MICROWAVE-ASSISTED SYNTHESIS OF BENZOFURAN ANALOGS OF FENAMATES AS NON STEROIDAL ANTI-INFLAMMATORY AGENTS

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ABSTRACT

A series of benzofuran analogs of anthranilic acid derivatives were easily synthesized by microwave irradiation and conventional heating method. The microwave irradiation method gives the comparable yield as that of conventional heating with a shorter reaction time. All the new compounds have been characterized by spectral data and screened for anti-inflammatory activity.

Key words: benzofuran, anthranilic acid, anti-inflammatory activity, microwave irradiation.

INTRODUCTION

The application of microwave as an energy source for chemical reactions and processes has been extensively studied during recent years¹. The combination of solvent-free conditions and microwave irradiation leads to large reduction in reaction time, enhancement in conversion, easier work up and sometimes in selectivity with several advantages of an ecofriendly approach². Further, its unique capabilities allow its applications in transformations which are difficult or impossible to carry out by means of conventional method³.

The fenamates are the class of the NSAIDs that have common structural features of an N-arylanthranilic acid such as mefenamic acid, meclofenamic acid and flufenamic acid⁴⁻⁶. These are the first line therapeutic agents for the clinical treatment of various inflammatory disorders⁷. In view of this several anthranilic acid derivatives have been prepared for investigation of anti-inflammatory activity. Many such compounds were found to possess potent anti-inflammatory⁸⁻¹⁰, cardiovascular¹¹ and analgesic¹² activities. Anthranilic acid derivatives are known to act by blocking the metabolism of arachidonic acid by inhibiting the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. Inhibiting CO may also increase the conversion of arachidonic acid to proinflammatory leukotrienes via the enzyme 5-Lipoxygenase (5-LO). Literature survey shows that modification of carboxylic group in anthranilic acid markedly modulates the activity. The modification of the carboxylic acid functionality not only retained the CO inhibitory activity of the parent but also inhibited 5-LO¹³⁻¹⁴.

Compounds containing benzofuran nucleus are widely distributed in nature amongst the plant kingdom. Such compounds are often associated with useful biological activities. This stimulated our interest in the synthesis of benzofuran analogs of anthranilic acid derivatives in which the benzene moiety of anthranilic acid is replaced by benzofuran moiety.

Ethyl 3-hydroxybenzofuran-2-carboxylate was prepared by single pot synthesis¹⁵ from methyl salicylate and diethylbromo malonate served as key starting material for the synthesis of target molecules. The reaction of this with various aromatic amines in presence of catalytic amount of hydrochloric acid produced ethyl-3-arylaminobenzofuran-2-carboxylates. This needs heating of the reaction mixture for 90-95°C for 9 hrs. This is a very time consuming reaction. The same reaction mixture when irradiated in microwave for different period of time at 500 W power gives the desired product. As compared to conventional heating method the microwave irradiation method for synthesis of ethyl -3-arylaminobenzofuran-2-carboxylates is simple and less time consuming. As this reaction does not involve use of any solvents so there is no any risk of explosion of the solvents during microwave irradiation.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The FT-IR spectra were recorded in KBr on SHIMADZU FTIR-8400S spectrophotometer. ¹H NMR spectra were recorded in CDCl₃ on a Varian Mercury YH-300, using TMS as an internal standard. Microwave irradiations were carried out in a LG intellocook MS-1921HE with RF output of 700W.

SCHEME

Preparation of Ethyl 3-arylaminobenzofuran-2-carboxylates (3a-h) by conventional heating method:

An intimate mixture of **1** (2.0g, 0.01 mol), aromatic amine (0.011 mol) and 3-4 drops of concd. hydrochloric acid was left overnight at room temperature and then heated at 90-95°C for 9 hr. The reaction mixture was cooled and extracted with ether (3x20ml). The combined organic layer was washed successively with 2N hydrochloric acid and aqueous sodium hydroxide (10%) to remove the unreacted starting materials, dried over anhydrous sodium sulphate. Removal of the solvent by evaporation gave the product, which was crystallized from aqueous ethanol.

Preparation of Ethyl 3-arylaminobenzofuran-2-carboxylates (3a-h) by Microwave irradiation method:

An intimate mixture of **1** (2.0g, 0.01 mol), aromatic amine (0.011 mol) and a 3-4 drop of concd. hydrochloric acid was transferred to the conical flask. The reaction mixture was subjected to Microwave irradiation for different time period as mentioned in table No-1 under 500W power. Then reaction mixture was cooled and extracted with ether (3x20ml). The combined organic layer was washed successively with 2N hydrochloric acid and aqueous sodium hydroxide (10%) to remove the unreacted starting materials and dried over anhydrous sodium sulphate. Removal of the solvent by evaporation gave the product, which was crystallized from aqueous ethanol. The characterization data is given in Table No-1 and Table No-2.

BIOLOGICAL ACTIVITY¹⁶⁻¹⁸

All the compounds were screened for anti-inflammatory activity by carrageenan induced rat paw edema method. Diclofenac sodium was used as standard. Rats were divided into control, standard and different test groups comprising of six animals in each group. They were fasted overnight with free access to water before experiment. In all groups acute inflammation was induced by subplantar injection of 0.1 ml of freshly prepared 1% suspension of carrageenan in the right hind paw of the rats and paw volume was measured Plethysmometrically at 0 hour and 3 hr after carrageenan injection. Rats of test groups were administered orally with test compounds 100 mg/kg and the standard group with diclofenac 100 mg/kg orally in 2% aqueous acacia one hr

before injection of carrageenan. Control group received only vehicle. Mean difference in paw volume was measured and percentage of inhibition of edema was calculated and given in Table No-4.

Table No- 1. Physical, analytical data of the compounds 3a-h

Compound	MP °C	Yield (%) Heating	Yield (%) MWI	Power W	Time Heating Min	Time MWI Min
3a	84	15	3	500	540	2
3b	128	27	27	500	540	2
3c	125	63	70	500	540	2
3d	98	23	20	500	540	4
3e	103	34	45	500	540	4
3f	111	15	13	500	540	5
3g	98	33	25	500	540	5
3h	102	64	57	500	540	4

All the compounds were recrystallised from aqueous ethanol.

Table No-2. Elemental analysis data for the compounds 3a-h

Sr. No	Compounds	Molecular formula	Elemental analysis Found (calculated) (%)		
			C	H	N
01	3a	C ₁₇ H ₁₅ NO ₃	72.50 (72.59)	5.25 (5.33)	4.78 (4.98)
02	3b	C ₁₈ H ₁₇ NO ₃	73.05 (73.22)	5.62 (5.76)	4.61 (4.74)
03	3c	C ₁₇ H ₁₄ NO ₃ Cl	64.55 (64.65)	4.35 (4.44)	4.32 (4.44)
04	3d	C ₁₈ H ₁₇ NO ₃	73.20 (73.22)	4.52 (4.74)	4.58 (4.74)
05	3e	C ₁₇ H ₁₃ NO ₃ ClF	51.70 (51.71)	3.12 (3.20)	4.02 (4.20)
06	3f	C ₁₇ H ₁₄ NO ₃ Cl	64.56 (64.65)	4.30 (4.44)	4.31 (4.44)
07	3g	C ₂₁ H ₁₇ NO ₃	76.05 (76.13)	5.10 (5.13)	4.05 (4.22)
08	3h	C ₁₈ H ₁₇ NO ₄	69.32 (69.45)	5.34 (5.40)	4.37 (4.50)

Table No- 3. Spectral data of the Compounds 3a-h

Compound	IR	¹ H NMR
3a	3360, 3440 (NH), 1685(C=O), 1610(C=N),1575(C=C), 1100-1120 (C-O-C)	1.5 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.6 (s, 1H, NH), 4.5 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7-7.8 (m, 9H, ArH)
3b	3350, 3450 (NH), 1680 (C=O), 1620 (C=N),1580 (C=C), 1095,1120 (C-O-C)	1.5 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.6 (s, 1H, NH), 2.4 (s, 3H, ArCH ₃), 4.5 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7-7.8 (m, 8H, ArH)
3c	3350(NH), 1685(C=O),1610(C=N), 1575(C=C),1100-1120(C-O-C)	1.4 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.7 (s, 1H, NH), 4.4 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7.1-7.8 (m, 8H, ArH)
3d	3190, 3315(NH), 1670(C=O), 1600(C=N),1580(C=C), 1095, 1120(C-O-C)	1.6 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.6 (s, 1H, NH), 2.4 (s, 3H, ArCH ₃), 4.5 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7-7.8 (m, 8H, ArH)
3e	3359(NH), 1666(C=O), 1604(C=N), 1577(C=C), 1101(C-O-C)	1.4 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.6 (s, 1H, NH), 4.4 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7-7.8 (m, 7H, ArH)
3f	3355(NH), 1670(C=O), 1610(C=N), 1580(C=C),1105(C-O-C)	1.4 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.7 (s, 1H, NH), 4.4 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7.1-7.8 (m, 8H, ArH)
3g	3350(NH), 1680(C=O), 1610(C=N), 1575(C=C), 1100, 1120(C-O-C)	1.6 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.5 (s, 1H, NH), 4.5 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 7-7.8 (m, 9H, ArH)
3h	3355(NH), 1670(C=O), 1605(C=N), 1570(C=C), 1100, 1125(C-O-C)	1.5 (t, 3H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 1.7 (s, 1H, NH), 3.9 (s, 3H, OCH ₃), 4.5 (q, 2H, CH ₂ CH ₃ , <i>J</i> =7.1 Hz), 6.9-7.7 (m, 11H, ArH)

Table No- 4. Biological activity data of the compounds 3a-h

Sr.No.	Compounds	Dose mg/kg	Mean difference in paw volume+ S.E after 3 hrs(ml)	Percentage of inhibition
01	Control	-	0.90±0.03*	-
02	Diclofenac	100	0.14±0.01*	84
03	3a	100	0.37±0.02*	58
04	3b	100	0.41±0.02*	54
05	3c	100	0.34±0.01*	62
06	3d	100	0.57±0.05*	36
07	3e	100	0.31±0.02*	65
08	3f	100	0.36±0.01*	60
09	3g	100	0.44±0.05*	51
10	3h	100	0.39±0.02*	56

Values are expressed as mean ± SEM (n=5)

* P < 0.001 when compared to control group

RESULTS AND DISCUSSION

All the compounds were synthesized by both conventional heating and microwave irradiation method. The conventional heating method is very time consuming while microwave irradiation method gives comparable yield with shorter reaction time. Though the reaction yields with MW irradiation were low there is no increase in yield observed after prolonged MW irradiation. All the compounds were characterized for IR and ¹H NMR spectral analysis and spectral data for compounds **3a-h** is given in table No-3. IR spectra of the compounds **3a-h** exhibited an absorption band in the region of 3400 cm⁻¹ due to NH and strong band in the region of 1700cm⁻¹ due to ester carbonyl. The ¹H NMR spectral data revealed a deuterium exchangeable broad singlet at δ 1.6-1.7 due to NH proton. All the new compounds have been screened for anti-inflammatory activity. Some of the compounds showed considerably anti-inflammatory activity compared to diclofenac sodium.

Substituted aromatic amines gives better reaction yields as compared to aniline. The para substituted aromatic amines gives the highest yield compared to ortho and bisubstituted aromatic amine. While the compound **3e** contain the bisubstituted aromatic amine moiety that gives the highest anti-inflammatory activity amongst all compounds synthesized.

CONCLUSION

In conclusion, we have described a highly efficient microwave-induced procedure for the preparation of Ethyl 3-arylaminobenzofuran-2-carboxylates from Ethyl 3-hydroxybenzofuran-2-carboxylate. This occurs remarkably fast, under mild condition, using inexpensive reagents and a household microwave oven as the irradiation source. The advantages of this microwave induced environmentally benign and safe protocol include a simple reaction set-up, application of commercially available reagents and catalyst with short reaction time.

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