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Note

9Microwave assisted rapid and efficient synthesis of 2,1-benzoisoxazoles

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A simple extremely fast and high yielding protocol has been developed for the synthesis of 2,1-benzisoxazoles under microwave irradiation.

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Acceleration of organic reactions by microwave dielectric heating has shown its utility in organic synthesis[1-5]. This is due to high reaction rates with formation of cleaner products, operational simplicity and is environmentally co-friendly. The conventional method for the preparation of title compounds which was reported from our laboratories earlier[6,7] involves the preparation of substituted cyclohexanones by Knoevenagel condensation of acetylacetone or ethyl acetoacetate with aromatic aldehydes in ethyl alcohol in the presence of piperidine followed by cyclisation to 2,1-benzoisoxazoles in refluxing alcohol with hydroxylamine hydrochloride. This method is not satisfactory because it requires very longer time period and yields are poor and is not environmentally benign also. In view of this and in continuation of our work on the use of microwaves in isoxazole synthesis[8,9], we have developed a better and efficient methodology for the synthesis of 2,1-benzoisoxazoles under microwave irradiation. It is noteworthy that the reaction which required 6-18 hr in conventional method in both steps, was completed within 1 minute under microwave conditions and yields have been remarkably improved from 30-45% to 80-95%.

Knoevenagel condensation of acetylacetone or ethyl acetoacetate with aromatic aldehydes in the presence of piperidine under microwave irradiation in 2:1 molar ratio in ethanol for 1 min afforded 3-aryl-2,4-diacetyl/dicarbethoxy-5-hydroxy-5-methyl-cyclohexanones **1** in excellent yields (**Table I**).

The reaction is clean and efficient. Furthermore, the products were obtained with a high degree of purity.

Table I — Substituted cyclohexanones **1**

Compd	R	Ar	Reaction period		MWI	Yield (%)	m.p. (lit[6,7] m.p °C)
			Microwave heating (min)	Conventional method (hr)	Conventional mode		
1a	CH_3	C_6H_5	1	2	95	50	161[a] (162)
1b	CH_3	4-$CH_3C_6H_4$	1	2	95	45	153[b] (153)
1c	CH_3	4-$OCH_3C_6H_4$	1	2	90	50	175[b] (176)
1d	CH_3	4-ClC_6H_4	1	2	95	55	187[b] (186)
1e	CH_3	4-$NO_2C_6H_4$	1	2	85	30	184[a] (184)
1f	CH_3	3-$NO_2C_6H_4$	1	2	85	35	203[a] (203)
1g	CH_3	3-OCH_3-4-OHC_6H_3	1	2	95	55	176[c] (175)
1h	CH_3	2,4-$Cl_2C_6H_3$	1	2	90	50	198[b] (197)
1i	OC_2H_5	C_6H_5	1	18	95	40	155[d] (155)
1j	OC_2H_5	4-$OCH_3C_6H_4$	1	18	95	45	131[d] (130)
1k	OC_2H_5	2-OHC_6H_4	1	18	90	50	115[d] (115)
1l	OC_2H_5	3-OCH_3-4-OHC_6H_3	1	18	90	50	170[d] (170)
1m	OC_2H_5	4-$CH_3C_6H_4$	1	18	95	40	129[d] (130)

Solvent of crystallisation: (a) benzene -ethyl acetate (b) pet. ether-benzene (c) benzene (d) aq. methanol

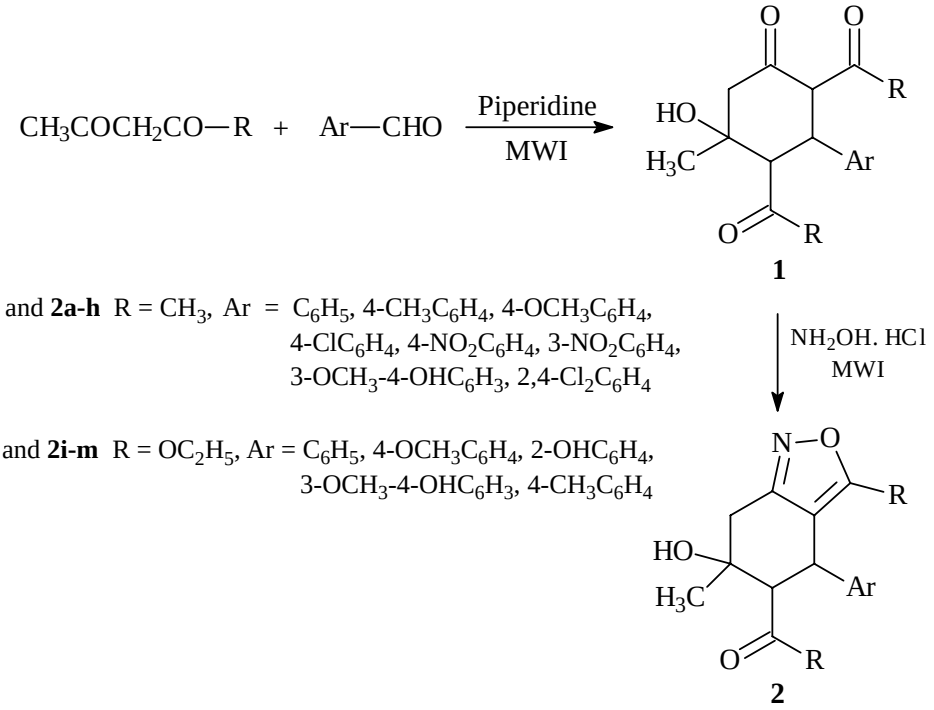
The cyclohexanones **1** containing a β-dicarbonyl system on reaction with hydroxylamine hydrochloride in ethanol under microwave irradiation, underwent cyclisation to give 4-aryl-5-acetyl/carbethoxy-3-methyl/ethoxy-6-hydroxy-6-methyl-4,5,6,7-tetrahydro-2,1-benzoisoxazoles **2** in quantitative yields (**Table II, Scheme I**).

It is very important to note that the conventional method employed for the preparation of both the cyclohexanones **1** and 2,1-benzoisoxazoles **2** required very long reaction times ranging from 6-18 hr and yields are very poor. There is a manifold decrease in the reaction time under microwave environment and yields are excellent

Table II — 2,1-Benzisoxazoles **2**

Compd	R	Ar	Reaction period		Yield (%)		m.p. (lit[6,7] m.p. °C)
			Microwave heating (min)	Conventional method (hr)	MWI	Conventional mode	
2a	CH_3	C_6H_5	1	8	95	50	145[a] (144)
2b	CH_3	4-$CH_3C_6H_4$	1	8	95	55	170[b] (170)
2c	CH_3	4-$OCH_3C_6H_4$	1	8	90	60	151[b] (150)
2d	CH_3	4-ClC_6H_4	1	8	95	45	153[c] (153)
2e	CH_3	4-$NO_2C_6H_4$	1	8	85	30	220[d] (220)
2f	CH_3	3-$NO_2C_6H_4$	1	8	85	35	228[b] (227)
2g	CH_3	3-OCH_3-4-OHC_6H_3	1	8	90	50	234[d] (235)
2h	CH_3	2,4-$Cl_2C_6H_3$	1	8	95	45	213[b] (215)
2i	OC_2H_5	C_6H_5	1	12	90	50	160[e] (160)
2j	OC_2H_5	4-$OCH_3C_6H_4$	1	12	95	55	195[e] (195)
2k	OC_2H_5	2-OHC_6H_4	1	12	95	50	211[e] (210)
2l	OC_2H_5	3-OCH_3-4-OHC_6H_3	1	18	90	45	230[e] (232)
2m	OC_2H_5	4-$CH_3C_6H_4$	1	12	95	50	204[e] (205)

Solvent of crystallisation: (a) aq. alcohol (b) pet. ether-benzene; (c) alcohol -acetone (d) benzene-ethyl acetate (e) aq. ethanol



Scheme I

(**Tables I** and **II**). The reaction is extremely fast, clean and neat with no side products.

All the products were characterized by comparing with authentic samples (m.p. and IR). The compounds **1a**, **1i** and **2a**, **2i** were characterized by IR, ^{1}H NMR and mass spectral data which are in agreement with earlier data[6, 7].

In conclusion, we have developed an extremely fast and high yielding protocol for the synthesis of 2,1-benzisoxazoles under microwave irradiation. High yields, low reaction times, mild reaction conditions, and easy set-up and work-up are advantages of this methodology over the conventional method.

This reaction may have wide applicability in building a variety of heterocycles by choosing cyclohexanones as a synthon. Hence, it may attract many synthetic organic chemists for utility of cyclohexanones in organic synthesis.

Experimental Section

Melting points were determined in open capillaries using cintex melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum BX-series FT-IR spectrometer as KBr discs; ^{1}H NMR (200 MHz) spectra on a Varian Gemini-200 spectrometer using TMS as internal standard; and EIMS on a Joel D-300 spectrometer at 70 eV. The reactions were carried out in a domestic microwave oven (LG-MS 257 PL) at 2450 MHz (900 watts).

General procedure for preparation of substituted cyclohexanones 1. Aromatic aldehyde (0.05 mole), acetyl acetone or ethyl acetoacetate (0.1 mole) and piperidine (0.05 mole) were taken in ethanol (10 mL) in Erlen Meyer flask capped with a funnel, placed in a microwave oven and irradiated at 260 watts for 1 min. The reaction mixture was allowed to attain room temperature and solid separated was filtered and washed with cold alcohol. The product was recrystallized from suitable solvent (**Table I**).

General procedure for preparation of 2,1-benzoisoxazoles 2. A mixture of **1** (0.05 mole) and hydroxylamine hydrochloride (0.05 mole) were taken in ethanol (10 mL) in Erlen Meyer flask capped with a funnel, placed in a microwave oven and irradiated at 260 watts for 1 min. After cooling, the reaction mixture was poured onto crushed ice, and isolated product was crystallized from suitable solvent (**Table II**).

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