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Note

An efficient synthesis of 9(10*H*)-acridinones under microwaves

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N-Phenylanthranilic acids have been subjected to cyclisation with different catalysts like silica gel, acidic alumina, strongly acidic montmorillonite (K10) clay, acetic acid, PTSA or Lewis acids like $ZnCl_2$, $AlCl_3$ and PPA under microwave irradiation to give 9(10*H*)-acridinones of which PPA has been found to be the best catalyst for cyclisation.

Keywords: Acridinones, microwaves, *N*-phenylanthranilic acids, PPA, cyclisation

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Development and application of microwave irradiation to organic reactions have added a new dimension to solid phase synthesis[1]. By using this technique many organic reactions such as aromatic nucleophilic substitution[2], condensation[3], cycloaddition[4], Michael addition[5], rearrangement[6] and other miscellaneous reactions[7] have been carried out due to the reduction in reaction times, operational simplicity, cleaner reactions, easier work-up and better yield[8].

Since the early days of the 20th century acridine derivatives have attracted the attention of medicinal chemists due to their broad-ranging biological properties including anti-carcinogenic[9], bactericidal[10], anti-malarial[11], DNA intercalating[12] and anti-fungal properties[13]. Also, some reports are available on the successful isolation and characterization of various acridine alkaloids from numerous plant sources[14-17]. The classical method[18] for 9(10*H*)-acridinone synthesis involves cyclisation of N-phenylanthranilic acid using sulphuric acid. However, it requires large amount of sulphuric acid at temperatures above 150°C and the reaction is often violent. Many other existing methods[19-21] for the synthesis of 9-acridinones are unsatisfactory with respect to yield, reaction conditions, generality and operational simplicity. In view of this, herein is described a simple, general and efficient procedure for the synthesis of this important heterocycle under microwave irradiation.

Results and Discussion

The reaction has been tried out by irradiation of N-phenylanthranilic acid in the absence of any catalyst (neat conditions), which could be expected to be the most economical method. But unfortunately, no cyclisation could be observed even at high power of microwave irradiation and maximum time (30 min).

Different solid supports, including silica gel, acidic alumina, strongly acidic montmorillonite (K10), acetic acid, PTSA, Lewis acids like $ZnCl_2$, $AlCl_3$ and PPA were checked to define the most effective (**Table I**) catalyst.

In a typical procedure, a mixture of N-phenylanthranilic acid **1a** (0.0005 mole) and the respective catalyst (0.001 mole) was taken in a beaker and thoroughly mixed with the help of a glass rod. The paste so obtained was irradiated in the microwave oven at a power of output 160W for appropriate time. After irradiation, boiling water was added and the solid obtained was boiled with sodium carbonate solution, filtered, dried and purified by recrystallization from a mixture of aniline and acetic acid to give a pale yellow solid, the structure of which was assigned as 9(10*H*)-acridinone **2a** on the basis of spectral and analytical data.

Thus, IR spectrum of the solid showed characteristic absorption band at 1635 cm^{-1} and in the range 3344-3280 cm^{-1} for >C=O and -NH groups respectively. The ^1H NMR spectrum showed the absence of signal for acidic proton, which confirmed the cyclisation. The spectrum consisted of the following resonances: a triplet at δ 7.25-7.29 for C_2-H and C_7-H, a doublet at δ 7.55 -7.57 for C_4-H and C_5-H, a triplet at δ 7.72-7.76 for C_3-H and C_6-H, a

Table I—Effect of solid support in dry media for the synthesis of **2a** under microwave irradiation (power = 160 W)

Support	Time (min)	Yield (%)
None	30	Nil
Silica gel	25	5
Acidic alumina	25	8
K10	25	10
AcOH	20	5
PTSA	8	93.80
$ZnCl_2$	5	92.70
$AlCl_3$	5.3	89.50
PPA	1.3	96

doublet at δ 8.23-8.25 for C_1-H and C_8-H and a singlet at δ 11.72 for >NH proton. The mass spectrum showed a molecular ion peak at m/z 195 ($M^{+\cdot}$, 53%) along with other fragment ion peaks at m/z 167 ($M^{+\cdot}$ –CO, 20%), 139, 111, 97, 85, 71, 57 (100%).

From the results obtained by using different solid supports, it is obvious that PPA is the most suitable catalyst for the synthesis of 9(10*H*)-acridinone **2a**, as it reduces the reaction time to minimum and increases the yield of the product to maximum (**Table I**). These conditions have thus been extended to the synthesis of other 9(10*H*)-acridinone derivatives **2b-k** (**Scheme I**) with very good results (**Table II**).

Experimental Section

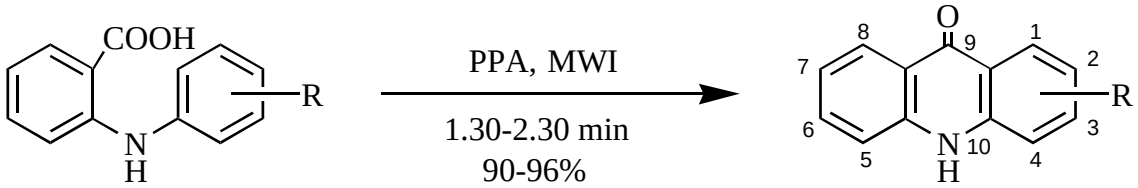
Melting points were recorded on Boetieus microheating table and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu-8201 FT spectrophotometer. ^{1}H NMR spectra were recorded on AMX-400 (400 MHz) spectrometer, using TMS as an internal reference, and mass spectra were recorded at 70 eV on a Joel JMS-D-300 instrument. The reactions were carried out in a domestic microwave oven (KENSTAR–OM-20ESP, 2450 MHz).

General procedure for the preparation of 9(10*H*)-acridinones, 2a-k

N-Phenylanthranilic acids (0.0005 mole) and polyphosphoric acid (0.001 mole) were taken in a 100 mL beaker and mixed well with the help of a glass rod and covered with a watch glass. The reaction mixture was irradiated in the microwave oven at 160W for the

Table II—Microwave synthesis of 9(10*H*)-acridinone derivatives **2a-g** using PPA as the catalyst (power= 160 W)

Compd	Reaction time (min)	Yield (%)
2a	1.30	96.00
2b	1.30	95.70
2c	1.40	95.50
2d	1.40	95.20
2e	1.35	95.00
2f	2.00	94.50
2g	2.20	93.00
2h	2.10	93.40
2i	2.20	92.00
2j	2.25	92.50
2k	2.30	90.00



1a-k **2a-k**

2a: R = H **2b**: R = 2-CH_3 **2c**: R = 4-CH_3 **2d**: 2-OCH_3 **2e**: R = 4-OCH_3 **2f**: R = 2-Br **2g**: R = 4-Br **2h**: R = 2-Cl **2i**: R = 4-Cl **2j**: R = 4-OH **2k**: R = $_{4\text{-}NO_2}$

Scheme I

Table III—Characterization data of compounds **2a-k**

Compd	^{1}H NMR (DMSO-d_6) δ, ppm	MS (70eV) $M^{+\cdot}$ (m/z)
2a	7.25-7.29 (t, 2H, C_2-H and C_7-H), 7.55-7.57 (d, 2H, C_4-H and C_5-H), 7.72-7.76 (t, 2H, C_3-H and C_6-H), 8.23-8.25 (d, 2H, C_1-H and C_8-H), 11.72 (s, 1H, NH)	195
2b	2.46 (s, 3H, C_2-CH_3), 7.25-8.38 (m, 7H, Ar-H), 10.95 (s, 1H, NH)	209
2c	2.48 (s, 3H, C_4-CH_3), 7.24-8.35 (m, 7H, Ar-H), 10.65 (s, 1H, NH)	209
2d	3.86 (s, 3H, C_2-OCH_3), 7.28-8.40 (m, 7H, Ar-H), 11.70 (s, 1H, NH)	225
2e	3.90 (s, 3H, C_4-OCH_3), 7.27-8.39 (m, 7H, Ar-H), 11.65 (s, 1H, NH)	225
2f	7.26-8.38 (m, 7H, Ar-H), 11.67 (s, 1H, NH)	273
2g	7.25-8.40 (m, 7H, Ar-H), 11.73 (s, 1H, NH)	273
2h	7.30-8.41 (m, 7H, Ar-H), 11.70 (s, 1H, NH)	229
2i	7.28-8.39 (m, 7H, Ar-H), 11.71 (s, 1H, NH)	229
2j	7.26-8.39 (m, 7H, Ar-H), 9.80 (s, 1H, C_4-OH), 11.25 (s, 1H, NH)	211
2k	7.24-8.40 (m, 7H, Ar-H), 10.34 (s, 1H, NH)	240

specified times. The progress of reaction was monitored at 30 s intervals by TLC. After completion of the reaction, the mixture was poured into boiling water. The solid obtained was boiled with sodium carbonate solution, filtered, dried and purified by recrystallization from a mixture of aniline and acetic acid. The spectral and analytical data of the compounds are given in **Table III**.

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