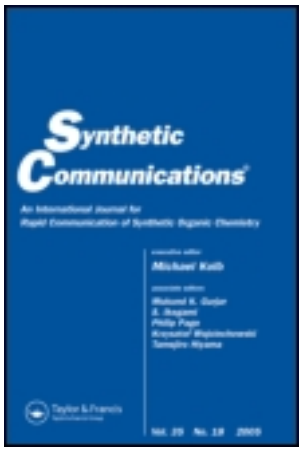

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MICROWAVE SYNTHESIS OF 9-SUBSTITUTED ACRIDINE DERIVATIVES

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ABSTRACT

Synthesis of 9-substituted acridine derivatives from diphenyl amine and appropriate carboxylic acid catalyzed by zinc chloride was carried out in the microwave reactor. Application of the microwave irradiation shortened the reaction time from 20–40 h to 5 min affording good (60–80%) yields of the products.

Acridine derivatives are frequently used in the industry, especially at production of dyes,[1,2] but also in pharmaceutical industry because acridine moiety is present in several antidepresives,[3] antimalarial and antitumor agents.[4,5] The general means of producing 9-alkyl- and 9-arylacridines is through the Bernthsen reaction,[6] which is heating of diphenylamine, aliphatic or aromatic carboxylic acid and $ZnCl_2$ at 200–220°C over a long reaction time. The yields achieved by this method are rather low, up to 30%. Graef[7] has modified this method using esterchlorides of dicarboxylic acids as the reagents. An interesting paper[8] was published very recently. The authors

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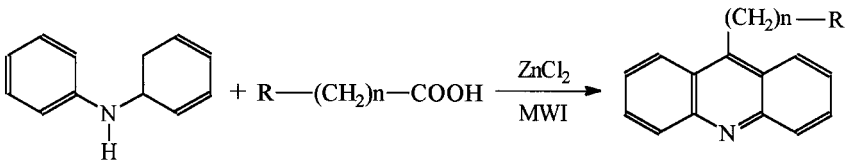
modified the Bernthsen's method by addition of 20% H_2SO_4 to the reaction mixture after heating it at 230°C for 20–40 h. This methodology raised the yields of acridinylalkanoic acids in some cases up to 80%. The beneficial effect of microwave irradiation on several organic reactions is well documented[9–14] and we decided therefore to explore if it could be applied also for synthesis of 9-substituted acridines.

The reaction route of the 9-substituted acridine derivatives is depicted in the scheme.



Scheme. R = COOH, n = 2, 3, 4, 8 or R = Aryl, n = 1

From the results given in Table 1 follows that reasonable yields (59–80%) of the products were achieved after only 3.5–6 min of microwave irradiation using the same reactant ratio as described in the literature[8] for dicarboxylic acids and in the literature[15] for arylacetic acids. The yields we achieved for dicarboxylic acids (Table 1, Entries 1, 2, 4–6) were 10–20% lower than described. This fact can be explained by the very short reaction time, but this time cannot be prolonged, as an extremely exothermic reaction leading to a polymer material was observed after prolonging the MWI. On the other hand, we did not observe exothermic polymerization when this reaction was carried out conventionally at 230°C (Entry 3).

It can be concluded that the exothermic reaction is not due to thermolysis, implying that specific (non-thermal) microwave effect was involved. It is known that microwave absorption depend on the polarity of the system.[16] The (3-acridin-9-yl)alkanoic acids contain the polar groups, they can absorb microwaves and, in addition, another reaction leading to polymer materials take place. Probably due to the very short reaction time we did not observe the formation of α,ω-*bis*(acridin-9-yl)alkenes, as presented in the literature,[8] even when the molar ratio diphenylamine : dicarboxylic acid : $ZnCl_2$ was changed from 1 : 3 : 5 to 2.5 : 1 : 5.

In conclusion, application of the microwave irradiation considerably enhanced the synthesis of 9-substituted acridine derivatives beginning with diphenylamine and appropriate carboxylic acids under $ZnCl_2$ catalysis.

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Table 1. Microwave-Assisted Preparation of 9-Substituted Acridine Derivatives $P = 120\,W$, $T_{fin} = 200^{\circ}C$

Entry	Compound	R	n	Time (min : s)	Yield (%)	M.P. (°C)	M.P.[ref.] (°C)
1	IIIa	COOH	1	8 : 20	57	decomp.	–
2	IIIb	COOH	2	6 : 00	80	308–9	305[17]
3*	IIIb	COOH	2	6 : 00	64	308–9	305[17]
4	IIIc	COOH	3	4 : 53	71	218–22	220[18]
5	IIId	COOH	4	4 : 17	72	266–70	265–69[7]
6	IIIe	COOH	8	3 : 50	60	207–9	207–8[7]
7	IIIf	phenyl	1	5 : 00	75	174–5	173[15]
8	IIIg	*p*-tolyl	1	5 : 00	60	146–7	–
9	IIIh	1-naphthyl	1	5 : 00	50	184–6	–

*The mixture was kept in an oil bath preheated to 230°C.

EXPERIMENTAL

The experiments were carried out in the SYNTHEWAVE 402, PROLABO microwave reactor. All initial materials were commercial reagents. The products were characterized by their physical properties and ^{1}H NMR spectral characteristics. Melting points were determined on Kofler apparatus and are not corrected. ^{1}H NMR spectra were measured at 300 MHz on Varian Gemini spectrometer in hexadeuteriodimethyl sulphoxide with hexamethyldisiloxane as an internal standard.

Preparation of ω-(Acridin-9-yl)alkanoic Acids (IIIa–e)

The mixture of diphenylamine **I** (0.01 mol), dikarboxylic acid **IIa–e** (0.03 mol) and anhydrous $ZnCl_2$ (2.0 g, 0.05 mol) was irradiated in the microwave reactor (120 W input power) for the time given in Table 1 until the temperature of the reaction mixture reached 200°C. The 20% aqueous solution of H_2SO_4 (50 ml) was then added to the reaction mixture, which was afterwards heated until all of the solid mass was dissolved. The aqueous solution of ammonia (25%) was then added to the cooled reaction mixture until neutralisation. The solid material was filtered off and dissolved continually into methanol. The residue left after vacuum evaporation of the methanol was pure product **IIIa–e**. The results are given in Table 1.

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Preparation of 9-Arylalkylacridines (IIIf–h)

The mixture of diphenylamine **I** (0.01 mol), arylacetic acid **IIf–h** (0.02 mol) and anhydrous $ZnCl_2$ (0.03 mol) was irradiated in the microwave reactor (120 W) until the temperature of the reaction mixture reached 200°C (5 min). Then the reaction mixture was dissolved in hot ethanol (100 ml) and then filtered. After evaporization of the solvent the crude product **IIIf–h** was recrystalized from benzene. The results are given in Table 1.

^{1}H NMR Spectra of 9-Substituted Acridines **IIIa–h**
((δ) = ppm, (*J*) = Hz)

IIIa: 3.31 (s, 2H, C**H**$_2$-COOH), 7.94–7.99 (m, 2H, Ar-**H**), 8.29–8.35 (t, 2H, Ar-**H**), 8.55 (d, 2H, *J* = 9.0, Ar-**H**), 8.80 (d, 2H, *J* = 9.0, Ar-**H**).

IIIb: 2.66 (t, 2H, *J* = 3.04, C**H**$_2$), 3.92 (t, 2H, *J* = 3.07, C**H**$_2$-COOH), 7.63–7.68 (m, 2H, Ar-**H**), 7.82–7.87 (m, 2H, Ar-**H**), 8.15 (d, 2H, *J* = 9.0, Ar-**H**), 8.41 (d, 2H, *J* = 9.0, Ar-**H**).

IIIc: 1.92–2.39 (m, 4H, 2 × C**H**$_2$), 3.68 (t, 2H, *J* = 8.1, C**H**$_2$), 7.59–7.64 (m, 2H, Ar-**H**), 7.79–7.82 (m, 2H, Ar-**H**), 8.12 (d, 2H, *J* = 8.7, Ar-**H**), 8.51 (d, 2H, *J* = 8.7, Ar-**H**).

IIId: 1.67–1.80 (m, 4H, 2 × C**H**$_2$), 2.29 (t, 2H, *J* = 7.2, C**H**$_2$), 3.66 (t, 2H, *J* = 7.2, C**H**$_2$), 7.61–7.67 (m, 2H, Ar-**H**), 7.79–7.84 (m, 2H, Ar-**H**), 8.12 (d, 2H, *J* = 8.7, Ar-**H**), 8.33 (d, 2H, *J* = 8.7, Ar-**H**).

IIIe: 1.25–1.75 (m, 12H, 3 × CH_2), 2.11 (t, 2H, *J* = 7.5, CH_2), 3.64 (t, 2H, *J* = 7.5, CH_2), 7.61–7.66 (m, 2H, Ar-**H**), 7.81–8.87 (m, 2H, Ar-**H**), 8.13 (d, 2H, *J* = 9.0, Ar-**H**), 8.39 (d, 2H, *J* = 9.0, Ar-**H**).

IIIf: 5.11 (s, 2H, CH_2), 7.13–7.21 (m, 5H, Ar-**H**), 7.63–7.68 (m, 2H, Ar-**H**), 7.83–7.87 (m, 2H, Ar-**H**), 8.18 (d, 2H, *J* = 8.7, Ar-**H**), 8.45 (d, 2H, *J* = 8.7, Ar-**H**).

IIIg: 2.27 (s, 3H, CH_3), 5.05 (s, 2H, CH_2), 6.96 (d, 2H, *J* = 8.1, Ar-**H**), 7.05 (d, 2H, *J* = 8.1, Ar-**H**), 7.61–7.66 (m, 2H, Ar-**H**), 7.91–7.97 (m, 2H, Ar-**H**), 8.32 (d, 2H, *J* = 9.0, Ar-**H**), 8.65 (d, 2H, *J* = 8.7, Ar-**H**).

IIIh: 5.52 (s, 1H, CH_2), 6.20 (d, 1H, Ar-**H**), 7.11 (m, 1H, Ar-**H**), 7.50–7.56 (m, 2H, Ar-**H**), 7.65–7.71 (m, 2H, Ar-**H**), 7.74–7.87 (m, 4H, Ar-**H**), 8.01 (d, 1H, *J* = 8.1, Ar-**H**), 8.18 (d, 2H, *J* = 8.7, Ar-**H**), 8.23 (d, 2H, *J* = 8.7, Ar-**H**), 8.65 (d, 2H, *J* = 8.7, Ar-**H**).

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