Chem Sci Trans., 2013, **2(1),** 246-250
DOI:10.7598/cst2013.280

Chemical Science Transactions
ISSN/E-ISSN: 2278-3458/2278-3318

RESEARCH ARTICLE

Synthesis and Chemical Characterization of 9-Anilinoacridines

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Received 30 June 2012 / Accepted 24 July 2012

Abstract: Chlorination of *N*-phenyl anthranilic acid **(1)** with phosphorus oxychloride affords 9-chloroacridine **(2)**. Further these compounds were treated with aromatic amines to obtain 9-substituted acridine derivatives **(3-9)**. All the synthesized compounds have been established on the basis of IR and ^{1}H NMR spectra data.

Keywords: Cyclization, *N*-Methyl-2-pyrollidone, Acridine

Introduction

Acridine is a π-electron deficient heterocycle, non-fluorescent in its crystalline state but shows blue fluorescence in aqueous or aqueous alcoholic solutions. Acridine itself is highly water insoluble but development of water soluble derivatives made them to act as primary reactant for synthesis of dyes[1], antitumor[2], antiviral[3], antimalarial[4], antiprotozoal[5], antibacterial[6] and multidrug resistance modulator agents[7]. The acridine moiety is responsible for intercalation between base pairs of double-stranded DNA through π-π interactions and therefore causes alteration in the cellular machinery. This interaction property confers to the molecules a high affinity for DNA, which is generally considered as the biological target for acridine anticancer agents[8]. Amsacrine (m-AMSA) is the best-known compound of 9-anilinoacridine series. It was one of the first DNA-intercalating agents to be considered as a topoisomerase II inhibitor[9]. 9-Anilino acridine derivatives have been extensively studied as potential antitumor agents, since they are capable of binding to DNA. Based on these findings, the present paper deals with the synthesis and characterization of some 9-anilino acridine derivatives.

Experimental

Melting points were determined by using Veego, microprocessor based programmable melting point apparatus in open capillaries and are uncorrected. The completion of the reaction was checked by TLC using chloroform:methanol (9:1) solvent system. IR spectra's were recorded in cm^{-1} using KBr pellets on PERKIN ELMER spectrophotometer. ^1H NMR spectra on BRUKER AVANCE II 400 NMR spectrometer using DMSO-d_6 solvent and TMS as internal standard (chemical shift values expressed in δ ppm).

*Synthesis of N-phenylanthranilic acid **(1)***

A mixture of *o*-chlorobenzoic acid (0.038 moles), aniline (0.038 moles) and copper powder (0.12 g) in 40 mL isoamyl alcohol, dry potassium carbonate (6 g) was slowly added and the contents were allowed to reflux for 6 to 8 hours. The isoamyl alcohol was removed by steam distillation and the mixture poured into 500 mL of hot water and filtered. The filtrate was acidified with concentrated hydrochloric acid. Precipitate formed was filtered, washed with hot water and collected. The crude product was dissolved in aqueous sodium hydroxide solution, boiled in the presence of activated charcoal and filtered. On acidification of the filtrate with concentrated hydrochloric acid, light yellowish precipitates were obtained and was washed with hot water and recrystallized from aqueous methanol to give light yellow solids. Yield 85%; m.p 182 ^0C.

*Synthesis of 9-chloroacridine **(2)***

In a 500 mL round bottom flask fitted with a water-cooled condenser, 0.023 mol of *N*-phenylanthranilic acid **(1)** is mixed with 0.176 moles of phosphorus oxychloride. The mixture was slowly heated for about 15 minutes to 85-90 ^0C on a water bath. After 15-20 min, when the boiling subsides somewhat, the flask was heated on a heating mantle for 2 hours at 140-150 ^0C. The excess phosphorus oxychloride was removed by distillation. The residue, after cooling was poured into a well-stirred mixture of 20 mL of concentrated ammonia solution, 50 g of ice and 20 mL of chloroform. The flask was rinsed by shaking with a little chloroform-ammonia mixture (about 25-30 mL). When no more undissolved solid remains (about 30 minutes is required), the chloroform layer is separated and the aqueous layer is extracted with an additional 10 mL of chloroform. The united chloroform extracts are dried over 1 g of calcium chloride and filtered and the solvent was removed either by evaporation or by distillation. The resultant greenish gray powder is dried at 70 ^0C for 20 minutes. Green solid, mp 116 ^0C, yield 80%; ^1H-NMR ($CDCl_3$): δ 7.54-7.58 (m, 2H, ArH), 7.73-7.77 (m, 2H, ArH), 8.17-8.20 (d, 2H, ArH), 8.32-8.34 (d, 2H, ArH).

*Synthesis of 9-anilinoacridine derivatives **(3-9)***

9-Chloroacridine **(2)** (0.0005 mol) and aromatic amines (0.001 mol) were dissolved in NMP containing one to two drops of concentrated hydrochloric acid and stirred at room temperature for different hours. The reaction was monitored by TLC and when complete, the mixture was poured into ethyl acetate (100 mL). The resulting precipitates were collected by suction filtration. The solids were dissolved in hot methanol and poured into ethyl acetate (100 mL) to re-precipitate. The solids formed were collected by suction filtration and dried under vacuum to yield the product as its hydrochloride salt.

*9-Phenylaminoacridine hydrochloride **(3)***

IR (KBr) cm^{-1}: 3075 (aromatic C-H), 1632, 1474 (aromatic C=C), 1341 (C-N), 753.4 (=C-H). ^1H-NMR (DMSO-d_6): δ 7.19-7.39 (m, 7H, ArH), 7.64-7.68 (t, 2H, ArH), 8.25-8.27 (d, 2H, ArH), 8.35-8.37 (d, 2H, ArH), 11.35 (br s, 1H, NH), 15.07 (br s, 1H, NH^+).

*4-(Acridin-9-yl-amino)-benzoic acid hydrochloride **(4)***

IR (KBr) cm^{-1}: 2886, 1709 1632.9, 1473.6 (aromatic C=C), 1375.8 (C-N), 752.4 (=C-H); ^1H NMR (DMSO-d_6): δ 7.42-7.48 (m, 4H, ArH), 7.88-7.94 (dd, 2H, *J* = 7.56 Hz, ArH), 7.96-8.05 (m, 2H, ArH,), 8.29-8.37 (dd, 2H, ArH), 8.52-8.54 (d, 2H, *J* = 8.8 Hz, ArH), 11.60 (br s, 1H, NH), 15.27 (br s, 1H, COOH).

*Acridin-9-yl-(4-methoxyphenyl)-amine hydrochloride **(5)***

IR (KBr) cm^{-1}: 3522 (-NH), 3162 (aromatic C-H), 3038 (alkane C-H), 1633.5, 1472 (aromatic C=C), 1343.1 (C-N), 754.8 (=C-H); ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 6.92-6.94 (d, 2H, *J* = 8.28 Hz, ArH), 7.26-7.30 (t, 4H, ArH), 7.74-7.77 (t, 2H, ArH), 8.28-8.32 (t, 4H, ArH), 11.39 (br s, 1H, NH), 14.82 (br s, 1H, NH^+).

*Acridin-9-yl-(3-chlorophenyl)-amine hydrochloride **(6)***

IR (KBr) cm^{-1}: 3440.5 (-NH), 3228.7 (aromatic C-H), 3075.8 (alkane C-H), 1633.4, 1475.5 (aromatic C=C), 1341.6 (C-N), 753.1 (=C-H); ^1H NMR (DMSO-d_6): δ 7.24-7.26 (d, 1H, *J* = 7.84 Hz, ArH), 7.31 -7.33 (d, 1H, *J* = 8.2 Hz, ArH), 7.37-7.45 (m, 3H, ArH), 7.87-7.93 (dd, 2H, *J* = 2.0 Hz, ArH), 8.29-8.36 (dd, 4H, ArH), 11.57 (br s, 1H, NH), 15.18 (br s, 1H, NH^+).

*Acridin-9-yl-(4-methylphenyl)-amine hydrochloride **(7)***

IR (KBr) cm^{-1}: 3464 (-NH), 3085 (aromatic C-H), 3029 (alkane C-H), 1633, 1473 (aromatic C=C), 1373 (C-N), 756 (=C-H); ^1H NMR (DMSO-d_6): δ 2.32 (s, 3H, CH_3) 7.23-7.12 (m, 6H, ArH), 7.71-7.76 (t, 2H, ArH), 8.22-8.20 (d, 2H, ArH), 8.29-8.26 (d, 2H, ArH), 11.26 (br s, IH, NH), 14.92 (br s, 1H, NH^+).

*2-(Acridin-9-yl-amino)-benzoic acid hydrochloride **(8)***

IR (KBr) cm^{-1}: 2951, 1721, 1632, 1522, (aromatic C=C), 1369 (C-N), 749.3 (=C-H); ^1H-NMR (DMSO-d_6): δ 7.24-7.26 (d,1H, ArH). 7.40-7.49 (m, 3H, ArH), 7.53-7.57 (m, 1H, ArH) 7.93-7.97 (t, 2H, ArH) 8.16- 8.20 (m, 3H, ArH), 8.42-8.44 (d, 2H, ArH), 11.70 (br s, 1H, NH), 15.53 (br s, 1H, NH^+).

*Acridin-9-yl-(3-triflouromethylphenyl)-amine hydrochloride **(9)***

IR (KBr) cm^{-1}: 3318 (-NH), 3023 (alkane C-H), 1638, 1472 (aromatic C=C), 1341.6 (C-N), 749.1 (=C-H); ^1H NMR ($CDCl_3$): δ 7.09-7.13 (t, 2H, ArH), 7.34-7.39 (t, 2H, ArH), 7.49-7.55 (q, 3H, ArH), 7.62-7.64 (d, 1H, ArH), 8.22-8.24 (d, 4H, ArH), 11.67 (br s, 1H, NH), 14.92 (br s, 1H, NH^+).

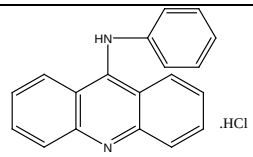
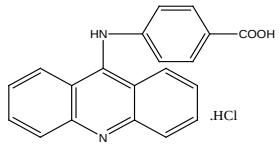
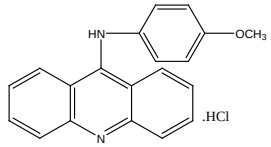
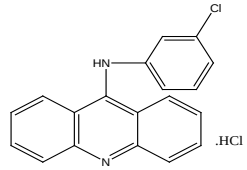
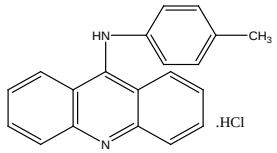
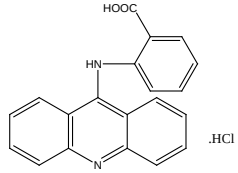
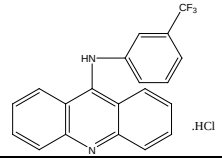
Results and Discussion

In present investigation we have prepared 9-anilinoacridine derivatives as shown in Table 1. In which 2-chloro benzoic acid was treated with aniline in the presence of potassium carbonate and Cu metal, *N*-phenyl anthranilic acid[10] (**1)** was obtained. Further, treatment of **1** with $POCl_3$ produced 9-chloro acridine[11](**2**). Compound **2** was then dissolved in *N*-methyl-2-pyrollidone (NMP) using different aromatic amines, in the presence of one to two drops of concentrated hydrochloric acid and stirred at room temperature for different hours to gives 9-anilinoacridine hydrochlorides as final product as shown in Scheme 1.

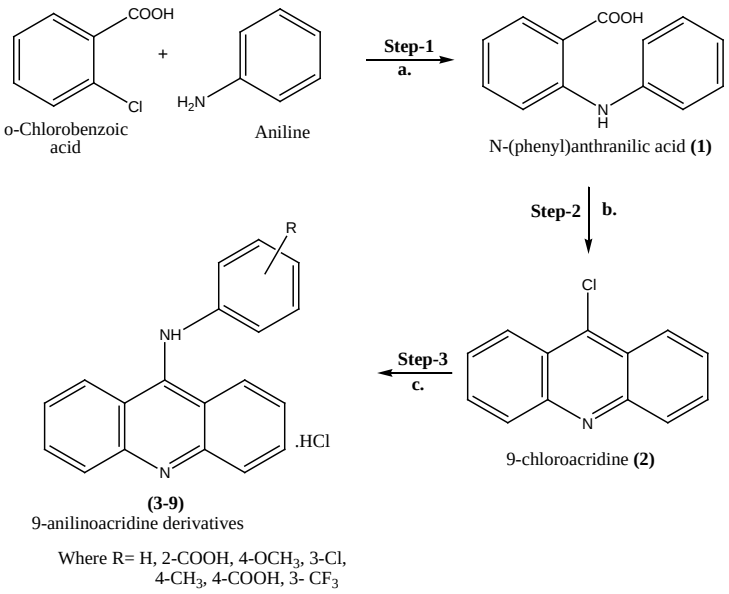
IR and ^1H NMR data reveals the structure of molecules of newly synthesized acridine derivatives. In IR, structure was confirmed by functional group identification. Secondary amine gave its peak at 3570-3400 cm^{-1}. >C=O peak of carboxylic group appeared at 1716-1714 cm^{-1}

along with broad peak of COOH at 3000-2800 cm^{-1}. C-F peaks appeared at about 1350-1300 cm^{-1}, where as C-Cl peaks appeared at about 750-700 cm^{-1}. C-O peak of ether appeared at 1345 cm^{-1}. In ^1H NMR, structure was confirmed by number of proton, splitting of signals and value of chemical shift in ppm. Peaks for NH protons appeared at about 11.2-11.4 ppm, where as for COOH proton peak appeared at about 11.6 ppm. The OCH_3 and CH_3 gave their peak at 2-5 ppm. These derivatives were prepared by various structural modifications on aromatic ring attached to 9-position of acridine ring.

Table 1. Physical data of 9-anilinoacridines

S. No.	Structure	mp, ^oC	Time for reaction, h	% Yield	R_f^* Value	Color
1.		310	2	75	0.70	Yellowish green
2.		315	3	80	0.69	Yellowish green
3.		275	24	65	0.80	Yellow
4.		286	25	55	0.64	Green
5.		282	26	90	0.72	Yellow
6.		262	4	86	0.78	Greenish yellow
7.		278	24	88	0.90	Orange

**Chloroform:methanol (9:1)*



Scheme 1. Step 1: a=Potassium carbonate, Cu powder and isoamyl alcohol heating at 160-170 ^{0}C for 6-8 h; Step 2: b=Cyclization by freshly distilled $POCl_3$; Step 3: c= NMP, conc. HCl stirring at different hours with aromatic amines.

Acknowledgement

The authors thank the Sophisticated Analytical Instruments Facility (SAIF), Punjab University, Chandigarh for spectral data.

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