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Note

Microwave assisted rapid and efficient synthesis of new 3-ethoxy-4,6-diaryl-4,5-dihydro-2,1-benzisoxazoles

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A simple, extremely fast and efficient synthesis of new 3-ethoxy-4,6-diaryl-4,5-dihydro2,1-benzisoxazoles has been achieved under microwave irradiation.

Keywords: Microwave synthesis, new 2,1-benzisoxazoles

Microwave dielectric heating is rapidly becoming popular in organic synthesis as a source of thermal energy, for organic reactions in organic solvents or dry media[1-6]. This is due to high reaction rates with formation of cleaner products, operational simplicity and is environmental co-friendly. The technique is believed to be a step towards green chemistry[7]. The usage of high dielectric solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) for rate enhancements are believed to be due to rapid super heating of the polar solvents[8]. The approach of using microwaves for chemical synthesis in polar solvents has blossomed in to a useful technique for several reactions of synthetic importance[9-11]. As a sequel to our work on microwave assisted synthesis of isoxazole derivatives[12-16], we now, wish to report an efficient and rapid synthesis of some new 2,1-benzisoxazoles.

The reaction of ethyl acetoactate **1** with benzylidene acetophenones (chalcones) **2** in the presence of piperidine under microwave irradiation in ethanol for 1 min afforded the corresponding ethyl-4,6-diaryl-2-oxo-cyclohex-3-ene-1-carboxylates in quantitative yields (80-90%). When the same reaction was carried out under conventional heating method in ethanol, it took nearly 4 hr for completion (monitored with TLC) and the yields only moderate (40-50%) **(Table I)**.

Ethyl acetoacetate undergoes Michael addition with chalcone in the presence of piperdine to give an addition product. Later, this undergoes intramolecular aldol reaction in the presence of piperdine to give cyclohexanones (**Scheme I**).

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

The cyclohexanones **3** containing β-dicarbonyl system on reaction with hydroxylamine hydrochloride in ethanol under microwave irradiation for 1 min underwent cyclization to afford 3-ethoxy-4,6-diaryl-4,5-dihydro-2,1-benzisoxazoles **4** in excellent yields (85-95%)(**Scheme II**). When the same reaction was carried out under conventional heating method in ethanol, it took 4-6 hr (monitored with TLC) for completion and the yields are between 40-50% only **(Table II)**.

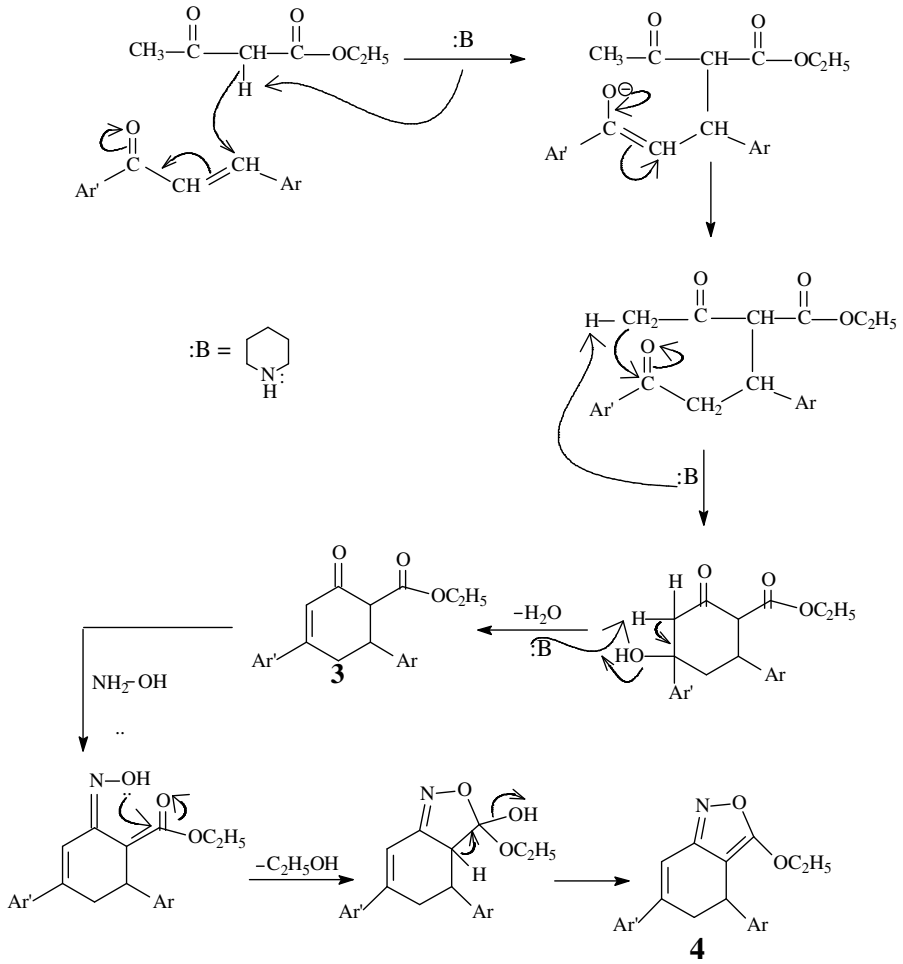
The β-keto ester **3** may cyclize either to isoxazolone **5** or to isoxazole **4**. Among the likely compounds, the actually formed one has been identified to be **4** by the mass spectrum, which gave the molecular ion peak $(M+H)^+$ at *m/z* 318. Further more, ^{1}H NMR spectrum of **4** shows ethyl group proton signals as triplet and quartet at δ 1.0 and 4.0 respectively. The IR spectrum of **4** did not show lactone carbonyl absorption ruling out the formation of **5**. Besides the spectral data, the product has shown negative ferric colour test supporting that the product is not isoxazolone **5**, which readily enolizes giving the ferric reaction. This is also in agreement with our earlier observation[17].

The formation of cyclohexanones **3** was supported by IR, ^{1}H NMR and mass spectral data. IR spectrum of **3** showed two strong absorptions at 1690 and 1740 cm^{-1} for the ketonic and ester carbonyl functional groups respectively. ^{1}H NMR spectrum of **3** exihibited a triplet at δ 1.0 and quartet at δ 4.0 due to ethoxy group protons. The benzylic protons and methine proton appeared as a multiplet at δ 3.6, where-as ethylenic proton appeared as a singlet at δ 6.5. Aromatic protons resonated as a multiplet between 7.2-7.6.The mass spectrum of **3** showed the molecular ion peak $[M+H]^+$ at *m/z* 321 supporting the formation of cyclohexanone.

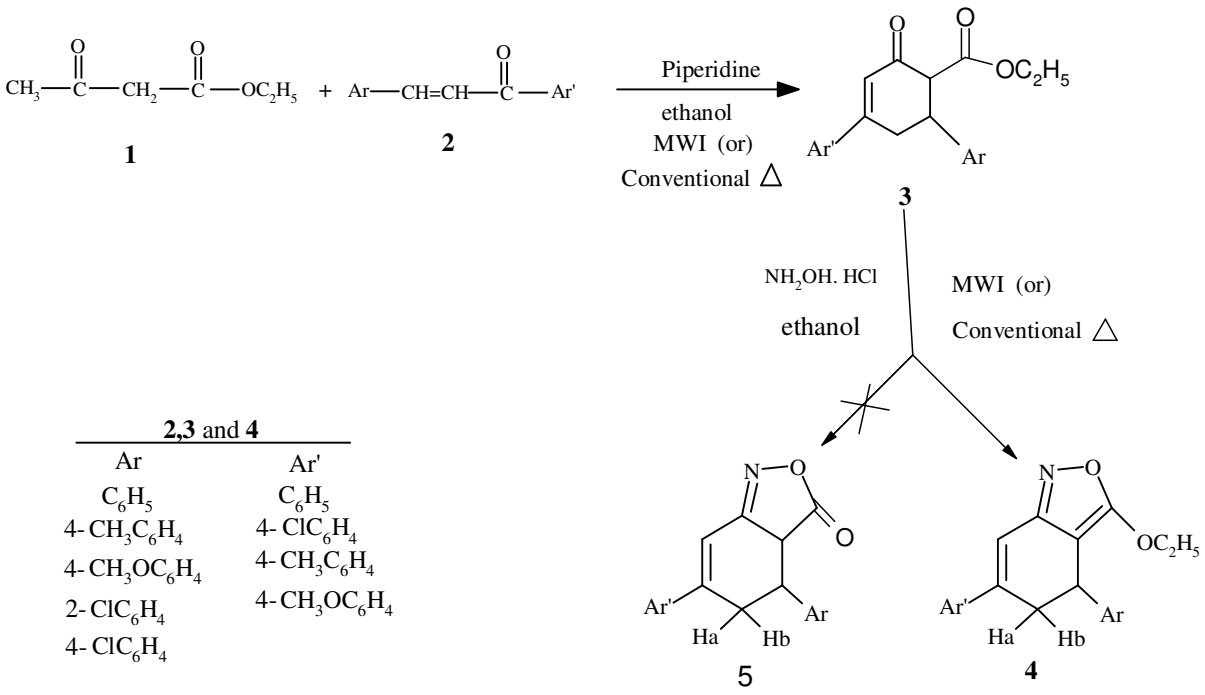
The isoxazole **4** structure was confirmed on the basis of IR, ^{1}H NMR and mass spectral data. IR spectrum of **4** did not show absorption due to

Table I — Characterization data of compound **3**

S.No	Ar	Ar'	m.p. °C	Reaction Period		Yield(%)		Mol. Formula	Found (%) (Calcd.)		
				MWI (min)	Conventional (hr)	MWI	Conventional		C	H	N
1	C_6H_5	C_6H_5	150	1	2	90	40	$C_{21}H_{20}O_3$	78.71 (78.75	6.22 6.25	— —)
2	4-$CH_3C_6H_4$	C_6H_5	135	1	2	80	40	$C_{22}H_{22}O_3$	79.00 (79.04	6.52 6.58	— —)
3	4-$CH_3OC_6H_4$	C_6H_5	165	1	2	85	40	$C_{22}H_{22}O_4$	75.38 (75.42	6.22 6.28	— —)
4	2-ClC_6H_4	C_6H_5	190	1	4	90	50	$C_{21}H_{19}O_3Cl$	71.12 (71.18	5.30 5.36	— —)
5	4-ClC_6H_4	C_6H_5	170	1	4	90	40	$C_{21}H_{19}O_3Cl$	71.15 (71.18	5.33 5.36	— —)
6	C_6H_5	4-ClC_6H_4	210	1	3	85	40	$C_{21}H_{19}O_3Cl$	71.14 (71.18	5.33 5.36	— —)
7	C_6H_5	4-$CH_3C_6H_4$	140	1	2	80	40	$C_{22}H_{22}O_3$	79.01 (79.04	6.51 6.58	— —)
8	C_6H_5	4-$CH_3OC_6H_4$	158	1	2	90	50	$C_{21}H_{20}O_3$	75.40 (75.42	6.23 6.28	— —)



Scheme I



Scheme II

Table II — Characterization data of compound **4**

S.No	Ar	Ar'	m.p. °C	Reaction Period		Yield(%)		Mol. Formula	Found (%) (Calcd.)		
				MWI (min)	Conventional (hr)	MWI	Conventional		C	H	N
1	C_6H_5	C_6H_5	180	1	6	95	50	$C_{21}H_{19}NO_2$	79.42 (79.49	5.93 5.99	4.38 4.41)
2	4-$CH_3C_6H_4$	C_6H_5	150	1	4	95	45	$C_{22}H_{21}NO_2$	79.71 (79.75	6.31 6.34	4.20 4.22)
3	4-$CH_3OC_6H_4$	C_6H_5	170	1	4	90	45	$C_{22}H_{21}NO_3$	76.02 (76.08	6.02 6.05	4.00 4.03)
4	2-ClC_6H_4	C_6H_5	215	1	6	80	50	$C_{21}H_{18}NO_2Cl$	71.75 (71.79	5.10 5.12	3.92 3.98)
5	4-ClC_6H_4	C_6H_5	190	1	6	95	50	$C_{21}H_{18}NO_2Cl$	71.76 (71.79	5.08 5.12	3.90 3.98)
6	C_6H_5	4-ClC_6H_4	220	1	5	95	45	$C_{21}H_{18}NO_2Cl$	71.74 (71.79	5.09 5.12	3.94 3.98)
7	C_6H_5	4-$CH_3C_6H_4$	158	1	4	90	40	$C_{22}H_{21}NO_2$	79.70 (79.75	6.30 6.34	4.19 4.22)
8	C_6H_5	4-$CH_3OC_6H_4$	165	1	5	85	45	$C_{22}H_{21}NO_3$	76.05 (76.08	6.03 6.05	4.01 4.03)

carbonyl functional group ruling out the formation of structure **5**. ^{1}H NMR spectrum of **4** showed ethoxy proton signals as triplet and quartet at δ 1.0 and 4.0 clearly supporting the structure **4**. The benzylic proton appeared as a multiplet at δ 3.8, whereas the methylene protons of the ring resonated at δ 2.8 as a multiplet. The mass spectrum confirms the structure **4** by showing the molecular ion peak $(M+H)^+$ at *m/z* 318.

It is very important to note that the conventional method employed for the preparation of cyclohexanones **3** and 2,1-benzisoxazoles **4** required very long reaction times (4-6 hr) and the yields are poor. There is a remarkable decrease in the reaction time under microwave environment and the yields are excellent (**Tables I** and **II**). All the reactions are extremely fast, clean and neat with no side products formation.

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

All the melting points were determined in open capillary on a 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 reference; and EIMS on a Jeol D-300 spectrometer at 70 eV. The reactions were carried out in a domestic microwave oven (LG-MS 257 PL) at 2450 MHz (900 W).

General procedure for the preparation of ethyl-2-oxo-4,6-diaryl-3-cyclohexen-1-carboxylates 3

Method A (MORE-Microwave-induced Organic Reaction Enhancement)

Ethyl acetoacetate (0.01 mole), benzylidene acetophenone (0.01 mole) and piperidine (0.05 mole) were taken in ethanol (10 mL) in Erlen Mayer flask capped with a funnel, placed in a microwave oven and irradiated at 260 W for 1 min. The reaction mixture was allowed to attain the RT and solid separated on cooling was filtered and washed with cold alcohol. The product was purified by recrystallization from benzene.

Method B (Conventional)

A mixture of ethyl acetoacetate (0.01 mole) and chalcone (0.01 mole) were refluxed in ethanol (10 mL) in the presence of piperdine (0.05 mole) for 4 hr. The reaction mixture was cooled and the product obtained was purified by recrystallization from benzene.

Compound 3a: (Ar and Ar$'$ =C_6H_5): IR (KBr): 1690 (C=O), 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_2CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.6(m, 2H, benzylic-H and CH), 4.0 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.2-7.6 (m, 10H, ArH); MS: *m/z* 321 $[M+H]^+$.

Compound 3b: (Ar = 4-$CH_3OC_6H_4$ and Ar$'$ =C_6H_5): IR (KBr): 1680 (C=O),1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_2CH_3), 2.7 (m, 2H, CH_2, Ha and Hb), 3.7 (s, 3H, OCH_3), 3.6(m, 2H, benzylic-H and CH), 4.0 (q, 2H, CH_2CH_3), 6.4 (s, 1H, C=CH), 7.0-7.5 (m, 9H, ArH); MS: *m/z* 351 $[M+H]^+$.

Compound 3c: (Ar= C_6H_5 and Ar$'$ =4-ClC_6H_4): IR (KBr): 1685 (C=O), 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_2CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.7(m, 2H, benzylic-H and CH), 4.0 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.1-7.6 (m, 9H, ArH); MS: *m/z* 355 $[M+H]^+$.

Compound 3d: (Ar= C_6H_5 and Ar$'$ =4-$CH_3C_6H_4$): IR (KBr): 1690 (C=O), 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_2CH_3), 2.5 (s, 3H, CH_3), 2.7 (m, 2H, CH_2, Ha and Hb), 3.6 (m, 2H, benzylic-H and CH), 4.1 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.1-7.6 (m, 9H, ArH); MS: *m/z* 335 $[M+H]^+$.

General procedure for the preparation of 3-ethoxy-4,6-diaryl-4,5-dihydro-2,1-benzisoxazoles 4

Method A (MORE-Microwave-induced Organic Reaction Enhancement)

A mixture of cyclohexanones **3** (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) were taken in ethanol (10 mL) in Erlen Meyer flask capped with a funnel, placed in a microwave oven and irradiated at 260 W for 1 min. After cooling, the reaction mixture was poured on to crushed ice, and the product obtained was purified by recrystallization from alcohol.

Method B (Conventional)

Cyclohexanones **3** (0.01 mole) and hydroxylamine hydrochloride (0.01 mole) in ethanol (10 mL) was heated under reflux for 6 hr. The reaction mixture is allowed to cool and poured on to crushed ice. The solid separated was filtered and was purified by recrystallization from alcohol.

Compound 4a: (Ar and Ar$'$ =C_6H_5): IR (KBr): 1645 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_2CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.8 (m, 1H, benzylic-H), 4.0 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.0-7.7 (m, 10H, ArH); MS: *m/z* 318 $[M+H]^+$.

Compound 4b: (Ar=4-$CH_3OC_6H_4$ and Ar$'$ =C_6H_5): IR (KBr): 1630 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 1.0 (t, 3H, CH_2CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.6 (s,

3H, OCH_3), 3.8 (m, 1H, benzylic-H), 4.0 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.1-7.6 (m, 9H, ArH); MS: *m/z* 348 $[M+H]^+$.

Compound 4c: (Ar= C_6H_5 and Ar' = 4-ClC_6H_4): IR (KBr): 1620 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_2CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.7(m, 1H, benzylic-H), 4.1 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.0-7.5 (m, 9H, ArH); MS: *m/z* 352 $[M+H]^+$.

Compound 4d: (Ar= C_6H_5 and Ar' =4-$CH_3C_6H_4$): IR (KBr): 1625 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 0.9 (t, 3H, CH_2CH_3), 2.5 (s,3H,CH_3), 2.8 (m, 2H, CH_2, Ha and Hb), 3.8(m, 1H, benzylic-H), 4.1 (q, 2H, CH_2CH_3), 6.5 (s, 1H, C=CH), 7.0-7.5 (m, 9H, ArH); MS: *m/z* 332 $[M+H]^+$.

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