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Microwave-assisted one-pot synthesis of polycyclic 4-quinolone derivatives

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ABSTRACT

A microwave-assisted solvent-free one-pot method to afford 1,2,3,4-tetrahydroacridin-9-one derivatives was developed, with shorter reaction time and from easily available starting materials compared to the known methods.

KEYWORDS: one-pot synthesis, microwave, cyclanones, 4-quinolones, Friedländer reaction

INTRODUCTION

Acridine derivatives have a wide spectrum of biological activities such as antibacterial, antimalarial, anticancer and mutagenic properties, principally connected with their ability to inhibit the enzymes acting on nucleic acids [1]. The importance of tacrine (9-aminotetrahydroacridine, THA, Scheme 1) in the treatment of Alzheimer´s disease has prompted several authors to synthesize a series of related compounds [2, 3].

The preparation of tetrahydroacridin-9(10*H*)-ones **1** as starting material has been carried out by two methods using anthranilic acid and cyclohexanone (Scheme 1). Method A (with or without isolating the intermediate Schiff base) was discovered by Tiedke [4]. Method B (with or without isolating the anil intermediate) was discovered by Sen and Basu [5, 6]. Both methods involve high temperatures and long reactions times with low yields. For this reason the preparation of some acridinone derivatives was improved by applying microwave irradiation (MW) for procedure A and the selected cyclanones were 3-methylcyclohexanone, menthone, pulegone, carvone and dihydrocarvone. On the other hand, THA derivatives were achieved under MW from anthranilonitrile and methylcyclohexanones with alumina as catalyst [3] while other authors used Lewis acids to perform the same synthesis, which was also classified as a Friedländer reaction [7].

Friedländer reaction [8] is a well-known method for preparing quinolines and, in its original form, is the reaction between an aromatic *ortho*-aminoaldehyde and an aldehyde or ketone bearing α-methylene functionality. In a previous work, we had reported a series of quinoline derivatives as potential antiparasitic agents prepared *via* microwave-assisted Friedländer synthesis [9]. Among these products, the acridine derivative **2** was obtained by employing cyclohexanone as starting material and more recently, compounds **3** and **4** were synthesized using 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and cycloheptanone, respectively (Figure 1). Owing to their interesting preliminary results as potential antineoplastic agents (antiproliferative *in vitro* testing at National Cancer Institute, NCI, USA) we were prompted to develop a new series of related polycyclic quinolone derivatives.

The condensation of anthranilic acid and cyclohexanone with IR-120 Resin catalysis under reflux toluene for 5-6 hours to give the intermediate enamine **5** was reported in 2006. Its further cyclization in presence of phosphorous oxychloride

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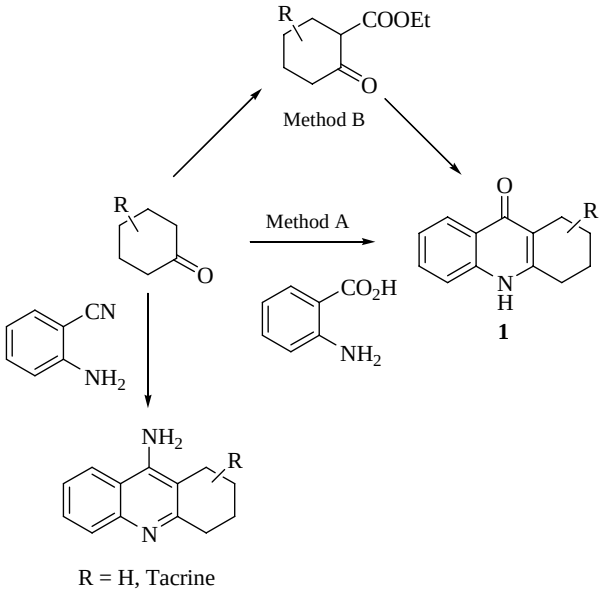
afforded 9-chloro-tetrahydroacridine **6** which in turn underwent nucleophilic substitution to result in 9-substituted tetrahydroacridines, proposed as antitubercular agents [10].



Scheme 1

However, when anthranilic acid and cyclohexanone were subjected to MW, the tetrahydroacridin-9(10*H*)-one **7** was obtained in two minutes as the sole product (Scheme 2).

MATERIALS AND METHODS

The structures of the synthesized compounds were established through their ^{1}H and ^{13}C-NMR, MS and IR spectra. Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded at room temperature using a Bruker 300 MHz spectrometer. The operating frequencies for protons and carbons were 300.13 and 75.46 MHz, respectively. The chemical shifts (δ) were given in ppm. IR spectra were recorded on an FT Perkin Elmer Spectrum One from KBr discs. Elemental analysis (C, H and N) were performed on an Exeter CE 440 and the results were within ± 0.4% of the calculated values. Analytical TLCs were performed on DC-Alufolien Kieselgel 60 F_{254} Merck. Microwave-assisted reactions were carried out in a CEM Discover oven.

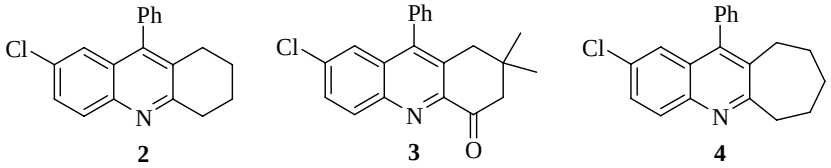
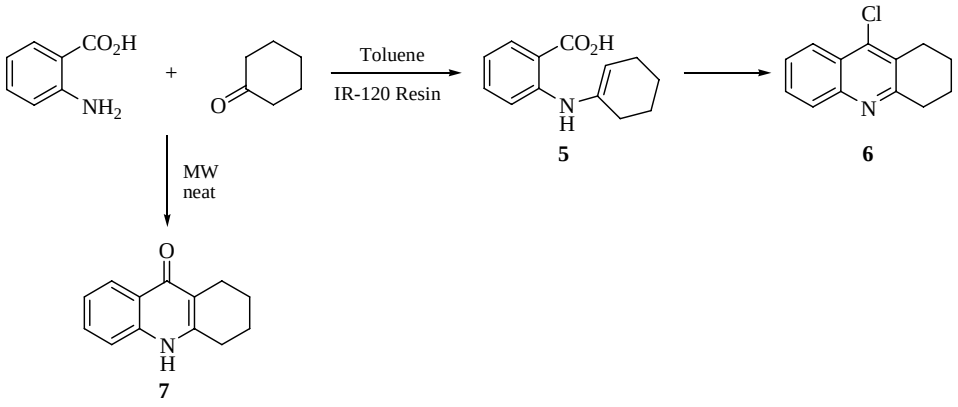


Figure 1. Acridine derivatives prepared *via* microwave-assisted Friedländer synthesis.



Scheme 2

General procedure for compounds 7-10: A neat mixture of anthranilic acid (3.8 mmol) and cyclanone (7.6 mmol) was subjected to MW irradiation, at 300 W and 250ºC. After completion of the reaction, the solid compound crystallized was filtered off and washed with EtOH. The product was triturated with EtOH at reflux temperature.

5,6,7,8-Tetrahydroacridin-9-(10*H*)-one (7): pale yellow powder, mp >300ºC (EtOH), yield 52%. IR spectrum, ν, cm^{-1}: 2922, 1639, 1552, 1355, 1169, 754, 691. ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.72 (4H, m); 2.42 (2H, t); 2.69 (2H, t); 7.21 (1H, t); 7.46 (1H, d, *J* = 7.0 Hz); 7.55 (1H, t); 8.04 (1H, d, *J* = 8.0 Hz); 11.42 (1H, s). ^{13}C NMR (DMSO-d_6), δ, ppm: 21.95; 22.14; 22.34; 27.58; 115.96; 117.85; 122.44; 123.64; 125.27; 131.40; 139.72; 147.34; 176.43. Found, %: C 77.96; H 6.32; N 7.18. $C_{13}H_{13}NO$. Calculated, %: C 78.36; H 6.58; N 7.03.

2,3-Dihydro-1*H*-cyclopenta[*b*]quinolin-9-(4*H*)-one (8): pale yellow powder, mp >300ºC (EtOH), yield 45%. IR spectrum, ν, cm^{-1}: 2935, 1640, 1549, 1350, 1149, 754, 660. ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.06 (1H, t, *J* = 7.0 Hz); 1.67-1.83 (2H, m); 2.70 (1H, t, *J* = 7.0 Hz); 2.98 (1H, t, *J* = 7.7 Hz); 7.24-7.31 (1H, m), 7.47-7.62 (1H, m), 7.87 (1H, d, *J* = 8.2 Hz), 8.07-8.09 (1H, m); 10.18 (1H, s). Found, %: C 78.15; H 5.67; N 7.43. $C_{12}H_{11}NO$. Calculated, %: C 77.81; H 5.99; N 7.56.

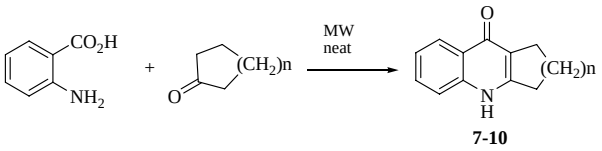
7,8,9,10-Tetrahydro-5*H*-cyclohepta[*b*]quinolin-11-(6*H*)-one (9): pale yellow powder, mp >300ºC (EtOH), yield 46%. IR spectrum, ν, cm^{-1}: 2944, 1635, 1555, 1348, 1150, 750, 689. ^{1}H NMR (DMSO-d_6), δ, ppm (*J*, Hz): 1.03 (6H, m); 2.08 (2H, m); 2.40 (2H, m); 5.35 (1H, s); 7.19 (1H, t); 7.23 (1H, d, J = 7.5 Hz); 7.60 (1H, t); 7.93 (1H, d, J = 7.5 Hz); 9.29 (1H, s). ^{13}C NMR (DMSO-d_6), δ, ppm: 23.0; 25.8; 27.2; 31.9; 33.5; 117.7; 120.6; 122.5; 123.5; 125.4; 130.8; 152.9; 174.8. Found, %: C 79.25; H 7.21; N 6.14. $C_{14}H_{15}NO$. Calculated, %: C 78.84; H 7.09; N 6.57.

3,4-Dihydro-3,3-dimethylacridine-1,9-(2*H*,10*H*)-dione (10): pale yellow powder, mp 296ºC (EtOH), yield 55%. IR spectrum, ν, cm^{-1}: 2956, 1681, 1609, 1566, 1450, 1275, 1145, 847, 756, 657. ^{1}H NMR ($DCCl_3$), δ, ppm (*J*, Hz): 1.15 (3H, s); 1.17 (3H, s); 2.43 (2H, s); 2.65 (2H, s); 6.83 (1H, s); 7.51 (1H, t, *J* = 8.2 Hz); 7.66 (1H, t, *J* = 7.0 Hz); 7.97 (1H, d, *J* = 8.5 Hz); 8.03 (1H, d, *J* = 6.2 Hz). Found, %: C 74.31; H 5.84; N 6.16. $C_{15}H_{15}NO_2$. Calculated, %: C 74.67; H 6.27; N 5.81.

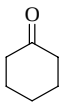
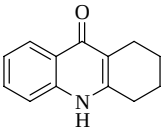
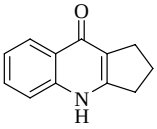
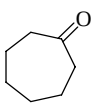
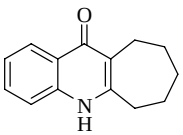
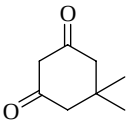
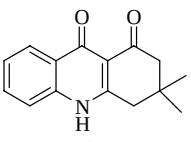
RESULTS AND DISCUSSION

The one-pot reaction shown in Scheme 2 was extended to prepare a series of polycyclic 4-quinolone derivatives **7-10** from a neat mixture of anthranilic acid and the corresponding cyclanone under MW (Table 1). These experimental conditions led to the final compounds without isolation of the intermediate Schiff base in good to moderate yields. Cyclopentanone, cyclohexanone, cycloheptanone and dimedone successfully afforded the expected products, meanwhile cyclobutanone did not react. This one-pot condensation and further cyclization

Table 1. Preparation of 4-quinolone derivatives from anthranilic acid and various cyclanones.



7-10

Entry	Cyclanone	Product	Time, min
1		 **7**	2
2		 **8**	4
3		 **9**	8
4		 **10**	4

can also be considered as a Friedländer reaction and showed several advantages and eco-friendly conditions compared to the reported methods in literature.

In 2006, the synthesis of compounds **7** and **8** was reported from the corresponding cyclanone and *o*-oxazoline-substituted aniline with a catalytic amount of *p*-toluensulfonic acid in dry butanol under reflux for 24 hours. The yields were 76 and 80%, respectively [11].

Moreover, compound **7** had also been synthesized in good yields by cyclisation of the corresponding ethyl 2-anilinocyclopent-1-ene carboxylate at 245°C under nitrogen atmosphere [12].

CONCLUSION

A novel MW-assisted solvent-free one-pot method to afford 1,2,3,4-tetrahydroacridin-9-one 7 and three analogous derivatives 8-10 was developed with shorter reaction time and from simple starting materials compared to the known methods. These products were designed with the aim to use them as intermediate reagents in the synthesis of substituted polycyclic quinoline and acridine derivatives as potential chemotherapeutic agents.

ACKNOWLEDGEMENTS

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