Microwave assisted benzoin condensation using thiamine as catalyst

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α-Hydroxyketones were prepared in appreciable yields at a very high speed, (by the benzoin condensation) under microwave irradiation using a catalytic amount of thiamine hydrochloride, from various aromatic as well as heteroaromatic aldehydes. They can be used as intermediates in NCE synthesis.

Keywords*:* α-hydroxyketones, thiamine, microwave irradiation, benzoin condensation, aromatic/heteroaromatic aldehydes

α-Hydroxyketones are versatile intermediates in organic synthesis. They can be converted into α-haloketones, which provide a variety of useful compounds[1] on reaction with a large number of nucleophiles. Also substituted amino ketones and amino alcohols derived from corresponding benzoin intermediates exhibit necrotising action against mammalian tumors.[2] Various halogenated benzoins possess antimalarial and antiinsecticidal activities;[2] they are also important intermediates in synthesising molecules having CNS activity and some are also found useful as inhibitors of cholesterol biosynthesis.[3] Several derivatives of substituted benzoins are found to be important drug intermediates for the synthesis of non-prostanoid prostacyclin mimetics.[4]

Benzils, the oxidised products of benzoins, also exhibit high antibacterial activity.[5] These on further rearrangement give benzilic acid derivatives. Benzoins, benzils and benzilic acids can also be used as intermediates in NCE synthesis.

Conventionally, benzoin condensation involves the use of KCN and other sources of cyanides as catalysts in aqueous alcohol.[6] The other catalysts explored for benzoin condensation are thiazolium salts[7] including thiamine under various reaction conditions.[8] Some other classes of catalysts for benzoin condensation include bi-(1, 3-dialkylimidazolidin-2-ylidenes)[9], *N*, *N′*-disubstituted *o*-phenylenes,[10] azolium salts,[11] and triazolium salts.[12]

Thus we see that several methods are reported in the literature for benzoin condensation, but the practical applications of the methods using potassium cyanide have been limited due to the poisonous nature of KCN. Also, to prepare α-hydroxyketones, using thiazolium salts as catalysts some substrates require extended reaction times of 12–16 h;[13] this could be overcome by carrying the reactions under microwave irradiations.

In recent years, microwave-assisted transformations have gained importance as microwave assistance has significant advantages as compared to classical heating techniques. Reactions such as Diels-Alder reactions, Claisen condensations and Knoevenagel reaction have been studied under microwave irradiation. However, no study of microwave-assisted benzoin condensations using thiamine or other thiazolium salts has been reported. Also, the applicability of the benzoin condensation to several substrates including aromatic compounds with *ortho*, *meta* and *para* substituents as well as heterocyclic compounds has not been explored in detail using thiamine. Herein we report the results of microwave-assisted benzoin condensation, showing its general applicability to various substituted aromatic and heteroaromatic aldehydes.

The method developed using microwave irradiation is clean, involves an easy workup procedure and the formation of few by-products. The reaction takes much less time than the conventional procedures to give appreciable yields of the corresponding α-hydroxyketones (see Table 1).

To gain preliminary information benzaldehyde was taken in a propylene glycol-water system containing a catalytic amount of thiamine hydrochloride. The pH was adjusted to 8–9 using triethylamine and then subjected to microwave irradiation for 20 s, which gave 71 % benzoin. In order to optimise the yield various reaction parameters were standardised.

Different solvents such as 2-ethylhexan-1-ol, dimethyl sulfoxide, dimethyl formamide, glycerine, glycerine-water, propylene glycol (PG), and propylene glycol-water were explored. Amongst these systems water–PG was found to give good results.

Bases like Et_3N, pyridine, aqueous NaOH, Na_2CO_3, and $NaHCO_3$ were examined for adjusting the pH. It was found that triethylamine at pH 8.5 gives the best yield. Also it was observed that further increase in pH results in lower yield, implying that pH plays a critical role in the benzoin condensation as it controls the formation of the ylid of thiamine which is essential for the catalysis of the benzoin condensation.

If microwave irradiation was increased beyond 20 s, however, yields decreased, partly due to the decomposition of the product. Control reactions in the microwave oven without using thiamine and a control reaction using thiamine but without microwaves did not lead to any product formation in comparable times (20–60 s).

To determine the general applicability of the reaction, various aldehydes were subjected to the conditions standardised above. The results are tabulated in Table 1.

From Table 1 it is observed that a wide range of substituted and unsubstituted aromatic as well as heteroaromatic aldehydes gives the corresponding α-hydroxyketones. It was also observed that substitution at the *meta* or *para* positions of the aromatic ring does not hinder the reaction, while bulky substitution at the *ortho* position lead to very low or no yields under these reaction conditions.

This method can be used with heteroaromatic aldehydes also. As reported in literature the conventional methods using cyanides give low yields with heteroaromatic aldehydes in 30 days.[6] With this newly-developed method a 70 % isolated yield of furoin within 20 s. was obtained and thiophene-2-aldehyde gave thenoin, an intermediate in drug synthesis,[4] in moderate yields and appreciable purity in 20–25 s. An easy work-up procedure was involved.

In conclusion, we have developed a clean, high speed, facile and practical method for the formation of α-hydroxyketones by the application of microwave irradiation using thiamine. Further work related to cross benzoin and acyloin condensations is in progress using microwave irradiation.

Experimental

All the reactions were performed in a domestic microwave oven (Kenstar, MWO 9817, 560W, 2450 MHz). The reagents, solvents and substrates were obtained from commercial sources. All the NMR spectra were recorded on a FT-NMR JEOL, 60 MHz or a Varian, 400 MHz, Mercury Plus spectrometer. Chemical shifts are expressed in δ units relative to the tetramethylsilane (TMS) signal as internal

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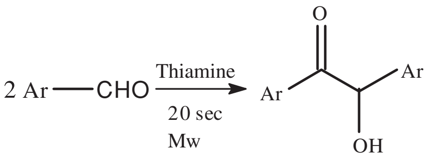
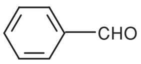
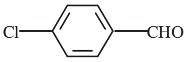
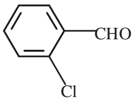
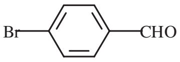
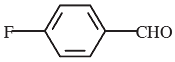
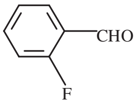
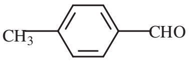
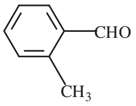
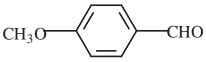
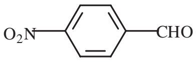
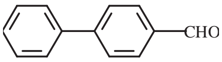
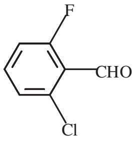
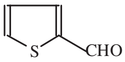
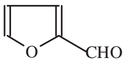
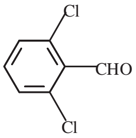
Table 1 Preparation of α-hydroxyketones under microwave irradiation for 20 s.



Ar = Aromatic / heteroaromatic moiety

Entry	Substrate[a]	% Yield of product[b,c]	Lit. % yield[14(a-j)] of product	M.p./°C	Lit m.p./°C
1		71	80[14a]	135–136	133–134[d]
2		69	88[2]	75–76	88[d]
3		52	20–40[14b]	62–64	63–64[d]
4		81	91[14c]	97–99	99–100[d]
5		60	67[14d]	74–76	72–73[e]
6		41	37[14d]	80–82	–
7		42	50[14e]	86–88	88–89[d]
8		15	63[14f] 38[14d]	76–77	79[d]
9		32	23[14a]	112–114	113[d]
10[f]		34	Trace qty [14g] 71[14h]	164–166	163–164[14h]
11		82	71.25 [14j]	172–174	168–170[14b]
12		25	–	68–71	–
13		55	30[6]	107–108	108–109[d,6]
14		70	37.5[14a]	136–137	138–139[d]
15		No reaction	–	–	–

[a] Substrates were obtained commercially.
[b] The structures of all the α-hydroxyketones were confirmed by their physical and spectroscopic properties (IR, ^{1}H NMR)
[c] Yields indicate isolated yields after column chromatography.
[d] *Dictionary of Organic Compounds*, 6th edn, Vol 1–8, Chapman and Hall, London.
[e] US 4,008,232 – Feb15, 1977.
[f] Reaction was done in DMF–H_2O system.

reference in $CDCl_3$. The mass spectrum was recorded on a Waters, Q/TOF Micromass spectrometer. IR spectra were recorded on a "Buck Scientific Infrared Spectroscopy M500" spectrophotometer using KBr based pellets. All the products gave spectroscopic (^1H NMR, IR) data consistent with assigned structure. Melting points were recorded on a Thermomik Campbell Electronic instrument, having an oil-heating system and are uncorrected.

General procedure – microwave enhanced benzoin condensation of aromatic/heteroaromatic aldehydes
A mixture of the aromatic aldehyde (1 mmol), thiamine hydrochloride (0.1 mmol) and PG-H_2O solvent (0.5 ml: 0.03 ml) was adjusted to pH 8.5 using triethylamine. This was then subjected to microwave irradiation (560W) for 20 s. The reaction mass was cooled to room temperature, diluted with water and extracted with DCM (5 × 2 ml). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Purification by silica gel column chromatography (1:1 *n*-hexane/DCM) afforded pure α-hydroxy ketones. IR ν_{max} (KBr, cm^{-1}): 3375–3431 (-OH stretching), 3115–3051 (aromatic/ heteroaromatic C–H stretching), 1673–1648 (–C=O stretching); ^1H NMR δ_H ($CDCl_3$): 7.68–7.31 (m, Ar heteroaromatic/aromatic protons), 5.98–5.92 (d, J = 6.1 Hz, 1H, CH, converted to singlet on D_2O exchange in case of aromatic substrate) or 6.38–6.03 (bs, 1H, CH in case of heteroaromatic substrate) and 4.55–4.42 (d, J = 6.1 Hz, 1H, OH).

1,2-Bis (2-chloro-6-fluorophenyl)-2-hydroxyethanone (entry 12): A mixture of 2-chloro-6-fluorobenzaldehyde (158 mg, 1 mmol), thiamine hydrochloride (34 mg, 0.1 mmol) and 0.02 ml propylene glycol-H_2O solvent (0.5 ml: 0.03 ml) was adjusted to pH 8.5 using triethylamine. This was then subjected to microwave irradiation (560W) for 20 s. The reaction mass was cooled to room temperature. This was then diluted with water and extracted with DCM (5 × 2 ml). The organic layer was dried on Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography (1:1 *n*-hexane/DCM) to give pure 1,2-bis (2-chloro-6-fluorophenyl)-2-hydroxyethanone (40 mg, 25 %) as an off-white solid. IR ν_{max}(KBr, cm^{-1}): 3430.4, 3074.8, 2820.0, 1680.6, 1503.9; ^1H NMR δ_H (400 MHz, $CDCl_3$): 7.05 (m, 8H, Ar H), 6.24 (d, J = 6.4 Hz, 1H, CH, converted into a singlet on D_2O exchange), 4.25 (d, J = 6.4 Hz 1H, OH); ^{13}C NMR ($CDCl_3$) δ196.20, 161.16, 160.89, 135.52, 135.42, 132.61, 131.07, 126.14, 125.95, 122.57, 122.36, 114.98, 114.50, 76.97; (In the absence of full characterisation data the characterisation of this product from entry 12 must be formally tentative but is supported by the above data and the product from the other reactions).

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