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One pot synthesis of acridine analogues from 1,2-diols as key reagents.

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Abstract: Lead tetraacetate have been demonstrated to be an efficient, low cost and mild reagent for the one pot synthesis of acridine derivatives from a variety of 1,2-diols. 1,2-Diols are oxidised *in situ* to aldehydes, which in turn undergo reaction with dimedone and ammonium acetate to yield acridine derivatives. The attractive features of this process are mild reaction conditions, short reaction times, broad functional group tolerance, easy isolation of products and excellent yields. Thus, the current method is utilizing 1,2-diols instead of benzaldehydes to synthesis acridines derivatives

Keywords: Acridine, lead tetraacetate, multicomponent reaction, 1,2-diols, dimedone, acetic acid, ammonium acetate.

Introduction

The multi-component reaction (MCR) is one pot process in which at least three or more different reactants react for the synthesis of target molecule. MCRs tactics are proclaimed to be economic, cost and time effective attributing its properties such as reducing the number of synthetic steps, isolation and purification process, energy consumption and waste production. Hence, developing new MCRs and improvement of existing MCRs are still important areas of research in the current synthetic and medicinal organic chemistry.¹⁻⁴

The synthesis of acridine derivatives, which contain 1,4-dihydropyridines parent nucleus is an important reaction, as these scaffolds are found to be a very important core in numerous synthetic, pharmaceutical and a wide variety of biologically active compounds.⁵⁻¹³ A large number of compounds bearing 1,4-dihydropyridines have entered preclinical and clinical trials over the last few years. Many commercially available drugs (Figure 1) including Nifedipine, Clevidipine, Lacidipine and Nisoldipine (calcium channel blocker), Nicardipine, Manidipine and Felodipine (antihypertensive compounds), Amlodipine (used in coronary artery disease) are derived from 1,4-dihydropyridines core entities.¹⁴

1,4-Dihydropyridines moieties are also important as anti-inflammatory,¹⁵ antimicrobial,¹⁶ anticancer,¹⁷ antimalarial,¹⁸ antituberculosis,¹⁹ antiherpes,²⁰ antiprotozoal activity,²¹ antiprion,²² antiviral²³ and antileishmanial agents.²⁴

Hence, the synthesis of acridine which contain 1,4-DHP's has evoked much attention, as a result of which a variety of synthetic methodologies have been reported. The most important approaches are: (i) one pot cyclocondensation of aldehydes with dicarbonyls and ammonium acetate,²⁵ (ii) one pot cyclocondensation of aldehydes with dicarbonyls and methyl amine,²⁶ (iii) one pot cyclocondensation of aldehydes with dicarbonyls and ammonium bicarbonate.²⁷ In the past years, a few methods have described the one-pot multicomponent synthesis of acridine derivatives based on catalysts such as DBSA,²⁸ L-proline,²⁹ amberlyst-15,³⁰ under microwave,³¹ TMSCl-NaI,³² I₂,³³ CeCl₃-7H₂O,³⁴ SiO₂-Pr-SO₃H,³⁵ Fe₃O₄ Nanoparticles,³⁶ MCM-41-SO₃H,³⁷ and ionic liquid.³⁸ However, these methods have limitations in terms of the use of excess amounts of expensive catalysts, product diversity and yields. Hence, the development of a simple and high yielding protocol for the one-pot multicomponent synthesis of acridine scaffolds is still warranted.

In continuation of our work on the development of useful synthetic methodologies,^{39,40} in this study we report the use of lead tetraacetate as an oxidizing agent for the one-pot synthesis of acridine derivatives under mild conditions. Lead tetraacetate function as oxidizing agent offering several advantages such as high yields and purity, broad functional group tolerance and easy work up when compared to traditional reagents. The byproduct lead acetate can be removed by oxidation with chlorine gas to give PbCl_2 . The PbCl_2 salt formed may be separated by filtration making use of its lower solubility. The lead acetate can also be removed by many advanced methods.⁴¹⁻⁴⁷

Though, lead tetraacetate has been identified as an oxidizing agent,⁴⁸ the wider scope and synthetic utility of this reagent in multicomponent reactions has not been explored. Here, we report a one pot approach for synthesis of acridine derivatives starting from various 1,2-diols, dimedone and ammonium acetate without the need for an additional catalyst. The tandem process involves oxidation, condensation, cyclisation and dehydration under mild condition at 70 °C.

Results and discussion

First, the reaction of 1,2-diphenyl-1,2-ethanediol with dimedone and ammonium acetate was selected as the model reaction for the optimization of the reaction conditions (Scheme 1). It was hypothesized that the careful judgment of lead tetraacetate might efficiently oxidizes 1,2-diols into the benzaldehyde followed by condensation with dimedone and cyclisation and dehydration with ammonium acetate in one pot. A preliminary examination showed that lead tetraacetate in dry ethanol, among several other solvents, effectively oxidized followed by acetic acid catalysed condensation, cyclisation and dehydration. Upon varying the temperature of the reaction from 40 to 70 °C, the best yield of 4a was

obtained at 70 °C. Further increase of the temperature neither increased the yield nor shortened the reaction time. The time taken to achieve complete conversions (monitored by TLC) and the isolated yields are recorded in Table 2. Of all the reactions using different quantities of reactant, the best results were obtained using a 1: 4: 2.2: 1 ratios of 1,2-diols, dimedone, ammonium acetate and lead tetraacetate respectively. When a mixture of 1,2-diphenyl-1,2-ethanediol, dimedone, ammonium acetate and lead tetraacetate respectively in dry ethanol were stirred at room temperature and then refluxed at 70 °C for 2 h, the fused heterocyclic product, 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4a) was obtained in excellent yield (95%).

The role of the solvent in the synthesis of acridine derivatives was then studied and the results are depicted in Table 1. Replacing ethanol by acetonitrile gave the product in high yield (entry 3) albeit lower than that obtained in ethanol (entry 4). The use of other solvents such as dioxane, acetone, THF and methanol afforded the desired product in average yields (70–80%, entries 2, 5, 6 and 7), while DCM, DMF and DMSO produced lower yields (entries 1, 8 and 9). The optimized conditions were established with a reaction temperature of 70 °C and time of 2 h in ethanol solvent.

This remarkable activation in the reaction rate prompted us to explore the potential of this protocol for the synthesis of a variety of acridine derivatives and the results are summarized in Table 2. All the aforementioned reaction proceeded expeditiously and delivered good to excellent product yields. The overall yield ranged from 95% for 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4a) (entry 1) to 82% for 9-(2,6-dichlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4n) (entry 14).

A probable mechanistic pathway for the formation of acridine derivatives is analogous to the established mechanism reported in the literature.⁴⁹ The lead tetraacetate oxidizes 1,2-diol to benzaldehyde giving acetic acid which in turn would be able to acid catalyse condensation between benzaldehyde and dimedone giving the chalcone. The chalcone undergoes Michael addition with enamine which is formed *in situ* by the reaction of dimedone with ammonium acetate that yields the corresponding acridine via the cyclisation followed by the dehydration.

Conclusion

We have developed an efficient, one pot strategy for the synthesis of acridine derivatives by *in situ* oxidation of 1,2-diols into benzaldehyde followed by the reaction with dimedone and ammonium acetate in excellent yields. Tandem nature, mild conditions, simple and convenient work-up are the main advantage of this reaction. This protocol is also applicable to the broad range of substrates. The current strategy reduces the number of steps in total synthesis.

Experimental

General information.

The melting points were determined by the open capillary method using an electric melting point apparatus and are uncorrected. The IR spectra were recorded on a Agilent Cary 630 FT-IR Spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer using CDCl₃ as a solvent and TMS as an internal standard. The chemical shifts are expressed in δ ppm. The mass spectrum was recorded on Thermo LCQ Fleet. The purity of the compounds was checked by TLC. The elemental analyses were carried out using an Elemental Vario Micro Cube CHNS Rapid Analyzer. All the compounds gave satisfactory

elemental analysis. All reagents were purchased from Sigma-Aldrich. Lead tetraacetate is a solid compound. The purity of lead tetraacetate is $\geq 99.99\%$.

Typical procedure for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione(4a).

Lead tetraacetate (0.44g, 1mmol) was added to a solution of 1,2-diphenylethane-1,2-diol (0.21g, 1mmol), dimedone (0.56g, 4mmol) and ammonium acetate (0.16g, 2.2mmol) in dry ethanol (10 mL) in a round-bottomed flask fitted with a reflux condenser and a guard tube. The resulting reaction mixture was stirred at room temperature for 5 minutes and heated at 70 °C in an oil bath for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 mL) was added and the reaction mixture was allowed to cool to room temperature. The solid was collected by filtration at pump, washed with cold ethanol and recrystallised from ethanol to obtain pure product.

2-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzotrile (4d)

A pale brown solid, 329 mg (88% yield). IR (ATR, cm^{-1}): 3320 (NH), 2230 (CN), 1740 (C=O), 1715 (C=O); mp 235-237 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 11.80 (s, 1H, NH), 7.48-7.26 (m, 4H, Ar-H), 5.49 (s, 1H, CH), 2.50-2.29 (m, 8H, 4CH₂), 1.23 (s, 6H, 2CH₃), 1.10 (s, 6H, 2CH₃) ppm. ^{13}C NMR (CDCl_3 , 400 MHz): δ 196.8, 168.7, 161.7, 157.7, 138.0, 136.7, 136.4, 134.6, 131.7, 130.0, 117.1, 80.0, 51.2, 41.0, 32.4, 30.5, 29.1, 28.5, 21.6, 21.2, 19.6, 14.6 ppm. ESI-MS: [M+H]⁺ 375.7. Anal. Calcd for C₂₄H₂₆N₂O₂: C, 76.98; H, 7.00; N, 7.48; found: C, 76.92; H, 6.95; N, 7.36%.

9-(4-(Benzyloxy)phenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8-(2H,5H,9H,10H)-dione (4h)

A white solid, 391 mg (86% yield). IR (ATR, cm^{-1}): 3396 (NH), 1731 (C=O), 1720 (C=O); mp 283-285 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 7.36 (s, 1H, NH), 7.34-6.78 (m, 9H, Ar-H), 5.01 (s, 1H, CH), 4.92 (s, 2H, OCH_2), 2.42-2.14 (m, 8H, 4 CH_2), 1.07 (s, 6H, 2 CH_3), 0.96 (s, 6H, 2 CH_3) ppm. ^{13}C NMR (CDCl_3 , 400 MHz): δ 195.6, 157.0, 149.3, 137.9, 132.2, 128.4, 128.2, 127.9, 127.2, 120.4, 111.9, 70.4, 50.9, 40.5, 32.3, 31.9, 29.5, 27.3 ppm. Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_3$: C, 79.09; H, 7.30; N, 3.07; found: C, 78.99; H, 7.20; N, 3.01%.

9-(4-Bromo-2-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8-(2H,5H,9H,10H)-dione (4k)

A white solid, 374 mg (84% yield). IR (ATR, cm^{-1}): 3298 (NH), 1734 (C=O), 1713 (C=O); mp 275-277 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.14 (s, 1H, NH), 7.30-6.93 (m, 3H, Ar-H), 5.01 (s, 1H, CH), 2.43-2.16 (m, 8H, 4 CH_2), 1.17 (s, 6H, 2 CH_3), 0.98 (s, 6H, 2 CH_3) ppm. ^{13}C NMR (CDCl_3 , 400 MHz): δ 196.2, 157.6, 155.2, 150.0, 143.9, 130.1, 127.8, 120.3, 120.1, 116.1, 115.9, 112.5, 50.8, 40.6, 33.3, 32.7, 29.5, 27.1 ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{BrFNO}_2$: C, 61.89; H, 5.65; N, 3.14; found: C, 61.79; H, 5.55; N, 3.11%.

9-(2-Bromo-6-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8-(2H,5H,9H,10H)-dione (4o)

A white solid, 299 mg (83% yield). IR (ATR, cm^{-1}): 3283 (NH), 1739 (C=O), 1721 (C=O); mp 256-258 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.14 (s, 1H, NH), 7.36-6.95 (m, 3H, Ar-H), 5.05 (s, 1H, CH), 2.33-2.05 (m, 8H, 4 CH_2), 1.08 (s, 6H, 2 CH_3), 0.97 (s, 6H, 2 CH_3) ppm. ^{13}C NMR (CDCl_3 , 400 MHz): δ 195.8, 193.1, 149.2, 133.4, 132.9, 131.9, 128.7, 116.0, 115.7, 112.7, 108.3, 105.0, 63.6, 51.6,

50.7, 50.5, 42.6, 40.8, 33.2, 32.7, 29.6, 28.8, 28.6, 27.2 ppm. Anal. Calcd for $C_{23}H_{25}BrClNO_2$: C, 59.69; H, 5.44; N, 3.03; found: C, 59.64; H, 5.39; N, 2.95%

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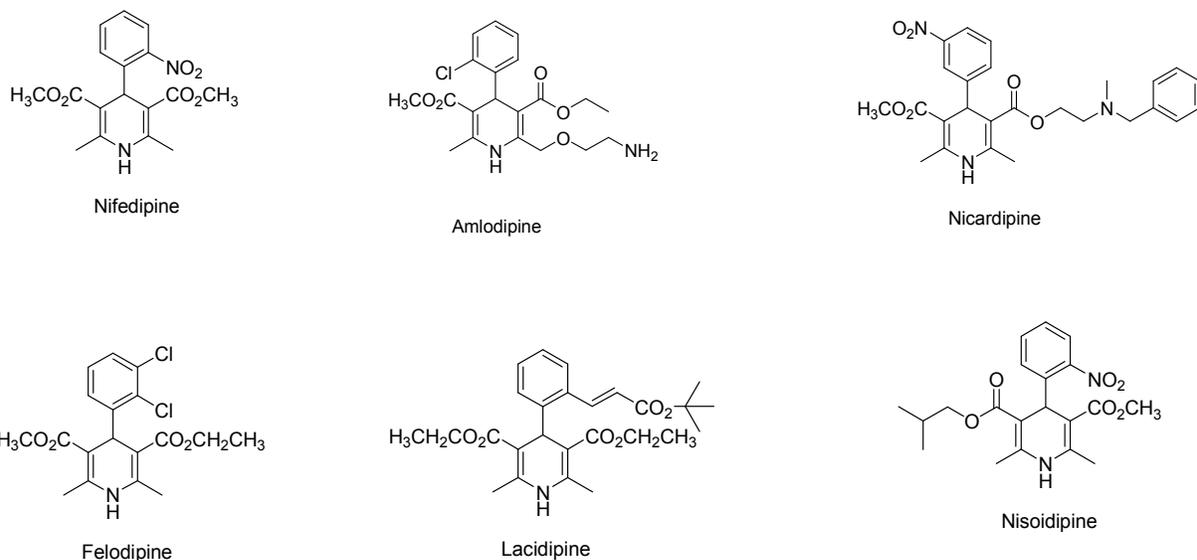
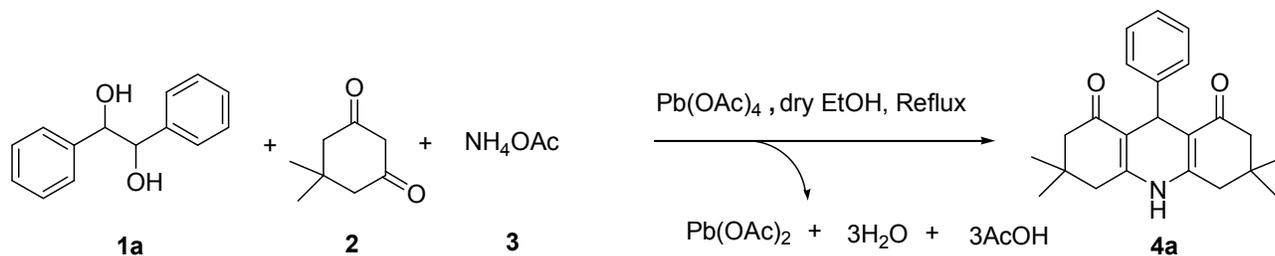


Figure 1: Commercially available drugs.

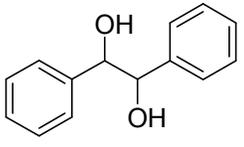
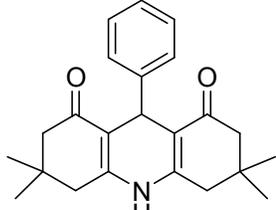
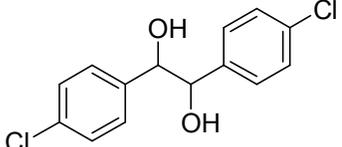
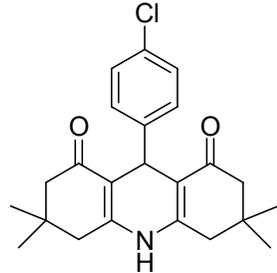


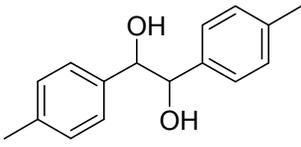
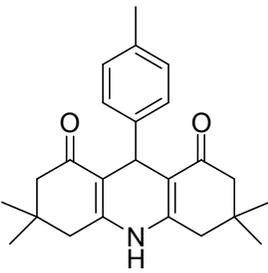
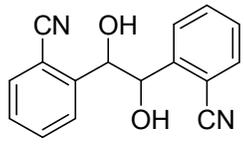
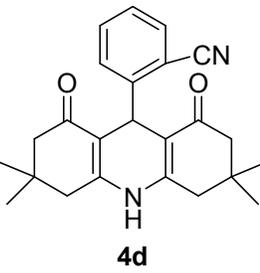
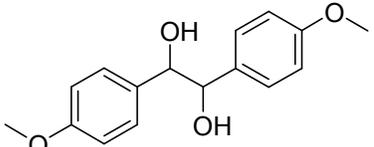
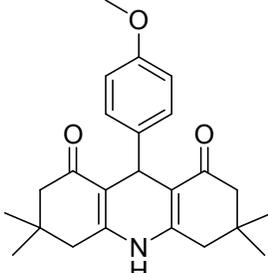
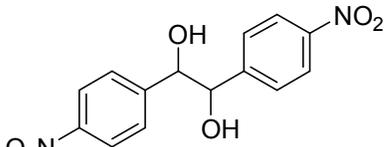
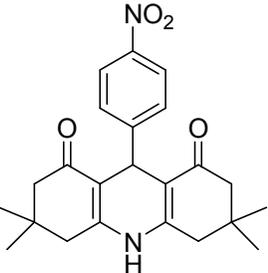
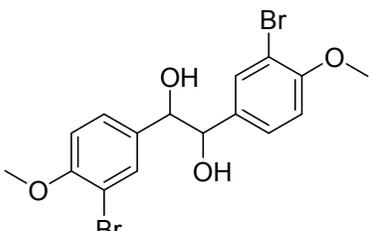
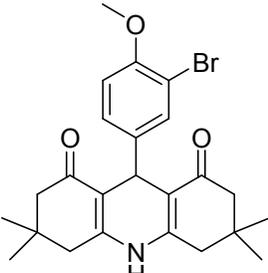
Scheme 1. Synthesis of 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (**4a**) using lead tetra acetate reagent.

Table 1. Optimization of solvents for the synthesis (**4a**).

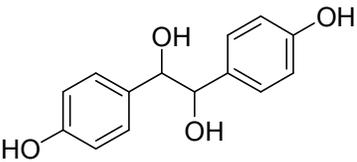
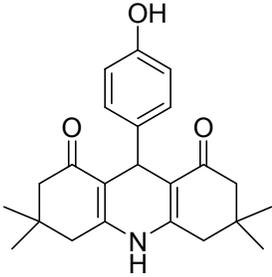
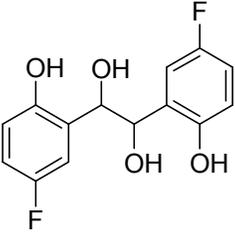
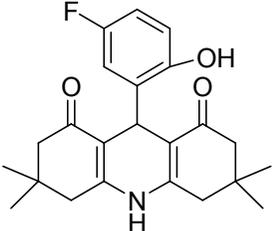
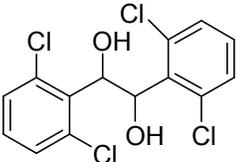
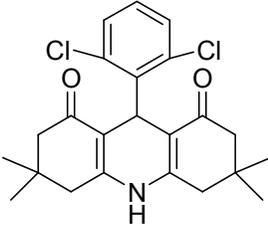
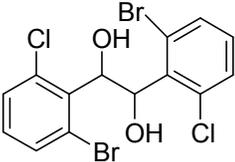
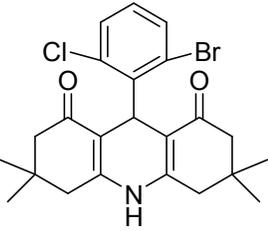
Entry	Solvents (Dry)	Time (h)	Yield (%)
1	CH ₂ Cl ₂	5.5	41
2	Dioxane	6.5	72
3	Acetonitrile	4	90
4	Ethanol	2	95
5	Acetone	4.5	70
6	THF	5	77
7	Methanol	3.5	80
8	DMF	5.5	45
9	DMSO	5.5	52

Table 2. Synthesis of acridine derivatives (**4a–o**).

Entry	1,2-diols	Products	Time (h)	Yield (%)
1	 1a	 4a	2	95
2	 1b	 4b	2.5	89

3	 1c	 4c	2	94
4	 1d	 4d	2.5	88
5	 1e	 4e	3	93
6	 1f	 4f	3.5	87
7	 1g	 4g	2	92

8	<p>1h</p>	<p>4h</p>	3	86
9	<p>1i</p>	<p>4i</p>	2.5	85
10	<p>1j</p>	<p>4j</p>	2.5	85
11	<p>1k</p>	<p>4k</p>	3	84

12	 1l	 4l	2	90
13	 1m	 4m	2.5	88
14	 1n	 4n	3	82
15	 1o	 4o	3.5	83

Graphical abstract:

Lead tetraacetate is an efficient, low cost and mild reagent for the one pot synthesis of acridine derivatives from a variety of 1,2-diols. 1,2-Diols are oxidised *in situ* to aldehydes, which in turn undergo reaction with dimedone and ammonium acetate to yield acridine derivatives.

