One pot multicomponent synthesis of acridinediones Employed by Trichloro salicylic acid as an efficient catalyst

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Abstract: A simple approach to the synthesis of acridinediones via one-pot three-component condensation of an aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and ammonium oxalate in isopropanol with use of as an efficient Trichloro salicylic acid catalyst is described. Excellent yields, catalyst recovery and reusability, and easy work-up are attractive features of this green protocol. All the synthesized acridinediones were characterized on the basis of their melting-points, elemental analysis and spectral data such as IR, 1HNMR, 13CNMR and LCMS.

Keywords: Acridinediones; aromatic aldehyde, TCSA; ammoniumoxalate, One-pot synthesis

1. INTRODUCTION:

Multicomponent reactions (MCRs) are a promising, vital field of chemistry because the synthesis of complicated molecules can be achieved rapidly and efficiently without the isolation of intermediates [1]. In MCR condensations, three or more compounds reacting a single event, but consecutively, to form a new product, which contains the essential parts of all the starting materials? MCRs meet the requirements of an environmentally friendly process, with fewer synthetic steps and less energy consumption and waste production. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions. Therefore, the search for new MCRs and full exploitation of known MCRs is of considerable interest.

Acridinediones dyes are a new class of laser dyes withlasing efficiency comparable to that of coumarin-102 [2, 3]. These dyes have been shown to mimic NADHanalogues to a greater extent because of their tricyclic structures, which protect the enamine moieties [4]. The design and synthesis of 1,3-dithiol-linked acridinediones functionalized gold nanoparticles was described recently[5], as was the design and synthesis of an acridinediones functionalized gold nanoparticle-based PET anion sensor [6]. 1,8-(2H,5H)-Acridinediones were synthesized with the Hantzsch procedure, which involves thermal reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone)with an aldehyde and ammonia. Various methods have been used to synthesize acridinediones, including the microwave [7, 8], ionic liquid [9,10], LiBr [11],proline [12], silica-bonded S-sulfonic acid [13], ceric Ammonium nitrate [14] and Methanesulphonic acid [28]catalysts. Acridinediones are also synthesized in aqueous media [15–18]; however, many of the methods described have drawbacks, such as use of hazardous organic solvents, long reaction times, low yields, formation of side products and multistep synthesis. Subsequently, there is a demand and scope for developing an efficient, easy, eco-safe approach to obtain acridinediones

We found that silica-supported sulphuric acid efficiently catalyzed the synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione derivatives in the reaction of substituted aromatic aldehydes, dimedone and ammonium oxalate in ethanol at 70◦C. The aim of the study reported here was to synthesize acridinediones with Trichloro salicylic acid as the catalyst

2. METHODS AND MATERIALS

2.1. EXPERIMENTAL:

Chemicals were purchased from Merck, Fluka and Aldrich Chemical companies. All yields refer to

isolated products unless otherwise stated. 1H Nuclear magnetic resonance (NMR) (500 MHz) and 13C NMR (125 MHz) spectra were obtained on a Bruker DRX-500 Avanceat ambient temperature, with tetramethylsilanes as the internal standard and dimethylsulfoxide (DMSO)-d6 as the solvent. Fourier transforms infrared (IR) spectra were obtained as KBr discs on a Shimadzu spectrometer. Mass spectra were determined on a Varion Saturn 2000 gas chromatograph–mass spectrometer. Elemental analyses were conducted with a Perkin Elmer 2400 CHN elemental analyser flowchart

2.2. General procedure for synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dionederivatives

A mixture of aldehyde 1 (1 mmol), dimedone 2(2 mmol), ammonium acetate 3 (1.5 mmol), trichlorosalicylic acid (1mmoll%) and isopropanol(25 mL) was placed in a 50 mL flask, heated at 70◦Cand stirred for the appropriate time as monitored by thin-layer chromatography (hexane: ethyl acetate; 6:4). After completion of the reaction, the mixture was cooled, and the resulting product was filtered, dried and recrystallized from methanol to afford the pure product 4a–4l (Scheme 1).All the products were crystalline and fully characterized on the basis of their melting-points, elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra (LCMS)).

SPECTRAL DATA FOR THE SYNTHESIZED COMPOUNDS:

2.2.1.9-Phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4a)

Red solid : Yield-84; M.P-197-199^{0}C ; IR (KBr, cm−1): 3284, 2957, 1674, 1644, 1603; ^{1}HNMR(400 MHz, $CDCl_3$) δppm:10.128(s,1H,NH), 7.524–7.581 (m, 5H, Ar-H), 5.103 (s, 1H, CH), 2.457–2.224 (m, 8H, 4×CH_2), 0.977 (s, 6H, 2×CH_3),0.914 (s, 6H, 2×CH_3);^{13}CNMR (100MHz,$CDCl_3$)δppm: 194.77, 150.07, 147.66, 128.96, 125.88, 114.75, 51.67, 41.55, 33.47, 31.99, 28.79, 27.04 ; LCMS (m/z): 350.45((M+H)+; Molecular formulae : $C_{23}H_{27}NO_2$: Analysis of Elements: Calculated : C- 79.08; H-7.74; N- 4.01; Obtained : C- 79.01; H- 7.71; N- 4.09.

2.2.2.9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4b)

Red solid : Yield-90%; M.P-205-207^{0}C ; IR (KBr, cm^{-1}): 3431, 3360, 3294, 2959, 1685, 1613; ^{1}HNMR(400 MHz, $CDCl_3$) δppm : 10.255 (s, 1H, NH),), 9.854 (s, 1H, OH), 7.259-7.012 (m,4H, Ar-H), 5.214 (s, 1H, CH), 2.514-2.276(m, 8H, 2×CH_2), 1.087 (s, 6H, 2×CH3), 0.954(s, 6H, 2×CH3 ; ^{13}CNMR(100MHz,$CDCl_3$) δppm : 193.55, 187.45, 146.95, 142.55, 128.74, 120.09,115.88,114.35,110.52,56.87,50.07, 44.56, 33.58, 31.54, 29.08, 27.07 ; LCMS (m/z): 366.22 (M+H)+; Molecular formulae : $C_{23}H_{27}NO_3$: Analysis of Elements: Calculated: C-75.62; H- 7.40; N- 3.83; Obtained: C- 75.55; H- 7.38; N-3.88

2.2.3.9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4c)

Red solid : Yield-94%; M.P- 225-217^{0}C ; IR (KBr, cm^{-1}): 3308, 2971, 1678, 1629, 1616; ^{1}HNMR(400 MHz, $CDCl_3$) δppm : 10.295 (s, 1H, NH), 7.457–7.271(m, 4H, Ar-H), 5.254 (s, 1H, CH), 3.714 (s, 3H, OCH_3),2.495–2.275 (m, 8H, 4×CH_2), 1.213 (s, 6H, 2×CH_3), 1.104 (s, 6H, 2×CH_3) ; 13C NMR (100MHz,$CDCl_3$) δppm : 195.22, 188.75, 147.89, 141.67, 129.84, 128.33, 116.08, 114.21, 56.28, 41.37, 32.54, 28.77, 27.07,

; LCMS (m/z):380.77 (M+H)+; Molecular formulae : $C_{24}H_{29}NO_3$: Analysis of Elements: Calculated: C-75.99; H- 7.65; N- 3.69; Obtained : C- 75.93;H-7.63; N-3.71.

2.2.4.9-(4-Methylphenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione (4d)

Red solid: Yield-90%;M.P-228-230^{0}C;IR(KBr, cm−1): 3281, 2965, 1646, 1612; ^{1}HNMR(400 MHz, $CDCl_3$) δppm : 10.314 (s, 1H, NH), 7.451–7.321 (m, 4H,Ar-H), 5.301 (s, 1H, CH), 2.289–2.028 (m, 8H, 4×CH_2),2.182 (s, 3H, CH_3), 0.989 (s,6H, 2×CH_3), 0.895 (s, 6H, 2×CH_3) ; 13C NMR (100MHz,CDCl3) δppm: 194.16, 188.32, 147.28, 141.36, 135.87, 129.04, 127.68, 116.32, 114.57, 57.28, 48.27, 45.65, 33.54, 30.08, 28.34, 27.24,21.05; LCMS (m/z): 364.44 (M+H)+; Molecular formulae : $C_{24}H_{29}NO_2$: Analysis of Elements: Calculated : C- 79.34; H-7.99;

N-3.86; Obtained : C-79.30;H- 7.97; N-3.90.

2.2.5.9-(4-Fluorophenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione(4e)

Red solid : Yield- 89%;M.P-225-227^{0}C ; IR (KBr, cm−1): 3291, 2984, 1702, 1614; 1HNMR(400 MHz, CDCl3) δppm: 10.298 (s, 1H, NH), 7.546–7.284 (m, 4H, Ar-H), 5.338 (s, 1H, CH), 2.354–2.147 (m, 8H, 4×CH_2) , 1.124 (s,6H, 2×CH_3),0.914 (s, 6H, 2×CH_3) ; 13C NMR (100MHz,$CDCl_3$) δppm: 195.25,189.44, 140.84, 128.86, 127.55, 115.64, 48.99, 42.05, 32.57, 30.88,29.45, 27.22; LCMS (m/z): 368.74 (M+H)+; Molecular formulae : $C_{23}H_{26}FNO_2$: Analysis of Elements: Calculated: C-75.20; H-7.08; N-3.81; Obtained : C-75.12; H- 7.06; N-3.88.

2.2.6. 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1, 8-dione (4f)

Red solid: Yield-88%; M.P-215-2170C ; IR (KBr, cm^{-1}): 3314, 2978, 1665, 1614; ^{1}HNMR(400 MHz, $CDCl_3$) δppm : 10.354 (s, 1H, NH), 7.512–7.321 (m, 4H, Ar-H), 5.123 (s, 1H, CH), 2.412–2.274 (m, 8H, 4×CH2), 1.114 (s,6H, 2×CH_3), 1.027(s, 6H, 2×CH_3) ; 13C NMR (100MHz,$CDCl_3$) δppm δ:195.77, 190.25, 142.58, 139.27, 128.66, 127.95, 116.54, 49.25, 43.25, 33.65, 29.25,27.54; LCMS (m/z):. 384.45 (M+H)+; Molecular formulae : $C_{23}H_{26}ClNO_2$: Analysis of Elements: Calculated : C- 71.98; H-6.78; N-3.65; Obtained : C-71.91; H-6.77; N-3.71.

2.2.7. 9-(4-Bromophenyl)-3,3,6,6-tetramethyl 3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1, 8-dione (4g)

Pale red solid : Yield-88%; M.P-212-214^{0}C ; IR (KBr, cm^{-1}): 3290, 2987, 1668, 1604; ^{1}HNMR(400 MHz, $CDCl_3$) δppm: 10.257 (s, 1H, NH), 7.540-7.325(m, 4H, Ar-H), 5.054 (s, 1H, CH), 2.492–2.414 (m, 8H, 4×CH_2), 0.968 (s, 6H, 2×CH_3), 0.924 (s, 6H, 2×CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm: 193.44, 144.07, 138.67, 128.25, 126.86, 114.65, 48.95, 43.44, 34.58, 32.57, 29.56, 27.54; LCMS (m/z):.428.49 (M+H)+; Molecular formulae :$C_{23}H_{26}BrNO_2$: Analysis of Elements: Calculated : C-64.50; H-6.08; N-3.27; Obtained : C-64.44; H- 6.06; N-3.33.

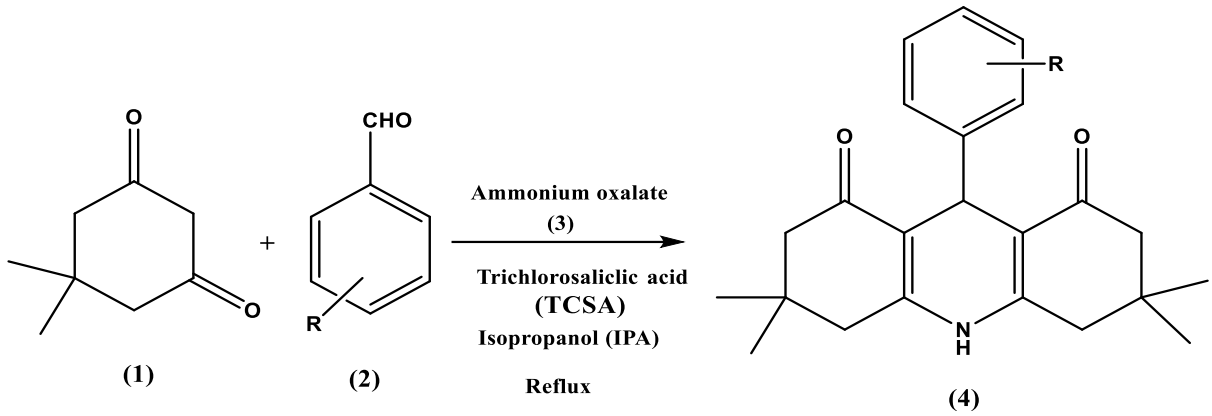
2.2.8. 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1, 8-dione (4h)

Red solid:Yield-87%;M.P-202-204^{0}C; IR (KBr, cm^{-1}): 3305, 2985, 1680,1613; ^{1}HNMR(400 MHz, $CDCl_3$) δppm : 10.258(s, 1H, NH), 7.884 (d, J = 8.0 Hz,2H, Ar-H), 7.362(d, J = 8.8 Hz, 2H, Ar-H), 5.145 (s, 1H,CH), 2.654–2.324 (m, 8H, 4×CH_2) 1.012 (s, 6H, 2×CH_3), 0.984 (s,6H, 2×CH_3); ^{13}CNMR (100MHz,$CDCl_3$) δppm :196.12, 188.74, 148.66, 145.32, 128.69, 125.67, 114.08, 52.33, 45.28, 33.68, 28.95, 27.11; LCMS (m/z): 395.54$(M+H)^+$; Molecular formulae: $C_{23}H_{26}N_2O_4$: Analysis of Elements: Calculated : C-70.05; H-6.60; N-7.11; Obtained ; C-69.93; H-6.58; N-7.20.

3. RESULTS AND DISCUSSION

The procedure afforded a versatile, environmentally benign, one-pot three-component synthesis of 9-arylacridinediones by the reaction of substituted aromatic aldehydes, dimedone and ammonium acetate under thermal condition in water with trichlorosalicylic acid as the catalyst (Scheme -1).

In an initial endeavour, substituted aromatic aldehydes (1 mmol), dimedone (2 mmol) and ammonium oxalate (1.5 mmol) were stirred at 70◦C in water under reflux conditions. After 4 h, only 60% of the expected product 4c was obtained. To developed the yield and optimize the reaction conditions, the same reaction were carried out in the presence of various amounts of trichlorosalicylic acid under similar conditions. In all reactions, the conditions were optimized for 100% conversion.



(4a-4h)

R = H, 4-OH, 4-OCH_3, 4-CH_3 , 4-F, 4-Cl, 4-Br, 4-NO_2

(Scheme-1)

The reaction condition of these derivatives was optimized at various catalyst, different amount of the catalyst and different solvent are used. The maximum yield of the compounds obtained in presence of Trichlorosalicylic acid (TSA) catalyst than oxidative related catalyst such as Silicasuported sulphuric acid (SSA), Methanesulphonic acid(MSA),P-toluene Sulphonic acid(PTSA), camphorsulphonicacid acid(CSA) and Trichlorosalicylic acid (TCSA) whereas different amount of catalyst utilized during the reaction (Table-I).

Table-I: The reaction of aryl aldehyde, dimedone, and ammonium oxalate: effecton catalysis.

Entry	Catalyst	Time (hrs)	Yield (%)
1	SSA	8	59
2	MSA	5	70
3	PTSA	10	68
4	CSA	7	78
5	TCSA	3	92

The different solvents were used during the reaction that were evaluated (DMF, Isopropanol acetonitrile, ethanol, methanol, cyclohexane) in the model reaction. It was found to be the best medium for the reaction, with 92% product yield and was therefore used as the solventforsubsequentreactions on the merits of higher yield, green nature and easy work-up.

Entry	Catalyst	Time (hrs)	Yield (%)
1	DMF	3	45
2	IPA	3	92
3	CH_3CN	3	62
4	EtOH	3	56
5	MeOH	3	67

Table-II: The reaction of aryl aldehyde, dimedone, and ammonium oxalate: effect of solvent

A significant improvement was identified, the yield of 4c being increased to 92%. Use of only 1.5m mol% was sufficient to drive the reaction forwards within 2.0hrs. The maximum amounts of the catalyst

did not improve the results. Although, use of 2.0mmol% trichlorosalicylic acid permitted the reaction time to be decreased to 1 h, the yield unexpectedly decreased to 77%as shown Table-III.

Table-III: Different amounts of catalyst in Isopropanol at reflux (4b):

Entry	Amount catalyst(mmol)	Time (hrs)	Yield (%)
1	0.5	3	Traces
2	1.0	3	42
3	1.5	3	58
4	2.0	3	92
5	2.5	3	75

4. CONCLUSIONS

We have developed a new, easy, an efficient process for synthesis of substituted acridinediones derivatives via one-pot three-component condensation of substituted aromatic aldehyde, dimedone and ammonium oxalate in an isopropanol medium with Trichloro salicylic acid as an efficient catalyst. The mildness of the conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives.

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