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A Review on Synthesis of Acridine and Acridine-1,8-dione Derivatives

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ABSTRACT

Acridinedione has attracted significant interest in the fields of material science, drug development, and chemical and medicinal chemistry. Recent research on the synthesis of acridine-1,8-dione derivatives, including cyclocondensation and multicomponent reactions, is included in this review. These substances have been used to make antibacterial, anticancer, and anti-inflammatory medications because of their strong biological activity. They serve as fluorescence probes in material science as well. The main objectives of recent developments have been to create more effective synthesis methods for acridine-1,8-diones and investigate new uses; and these approaches are discussed here.

1. Introduction

Acridine (Fig. 1) is a nitrogen-containing heterocyclic organic compound with the formula $C_{13}H_9N$. Acridines are substituted derivatives of the parent ring. It's a planar molecule with one of the central -CH groups replaced by nitrogen. It's structurally similar to anthracene. Acridine, like the related chemicals pyridine and quinoline, is a slightly basic compound. It's an almost colourless solid with needle-like crystals [1].

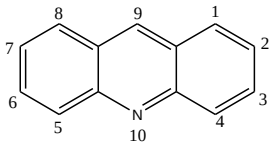

Fig. 1 Structure of acridine

In 1870, Carl Grabe and Heinrich Caro in Germany successfully isolated acridine for the first time, starting with a high boiling percentage of coal tar. Ehrlich and Benda discovered acridine's antimicrobial properties in 1917 [2]. Australian chemist Adrien Albert was the first to identify the link between the antibacterial properties of acridine and its structure. His research revealed that the antibacterial effect of the compound depends on cationic ionization and the surface area of the planar molecule = 38 Å. Researchers were able to create mepacrine, an antimalarial drug based on acridine, as a result of the World War II quinine scarcity. Even though acridine has been used for a long time, the massive increase in bacterial infections that are resistant to medicine has made it more popular again. In the literature, acridine derivatives have been found to have anti-inflammatory and anticancer [3], anthelmintic [4], anti-glaucoma [5], antifungal [6], and antitumor activity [7], with the most important of these properties is anticancer. Acridine is extracted from coal tar by shaking it off with diluted sulfuric acid and then using potassium dichromate to precipitate it out of the sulfuric acid solution. In the final step, the produced acridine dichromate is broken down using ammonia. Acridine is a stable chemical compound with a mildly basic characteristic, as are its homologues. The pKa value of 5.6 for pyridine and 5.6 for acridine are nearly identical.

Acridine derivatives exhibit a wide range of biological activities, including as mutagenic, antibacterial, antimalarial, and anticancer effects. Many people are interested in acridine systems because of their possible pharmacological action. Since the 19th century, acridine and its derivatives have been used extensively as pigments and dyes, and they have a variety of industrial uses.

Acridinedione derivatives, a type of nitrogen heterocyclic compounds with a 1,4-dihydropyridine (DHP) ring, are found in many complex molecules. DHPs are useful therapeutic ingredients and active intermediates in medicinal chemistry and organic synthesis [8]. Acridinediones and its derivatives also have the ability to bind DNA, block carbonic anhydrase, have antibacterial, antimicrobial, antitumor, anticancer, antimalarial, antifungal, and anti-glaucoma properties [9–13]. An efficient method for synthesis of acridinedione derivatives is the multi-component Hantzsch type reaction, which uses aldehydes, -diketones, and different nitrogen sources such aniline, urea, methylamine, ammonium acetate, or appropriate primary amines as starting ingredients [14].

The aim of this review is to comprehensively summarize the reported synthetic methodologies for acridinediones derivatives. Emphasis is placed on reaction strategies, catalytic systems, multicomponent reactions, and green chemistry approaches. By critically analysing recent advances and existing challenges, this review seeks to provide valuable insights and guidance for researchers engaged in heterocyclic synthesis, medicinal chemistry, and related areas. A brief summary of various methods is summarized.

2. Synthesis Methods

B. Kilbas et. al has reported the synthesis of hexahydroacridine -1,8 (2H, 5H)-dione derivative from three condensations of aromatic aldehyde, dimedone, and ammonium acetate use of highly active and reusable Pd/AlO(OH) heterogeneous catalyst (Fig. 2) [15].

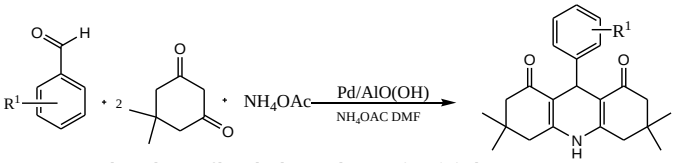

Fig. 2 General synthesis of hexahydroacridine-1,8(2H,5H)-dione

Acridine is synthesized from anthranilic acid derivatives and aryl halides, or 2-Chlorobenzoic acid and aryl amines. in four steps (Fig. 3) [16].

H. Alinezhad et. al. has reported the Hantzsch three-component condensation reaction of various aromatic aldehyde, 1,3- dione, and aniline derivatives in the presence of 2-methyl pyridinium trifluoro methanesulphonate ([2- MPyH]OTf) as green and highly efficient catalysts in water affords 1,8- dioxodecahydroacridine derivatives (Fig. 4) [17].

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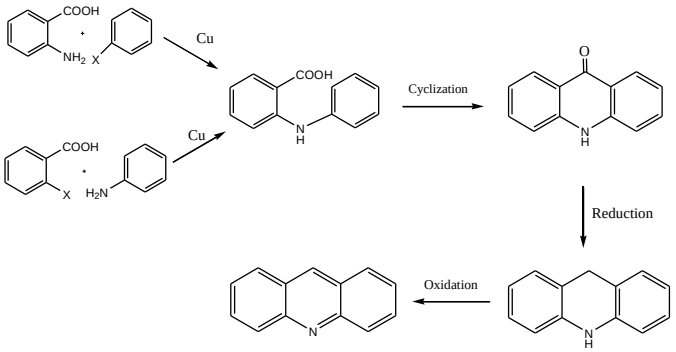

Fig. 3 Synthesis of acridine from anthranilic acid derivatives and aryl halides, or 2-chlorobenzoic acid and aryl amines

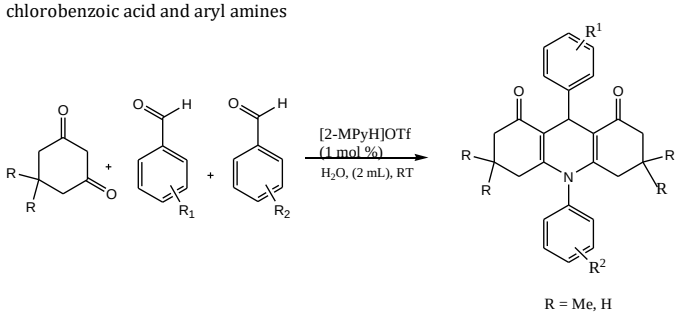

Fig. 4 Synthesis of 1,8-dioxodecahydroacridines catalysed by protic pyridinium ionic liquid

The above-mentioned strategies have been modified by different researchers to obtain diversely functionalized acridines or to improve the reaction conditions. Bernthsen's method was modified by Seijas et al. using microwave assistance, which reduced the reaction time drastically from hours to minutes and avoided the use of higher temperatures (200-270 °C) (Fig. 5) [18].

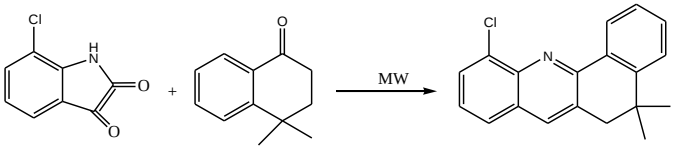

Fig. 5 Synthesis of acridine by microwave radiation

B. Zeynizadeh et. al. has reported the Hantzsch dihydropyridine synthesis of acridine-1,8-dione by using condensation of aromatic aldehyde, dimedone, and ammonium acetate (Fig. 6) [19].

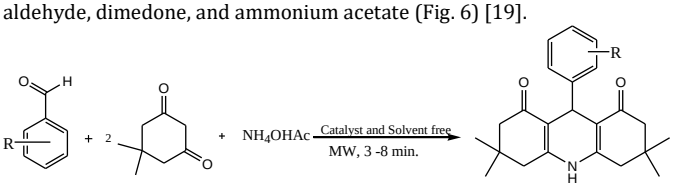

Fig. 6 Synthesis of acridinediones promoted by microwave radiation

J. R. Sunkarai et.al reported the synthesis of 1,3-cyclohexanedione, aldehydes and ammonium acetate using nano ferrite at 120 °C for the preparation of acridinediones and their derivatives (Fig. 7) [20].

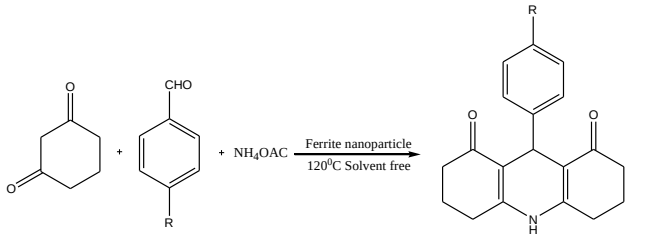

Fig. 7 Synthesis of 3,4,6,7-tetrahydro-9-phenylacridine-1,8(2H,5H,9H,10H)-dione employing reusable nano ferrite as catalyst

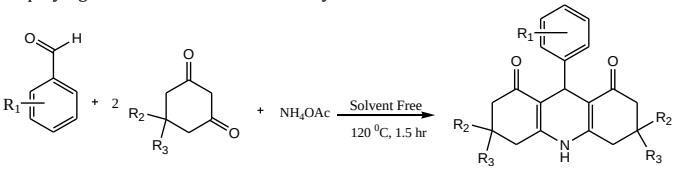

Fig. 8 Synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-dione under solvent free condition

Shen et. al. has reported the synthesis of acridinediones under the thermal heating condition from the condensation reaction of aromatic aldehyde, dimedone, and ammonium acetate (Fig. 8) [21].

S.R. Mousavi et. al. has reported the synthesis of Acridine derivatives via reaction of dimedone, aromatic amines/ammonium acetate and various aromatic aldehydes in the presence of a new and green graphene oxide incorporated strontium magnetic nanocatalyst (MSrGO NCs) under solvent-free conditions (Fig. 9) [22].

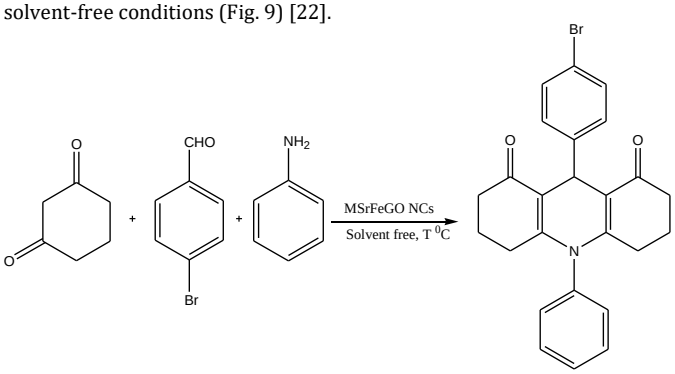

Fig. 9 Synthesis of acridine derivatives by MSrGO NCs under solvent-free conditions

Buu-Hoi et al. synthesized 2-chloro-5, 6-dihydro-9-methylbenzacridine-7-carboxylic acid by Pfitzinger's method using 5-methylisatin and 7-Chloro-3,4-dihydro-l (2H)-naphthalenone as starting materials [23]. Recent literature surveys also revealed a few examples of acridine synthesis by Pfitzinger's method (Fig. 10) [24, 25].

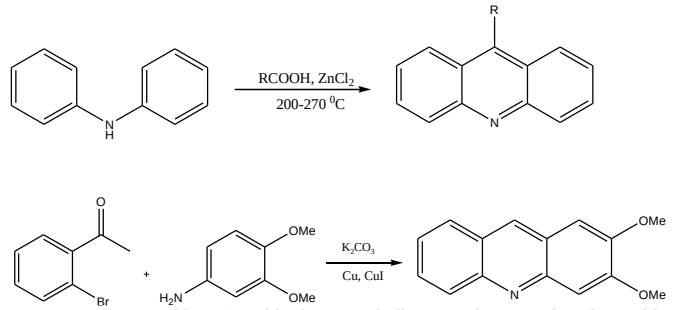

Fig. 10 Synthesis 2-chloro-5, 6-dihydro-9-methylbenzacridine-7-carboxylic acid by Pfitzinger's method

Investigation of acridinedione derivative synthesis with versatile morphologies of Bi_2O_3 nanoparticles reported by H. Ghafuri (Fig. 11) [26].

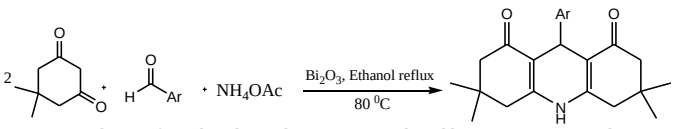

Fig. 11 Synthesis of acridinedione derivatives catalyzed by Bi_2O_3 nanoparticles

S.S. Mansoor et.al. have reported the synthesis of acridinediones via one-pot three condensations of aromatic aldehyde, dimedone, and ammonium acetate with the use of silica-supported sulfuric acid as an efficient catalyst (Fig. 12) [27].

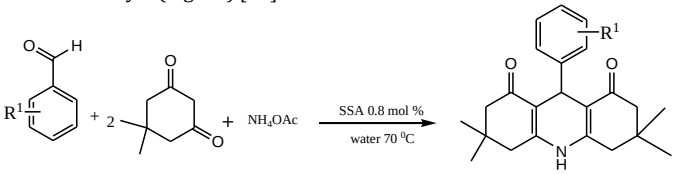

Fig. 12 Synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione derivatives by the reactions of aromatic aldehydes with dimedone and ammonium acetate

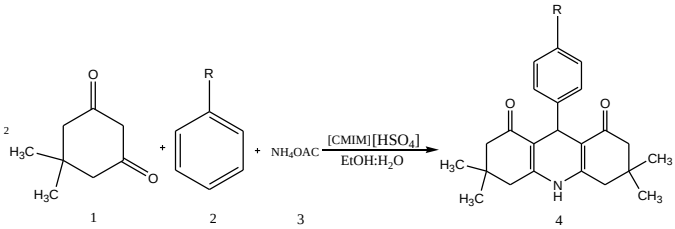

Fig. 13 Synthesis of 3,3,6,6-Tetramethyl-9-(4-methoxyphenyl) 3,4,6,7,9,10-hexahydro acridine-1,8-dione (1) and 3,3,6,6 Tetramethyl-9-(4-methylphenyl)-3,4,6,7,9,10-hexahydroacri dine-1,8-dione

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D. Kour et.al. Synthesis of 3,3,6,6-Tetramethyl-9-(4-methoxyphenyl) 3,4,6,7,9,10-hexahydroacridine-1,8-dione (1) and 3,3,6,6 tetramethyl-9-(4-methylphenyl)-3,4,6,7,9,10-hexahydroacridine-1,8-dione(2) by using mixture of dimedone, 4-methoxy or 4 methyl benzaldehyde, and ammonium acetate in mixture of aqueous ethanol was stirred at RT for 5min (Fig. 13) [28].

F. Moeinpour et. al. has reported the synthesis of 1, 8-dioxodecahydroacridines via one-pot three-component condensation reaction of aromatic aldehyde, dimedone, and ammonium acetate using silica gel supported polyphosphoric acid under the solvent-free condition at 100 °C (Fig. 14) [29].

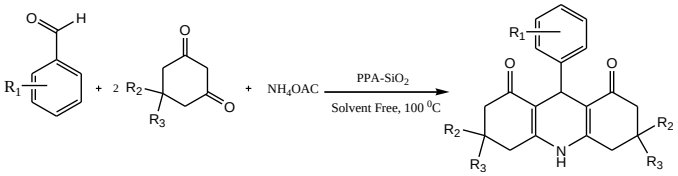

Fig. 14 Synthesis of 1,8-dioxodecahydroacridines using silica-supported polyphosphoric acid (PPA-SiO_2) under solvent-free conditions

K. Niknam et.al. has reported silica-bonded S-sulfonic acid as recyclable catalyst for the one-pot synthesis of 1,8-dioxo-decahydroacridines and 1,8-dioxooctahydroxanthenes derivatives using dimedone, substituted belzaldehyde and ammonium acetate (Fig. 15) [30].

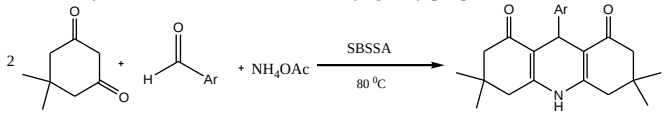

Fig. 15 Synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2H,5H)-acridine-1,8-dione derivatives by the reactions of aromatic aldehydes with dimedone and ammonium acetate

Graphene oxide was used as a highly effective and readily recyclable catalyst for the one-pot synthesis of 1,8-dioxoacridine derivatives by Burak Aday et.al (Fig. 16) [31].

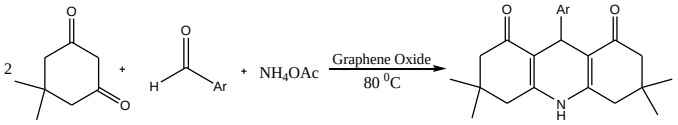

Fig. 16 Synthesis of acridinedione compounds catalyzed by graphene oxide

Jaipraksh N. Sangshetti et. al. has reported the water-mediated oxalic acid-catalyzed one-pot synthesis of 1, 8- dioxodecahydroacridines from the condensation of aromatic aldehydes, cyclic diketones, and ammonium acetate (Fig. 17) [32].

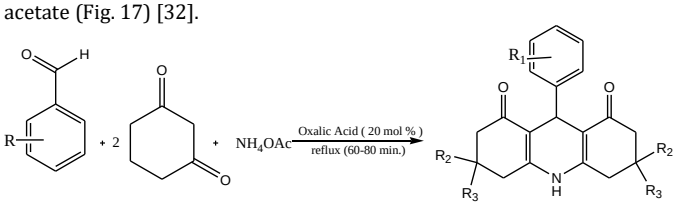

Fig. 17 Synthesis of 1,8-dioxodecahydroacridines catalyzed by oxalic acid using water as a medium

R. Ulus et.al. reported the functionalized multi-walled carbon nanotubes (f-MWCNT) as highly efficient and reusable heterogeneous catalysts for the synthesis of acridinedione derivatives (Fig. 18) [33].

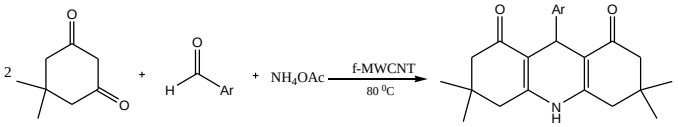

Fig. 18 Synthesis of acridine derivatives by f-MWCNT catalyst

Jing –Jing Xia et. al. has reported the synthesis of acridinedione by one one-pot Hantzsch condensation of an aromatic aldehyde, 5, 5- dimethyl-1,3-cyclohexanedione, and aniline/4-methyl aniline in refluxing water (Fig. 19) [34].

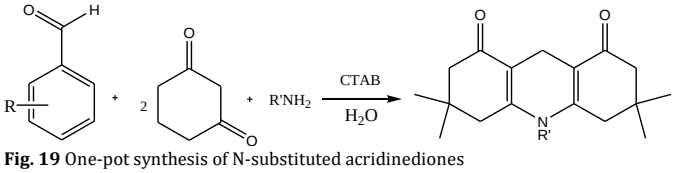

Fig. 19 One-pot synthesis of N-substituted acridinediones

3. Conclusion

The present review article summarized various synthetic methods for the preparation of acridine and acridinedione derivatives. From this study, it has been found that there is need for synthetic methods including multicomponent reactions, solvent-free conditions which are ecofriendly, such as very good yield, low catalyst amount, less reaction time, green catalytic systems and enhanced environmental compatibility. Also, this study has focused on the wide range of biological activities viz. cancer, bacterial, parasitic, viral, tuberculosis, Alzheimer's disease, and other disorders are caused by acridine and its derivatives. Thus, this article reveals that acridinedione derivative is an important motif in the heterocyclic chemistry which needs much modification or derivatization to develop and design highly effective biological compounds.

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