agents.

INTRODUCTION

Acridines are interesting heteroaromatic structures that are much in demand due to their broad biological properties such as antibacterial,[1] anticancer,[2] anti-tumor,[3] analgesic and anti-inflammatory activities.[4] Acridine derivatives have been also used as pigments and dyes. The synthesis, electrochemistry and physical properties of acridine-1,8-dione dyes are particularly well explored.[5,6] The synthesis of acridine-1,8-diones from dimedone and substituted aldehydes by conventional heating in organic solvents have been reported.[7] Reducing or eliminating the use of volatile organic solvents can minimize the generation of waste, which is a requirement of one of the principles of green chemistry.[8-9] Recently, PEG is found to be an interesting solvent system. PEG as environmentally benign protocol prompted to have many applications, in substitution, oxidation and reduction reactions due to. their solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, ease of work-up, eco-friendly nature and economical cost.

MATERIALS AND METHODS

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis of chalcone derivatives 3(a-h)

A mixture of sartalone **1** (2 mmol) and aromatic aldehyde **2** (1 mmol) were dissolved in alkaline polyethylene glycol (PEG-400) (20 mL) solution. Just warm the reaction mixture for 5 minutes. Then 5 mL of liquor ammonia was added. Then the reaction mixture was heated for the period as shown in table 1. After completion of the reaction (monitored by TLC), the contents were poured into ice cold water. The solid obtained was filtered, washed with cold water. To furnish the pure product **3** was crystallized from ethanol.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-hydroxy phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3a):

Color, White; IR (KBr): 3326, 3058; ^{1}H NMR (DMSO-d_6): δ 2.28-2.39 (m, 4H, 2CH$_2$), δ 3.41-3.46 (m, 2H), δ 5.62 (s, 1H, C$_7$-H), δ 7.12-8.26 (m, 18H, Ar-H), δ 8.43 (s, 1H, -NH) ppm; EIMS (*m/z*): 667 (M$^+$); Anal. Calcd for $C_{39}H_{27}NOCl_4$: C, 70.18; H, 4.08; N, 2.11%. Found: C, 70.11; H, 4.05; N, 2.15%.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-chloro phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3b):

Color, White crystals; IR (KBr): 3348, 3052; ^{1}H NMR (DMSO-d_6): δ 2.35-2.41 (m, 4H, 2CH$_2$), δ 3.38-3.45 (m, 2H), δ 5.68 (s, 1H, C$_7$-H), δ 7.18-8.31 (m, 18H, Ar-H), δ 8.45 (s, 1H, -NH) ppm; EIMS (*m/z*): 685 (M$^+$); Anal. Calcd for $C_{39}H_{26}NCl_5$: C, 68.29; H, 3.82; N, 2.04%. Found: C, 68.34; H, 3.76; N, 2.08%.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-methoxy phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3c):

Color, White crystals; IR (KBr): 3296, 3046; ^{1}H NMR (DMSO-d_6): δ 2.26-2.35 (m, 4H, 2CH$_2$), δ 3.22-3.28 (m, 2H), δ 3.42 (s, 3H, OCH$_3$), δ 5.56 (s, 1H, C$_7$-H), δ 7.21-8.25 (m, 18H, Ar-H), δ 8.41 (s, 1H, -NH) ppm; EIMS (*m/z*): 681 (M$^+$); Anal. Calcd for $C_{40}H_{29}NOCl_4$: C, 70.51; H, 4.29; N, 2.06%. Found: C, 70.58; H, 4.35; N, 2.11%.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-nitro phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3d):

Color, Yellowish white; IR (KBr): 3328, 3064; ^{1}H NMR (DMSO-d_6): δ 2.31-2.38 (m, 4H, 2CH$_2$), δ 3.35-3.41 (m,

2H), δ 5.78 (s, 1H, C_7-H), δ 7.18-8.28 (m, 18H, Ar-H), δ 8.51 (s, 1H, -NH) ppm; EIMS (*m/z*): 696 (M^+); Anal. Calcd for $C_{39}H_{26}N_2O_2Cl_4$: C, 67.26; H, 3.76; N, 4.02%. Found: C, 67.35; H, 3.71; N, 4.08%.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-fluoro phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3e):

Color, White; IR (KBr): 3356, 3041; ^{1}H NMR (DMSO-d_6): δ 2.35-2.41 (m, 4H, $2CH_2$), δ 3.41-3.46 (m, 2H), δ 5.72 (s, 1H, C_7-H), δ 7.11-8.22 (m, 18H, Ar-H), δ 8.48 (s, 1H, -NH) ppm; EIMS (*m/z*): 669 (M^+); Anal. Calcd for $C_{39}H_{26}NFCl_4$: C, 69.97; H, 3.91; N, 2.09%. Found: C, 69.91; H, 3.98; N, 2.14%.

5,9-Bis-(2,4-dichlorophenyl)-7-(4-N, N, dimethyl phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3f):

Color, White; IR (KBr): 3288, 3062; ^{1}H NMR (DMSO-d_6): δ 2.26-2.32 (m, 4H, $2CH_2$), δ 2.61 (s, 3H, $2CH_3$), δ 3.32-3.41 (m, 2H), δ 5.65 (s, 1H, C_7-H), δ 7.15-8.26 (m, 18H, Ar-H), δ 8.52 (s, 1H, -NH) ppm; EIMS (*m/z*): 694 (M^+); Anal. Calcd for $C_{39}H_{32}N2Cl_4$: C, 70.91; H, 4.64; N, 4.03%. Found: C, 70.95; H, 4.61; N, 4.09%.

5,9-Bis-(2,4-dichlorophenyl)-7-(2-hydroxy phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3g):

Color, White; IR (KBr): 3336, 3051; ^{1}H NMR (DMSO-d_6): δ 2.21-2.26 (m, 4H, $2CH_2$), δ 3.28-3.32 (m, 2H), δ 5.72 (s, 1H, C_7-H), δ 7.21-8.28 (m, 18H, Ar-H), δ 8.48 (s, 1H, -NH) ppm; EIMS (*m/z*): 667 (M^+); Anal. Calcd for $C_{39}H_{27}NOCl_4$: C, 70.18; H, 4.08; N, 2.11%. Found: C, 70.15; H, 4.12; N, 2.16%.

5,9-Bis-(2,4-dichlorophenyl)-7-(2-hydroxy phenyl)-5,6,7,8,9,14-hexahydro-dibenzo[c,h] acridine (3g):

Color, White crystals; IR (KBr): 3325, 3068; ^{1}H NMR (DMSO-d_6): δ 2.25-2.32 (m, 4H, $2CH_2$), δ 3.35-3.41 (m, 2H), δ 5.68 (s, 1H, C_7-H), δ 7.18-8.22 (m, 16H, Ar-H), δ 8.56 (s, 1H, -NH) ppm; EIMS (*m/z*): 825 (M^+); Anal. Calcd for $C_{39}H_{25}NOCl_4Br2$: C, 56.76; H, 3.05; N, 1.71%. Found: C, 56.71; H, 3.11; N, 1.75%.

Antimicrobial activity

The antimicrobial activities of the synthesized compounds **3(a-h)** were determined by agar diffusion method.[13] The compounds were evaluated for antibacterial activity against *Bacillus subtilis* (MTCC 1789), *Proteus vulgaris* (MTCC 1771), *Staphylococcus aureus* (MTCC 96) and *Escherichia coli* (MTCC 2939), were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic Tetracycline (25µg/mL) was used as reference antibacterial substance for comparison. Dimethyl sulphoxide (1%, DMSO) was used a control.

The culture strains of bacteria were maintained on nutrient agar slant at 37±0.5°C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10^5 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25µg/mL separately for each bacterial strain. All the plates were incubated at 37±0.5°C for 24 h. Zone of inhibition of compounds in mm were noted.

Table 1: Physico-chemical data of synthesized products 3(a-h)

Entry	Product	R	Time (min)	Yield (%)	M.P. (°C)
1	**3a**	4-OH-C_6H_4	20	80	125-128
2	**3b**	4-Cl-C_6H_4	15	85	136-138
3	**3c**	4-OMe-C_6H_4	20	78	112-114
4	**3d**	4-NO_2-C_6H_4	25	70	145-147
5	**3e**	4-F-C_6H_4	20	75	120-122
6	**3f**	4-$N(CH_3)_2$-C_6H_4	20	72	152-154
7	**3g**	2-OH-C_6H_4	20	80	130-132
8	**3h**	2-OH-3,5-dibromo-C_6H_2	15	82	162-164

Table 2: Antibacterial activity of synthesized compounds 3(a-h)

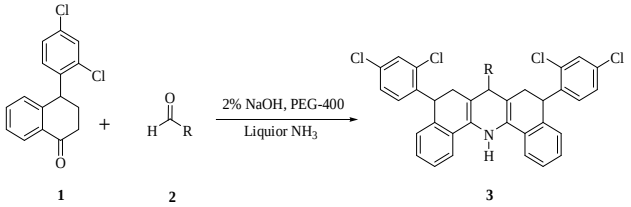
Product	BS	PV	SA	EC
3a	18	14	20	16
3b	18	15	20	18
3c	16	14	14	15
3d	14	12	15	14
3e	15	16	16	17
3f	14	12	12	15
3g	16	15	18	16
3h	15	15	16	16
Tetracycline	20	18	22	18

Zone of inhibitions are expressed in mm

BS=*Bacillus subtilis*, PV-*Proteus vulgaris*, Sa- *Staphylococcus aureus*, EC=*Escherichia coli*

RESULTS AND DISCUSSION

The one-pot condensation reactions have significant attention 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 molecules. Continuing our studies on the development of new, selective, and environmentally friendly methodologies using poly ethylene glycol (PEG-400) as a solvent for the preparation of biologically active compounds,[10-12] herein we report the synthesis of some novel acridine derivatives by the one-pot condensation of sartalone, substituted aldehydes, and liquor ammonia as the reagents in poly ethylene glycol (PEG-400) as reaction solvent at mild temperature (Scheme-1).

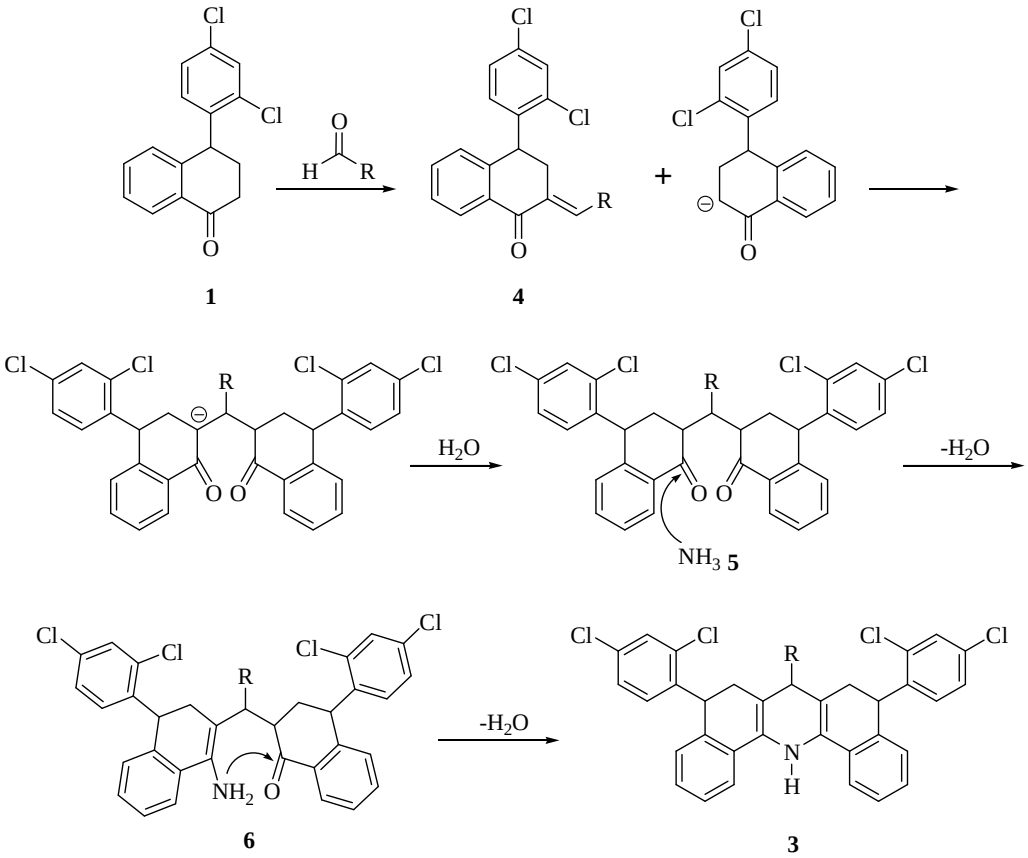


Scheme-1: Synthesis of acridine derivatives

The formation of the products **3** can be explained by the possible mechanism (Scheme-2). Initially, one molecule of the sartolone **1** was first condensed with aldehyde to formed **4**. Then the active methylene group of another molecule of sartalone was reacted with **4** by conjugate addition reaction to give the intermediate **5.** The intermediate **5** was attacked by ammonia on hydroxyl group to give another intermediate **6.** Finally, the intermediate **6** was cyclised by the nucleophilic attack of NH_2 on another hydroxyl gave the product **3.**

The structure of compounds **3(a-h)** were confirmed by spectral analysis. The IR spectra of the compounds showed absence of band near at 1680-1700 cm^{-1} due to carbonyl group and presence of broad band in the region 3280-3350 cm^{-1} revealed to the –NH group. ^1H NMR spectra of the compounds showed a singlet at δ 5.52-5.78 due to the C_7-H proton and a singlet at δ 8.41-8.58 assigned to the -NH proton. The other aromatic and aliphatic protons were observed at expected regions. Also, the mass spectra (EIMS) of compounds were also in agreement with their molecular formula.

The results of the antibacterial data are given in Table-2. The antimicrobial data revealed that most of the compounds showed interesting biological activity. In comparison with standard tetracycline, compounds **3a** and **3b** showed very good activity against *B. subtillis*. Compounds **3b**, **3g** and **3h** were displayed good activity against *P. vulgaris*, while compounds **3e** showed excellent activity. Compounds **3a**, **3b** and **3c** were displayed good activity against *S. aureus*. All the compounds were found to be effective against *E. coli*. Compounds **3a**, **3e**, **3g**, and **3h** were showed very good activity against *E. coli*. Only the compound **3b** showed similar level of activity against *E. coli*.



Sheme-2: Possible mechanism of formation of acridine derivatives

When structure activity relationship was investigated, compounds bearing *p*-chloro phenyl, *p*-hydroxy phenyl and *p*-methoxy phenyl and *p*-fluoro phenyl at C_7-position emerged as active for antibacterial screening. The substitution of *o*-hydroxy in combination with bromine as substituent on the phenyl ring may increase the antibacterial activity against various pathogens.

CONCLUSION

In summary, we have developed a simple and efficient one-pot condensation method for the synthesis of acridine derivatives using sartalone, substituted aldehydes and liquor ammonia. After evaluation of antibacterial activity, compounds **3a**, **3b**, **3e** and **3h** were displayed promising activity. Only the compound **3b** showed similar activity against *E. coli*. Thus, it was concluded that some of the compounds of the series proved to be promising antibacterial agents and hence deserve further pharmacological studies.

Acknowledgements: SGK is thankful to UGC-New Delhi for D. S. Kothari Post Doctoral Fellowship [F.4-2/2006(BSR)/13-301/2008(BSR)].

REFERENCES

1. H. P. Kavitha, Synthesis and antimicrobial activity of 1-(9'-acridinyl)-5-(4-substituted phenyl) tetrazoles, *Asian J. Chem*., 16, 2004, 1191.
2. F. Charmantray, M. Demeunynck, D. Carrez, A. Croisy, A. Lansiaux, C. Bailly, P. Colson, 4-Hydroxymethyl-3-aminoacridine derivatives as a new family of anticancer agents, *J. Med. Chem.*, 46, 2003, 967
3. R. A. Heald, M. F. G. Stevens, Antitumour polycyclic acridines. palladium(0) mediated syntheses of quino[4,3,2-*kl*]acridines bearing peripheral substituents as potential telomere maintenance inhibitors, *Org. Biomol. Chem*., 1, 2003, 3377.
4. S. M. Sodhi, M. Johar, N. Singh, Synthesis of sulpha drug acridine derivatives and their evaluation for anti-inflammatory, analgesic and anticancer activity, *Indian J. Chem*. 41B, 2002, 2659
5. N. Srividya, P. Ramamurthy, V. T. Ramakrishnan, Photophysical studies of acridine(1,8)dione dyes: a new class of laser dyes, *Acta Spectrochemica* 54, 1998, 245.
6. N. Srividya, P. Ramamurthy, P. Shanmugasundaram, V. T. Ramakrishnan, Synthesis, characterization, and electrochemistry of some acridine-1,8-dione Dyes, *J. Org. Chem.* 61, 1996, 5083.
7. T. Josephrajan, V. T. Ramakrishnan, G. Kathiravan, J. Muthumary, Synthesis and microbial studies of some acridinediones and their thiourea derivatives, *Arkivoc*, XI, 2005, 124.
8. R. L. Lankey, P. T. Anastas, Life-cycle approaches for assessing green chemistry technologies, *Ind. Eng. Chem. Res.*, 41, 2002, 4498.
9. P. T. Anastas, J. C. Warner, *Green chemistry: Theory and practice*, Oxford University Press, New York, 1998.
10. B. S. Dawane, S. G. Konda, R. G. Bodade, R. B. Bhosale, An efficient One-pot Synthesis of Some New 2, 4-Diaryl pyrido [3, 2-c] Coumarins as Potent ntimicrobial Agents, *J. Het. Chem.*, 47(1), 2010, 237.
11. B. S. Dawane, S. G. Konda, B. M. Shaikh, R. B. Bhosale, An improved procedure for synthesis of some new 1, 3-diaryl-2-propen-1-ones using PEG-400 as a recyclable solvent and their antimicrobial evaluation, *Acta Pharm*. 59, 2009, 473.
12. B. S. Dawane, S. G. Konda, G. G. Mandawad, B. M. Shaikh, Poly (ethylene glycol) (PEG-400) as an alternative reaction solvent for the synthesis of some new 1-(4-(4'-chlorophenyl)-2-thiazoly)-3-aryl-5-(2-butyl-4-chloro-1H-imidazol-5yl)-2-pyrazolines and their *in vitro* antimicrobial evaluation, *Eur. J. Med. Chem.*, 45, 2010, 387.
13. D. Shrinivasan, N. Sangeetha, T. Suresh, P. Lakshmanaperumalsamy, Antimicrobial activity of certain Indian medicinal plants used in folkloric medicine, *J. Ethnophrmacol* 74, 2001, 217.

****