Recent Advances in the Morita-Baylis-Hillman Reaction Under Microwave Irradiation

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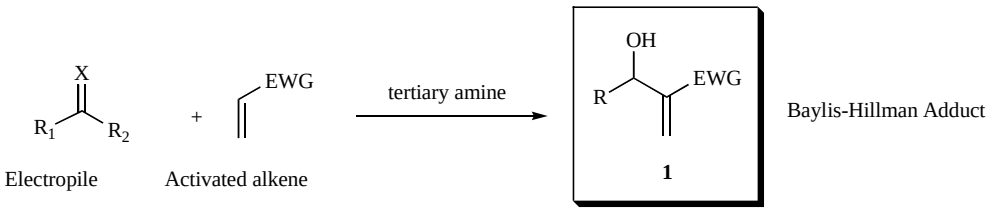
Abstract: The Morita-Morita-Baylis–Hillman reaction (MMBHR) is one of the most important carbon–carbon bond forming reactions, and involves the selective atom-economical construction of a carbon–carbon bond at the α-position of an activated alkene, providing densely functionalized molecules. One of the major drawbacks of the MBHR is the low reaction rate, requiring long reaction times. In this review, the MBHR, in combination with microwave irradiation is summarized for the synthesis of highly functionalized molecules with the advantages of green process and shorter reaction times.

Keywords: Microwave irradiation, Baylis-Hillman reaction, biological activity, DABCO, conventional heating, microwave effect, nonthermal effects.

INTRODUCTION

Carbon-carbon bond formation is one of the most important and powerful synthetic organic transformation and, therefore, it is a challenging area of the major interest in chemistry. The Morita-Morita-Baylis–Hillman reaction (MBHR) is an interesting reaction, which involves the selective atom-economical construction of a carbon–carbon bond at the α-position of an activated alkene. The reaction is catalyzed by a tertiary amine providing densely functionalized molecules such as 1, known as Baylis Hillman adduct (Scheme **1**).



EWG= CO_2R, $CONR_2$, CN, COR, NO_2, SO_2Ph, SO_3Ph, $POPh_2$, etc.

R_1 = Alkyl, Aryl or hetereoaryl
R_2 = H, CO_2R, alkyl

X = O, NCO_2R, NTs, NSO_2Ph, etc.

Scheme 1. Morita-Baylis-Hillman reaction.

This reaction has been the subject of several reviews and a large number of research papers [1-5]. The mechanism of the reaction has been the subject of a number of studies from various groups [6-8], being the independent works of McQuade [9, 10], Aggarwal [11, 12] and Coelho [13-15] crucial for better understanding of the Baylis-Hillman mechanism. The dualistic nature of the mechanism has become evident from the studies of McQuade and Aggarwal (Scheme **2**), which was supported by Coelho and co-workers through ESI-MS experiments.

Both proposals agree that the first step of the Morita-Baylis-Hillman reaction is the nucleophilic Michael addition of the tertiary amine **2** to the activated alkene **3**, followed by the addition of the zwitterionic enolate **4** to the aldehyde, leading to the formation of the common intermediate **5**. According to Aggarwal and co-workers, the intermediate **5** reacts through an alcohol-catalyzed pathway in which alcohol acts as a shuttle to transfer hydrogen from the α-position to the alkoxide, through six membered transition state **7** which finally leads to the formation of the Morita-Baylis-Hillman adduct. McQuade and *co-workers*, proposed that a second equivalent of aldehyde attacks intermediate **5** to form a hemiacetal alkoxide **6** followed by rate-limiting hydrogen transfer to give the MBH adduct. All these intermediates were successfully intercepted and structurally characterized *via* ESI-MS(/MS) by Coelho and co-workers group.

Since its discovery, one of the major drawbacks of the MBHR is the requirement for a long reaction time, which makes this issue an important one. MBHR are usually slow and the reaction may take from days to weeks for completion depending on the reactivity of the activated alkene, electrophile and catalyst. Due to the synthetic potential of the MBH adducts, many of which are biologically active (Fig. **1**) [16-26], several protocols have been proposed to accelerate this reaction, such as the use of ultrasound [27], addition of salts [28], high pressure [29], ionic liquids [30-32] and microwave irradiation.

Recently, several publications have shown that microwave irradiation can accelerate the rate of chemical reactions, often with increased yields leading to cleaner and enhanced chemical processes. Microwave is defined as an electromagnetic wave with a frequency up to 300 GHz. Domestic microwave ovens and dedicated microwave reactors for organic synthesis operate at a frequency of 2.45 GHz. The energy of the microwave photon is equivalent to 0.0016 eV (0.034 Kcal/mol), which is too small to

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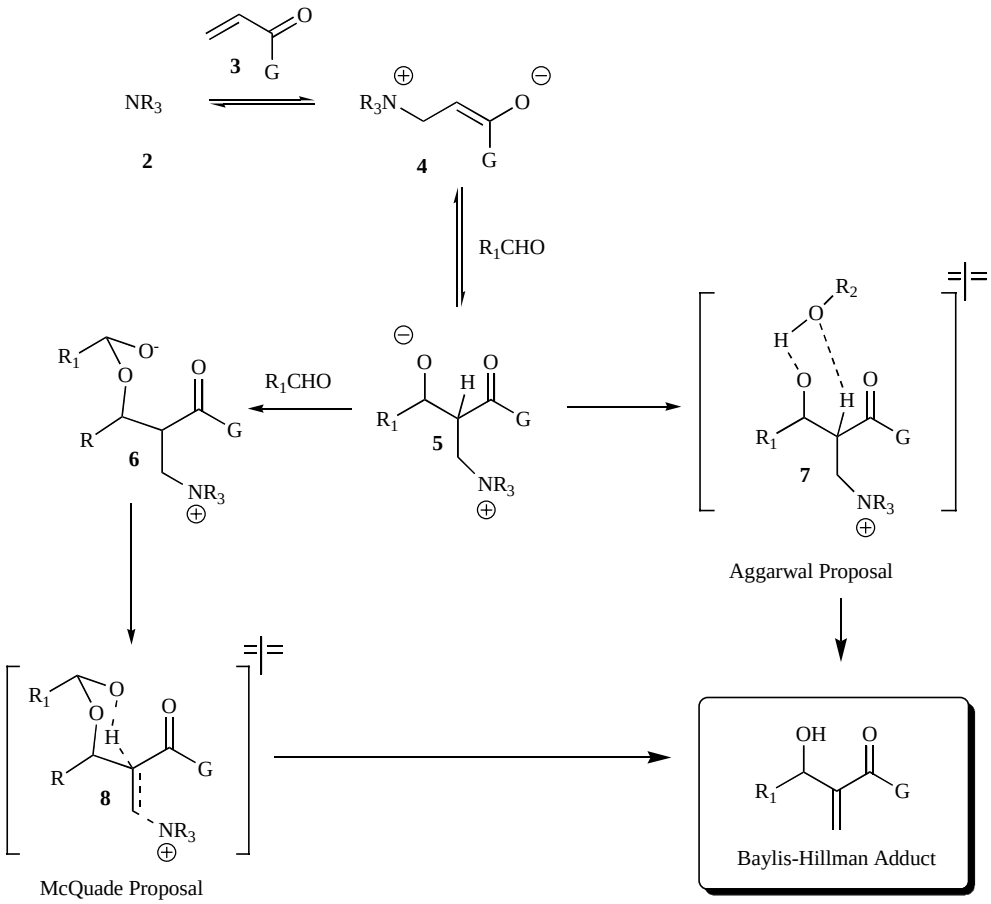


Scheme 2. Morita-Baylis-Hillman mechanism.

break chemical bonds [33]. The controversy about thermal or non-thermal microwave effects is still active in the literature and is not the center of attention in this work.

This Mini-Review highlights the application of dedicated microwave reactors and domestic microwave ovens in the MBHR and in the transformation of the MBH adduct. The examples have been taken from the literature since the first work dated from 1994.

APPLICATION OF MICROWAVE IRRADIATION ON THE BAYLIS-HILLMAN REACTION

While microwave (MW) irradiation has been extensively applied in the transformation of Morita-Baylis-Hillman adducts, few examples exists on the application to the MBHR.

To the best of our knowledge, the first report using MW irradiation to accelerate the MBHR was in 1994, when Bhat and co-workers [34] reported significant rate acceleration using a domestic microwave oven (650W). In their work, the authors studied the reaction between aldehydes and acrylic acid derivatives catalyzed by DABCO, without the use of solvent. Significant rate enhancements were reported, when compared with the same reaction at room temperature. While at room temperature the reactions take days to furnish the adducts in low yields, under microwave irradiation these reactions took place in a few minutes and the yields ranged from moderate to good yields (Table **1**). Remarkably the reaction with acrylamide (entry 6), which did not occur at room temperature even after 3 days, result in 40% yield after only 25 minutes when subjected to MW irradiation.

In the same year, Strauss and co-workers [35] reported the development and application of a continuous microwave reactor for organic synthesis, where several organic reactions were investigated, including the MBHR. The system studied was the reaction between methyl acrylate and aqueous formaldehyde under DABCO catalysis. The same reaction is reported by Kress and co-workers [36] to take several days to reach 30% yield at room temperature. Under microwave irradiation, comparable yields were reached in 90 minutes.

In 2003, Vasconcellos and co-workers [37] studied the MBHR between aromatic aldehydes and methyl acrylate using DMAP (10 mol%) as catalyst, with an excess of methyl acrylate as the solvent. While few aldehydes were studied, this was the first report to compare the domestic microwave irradiation with conventional heating in the MBHR under DMAP catalysis. Large rate acceleration was observed with p-nitrobenzaldehyde, where an excellent yield was reported with only 15 minutes of irradiation as depicted in Table **2**, entries 1-2. Improvement was also observed for the β-naphtylaldehyde (entries 3-4). On the other hand no improvement was observed for the less reactive piperonal (entries 5-6).

Subsequently, Lamaty and co-workers [38] presented their results on the microwave assisted aza-Baylis-Hillman reaction, which is an efficient method for the preparation of α-unsaturated β-aminoesters. The authors used a PEG supported amine to generate the polyethylene glycol (PEG) supported aminoesters *via* a Morita-Baylis-Hillman reaction using microwave irradiation (Personal Chemistry Liberator Synthesizer equipment). Activated and moderately activated aldehydes were used in the reaction with methyl or ethyl acrylate and various tertiary amine catalysis. Yield improvement and short reaction time can be observed under microwave irradiation when the reaction is heated above 70°C, as can be seen with the example between benzaldehyde and ethyl acrylate, (Table **3**).

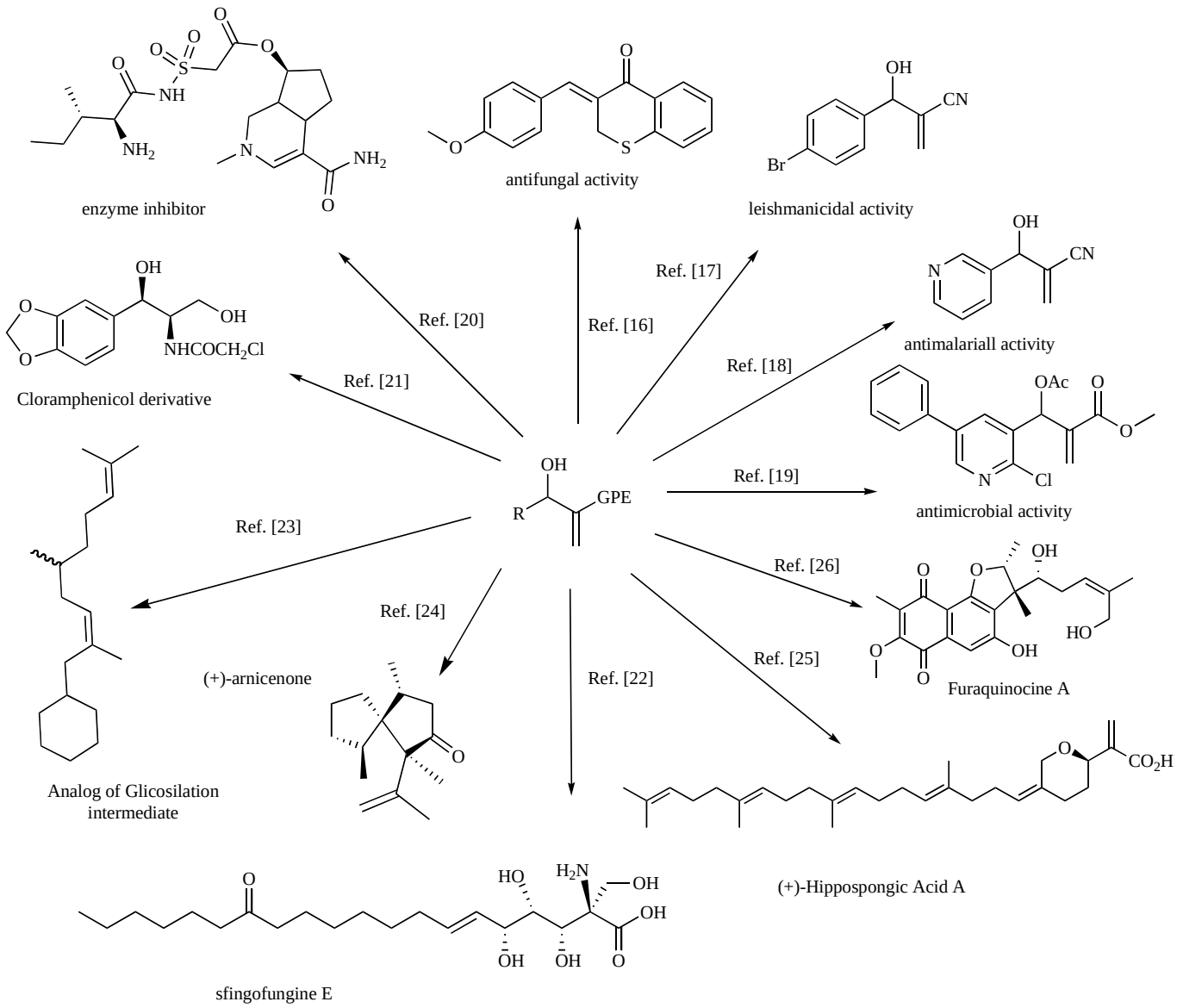
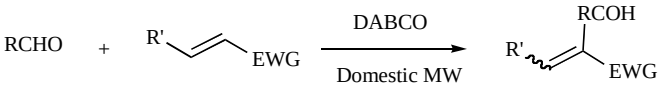


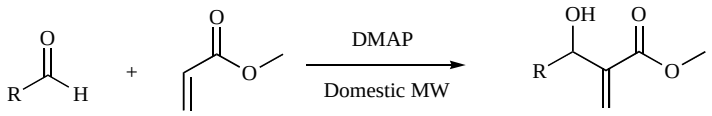
Fig. (1). Several biological active molecules derived from Morita-Baylis-Hillman adducts.

Table 1. Microwave Irradiation in the Morita-Baylis-Hillman Reaction



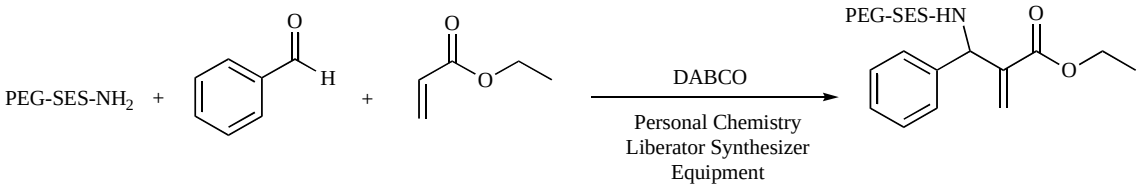
Entry	R	R'	EWG	Room Temperature		Microwave	
				Time (days)	Yield (%)	Time (min)	Yield (%)
1	2-OHC_6H_4	H	$COOCH_3$	3	10	10	70
2	3,4,5-$(CH_3O)_3C_6H_2$	H	$COOCH_3$	4	5	30	15
3	3,4,5-$(CH_3O)_3C_6H_2$	H	CN	3	80	10	55
4	4-$CH_3OC_6H_4$	H	CN	3	13	10	25
5	4-$NO_2C_6H_4$	H	CN	3	45	10	95
6	3,4,5-$(CH_3O)_3C_6H_2$	H	$CONH_2$	3	0	25	40
7	$C_6H_5CH=CH$	H	$COOCH_3$	14	28	45	15
8	CH_3CH_2	H	$COOCH_3$	4	61	10	70

Table 2. Vasconcellos and Co-Workers Results on the Morita-Baylis-Hillman Reaction Using Microwave Irradiation



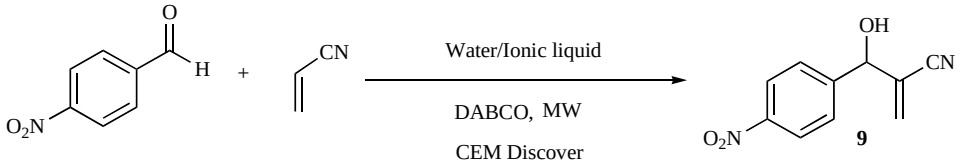
Entry	R	Temperature	Time	Yield (%)
1	4-$NO_2C_6H_4$	76	5h	>99
2	4-$NO_2C_6H_4$	Microwave	15 min	93
3	β-$C_{10}H_7$	76	5 days	60
4	β-$C_{10}H_7$	Microwave	3h	15
5	3,4-OCH_2O-C_6H_3	76	6 days	47
6	3,4-OCH_2O-C_6H3	Microwave	1h	No reaction

Table 3. Lamaty and Co-Workers Results on the Microwave Assisted aza-Morita-Baylis-Hillman Reaction



Entry	Temp. (°C)	Time (h)	Conversion (%)
1	90	0.5	55
2	110	0.5	69
3	130	0.5	83
4	150	0.5	68

Table 4. De Souza and Co-Workers Results on the Morita-Baylis-Hillman Reaction Under Microwave Irradiation



Entry	Ionic liquid	R	Pressure	DABCO (eq)	Time (min)	Yield (%)
1	[bmim][PF_6]	CN	Open vessel	2	2	>97
2	[bmim][BF_4].	CN	Open vessel	2	7	>97
3	[bmim][PF_6]	$COOCH_3$	Open vessel	2	60	90
4	[bmim][BF_4].	$COOCH_3$	Open vessel	2	60	36

Recently [39], our group reported the microwave assisted DABCO catalyzed MBHR in a water/ionic liquid solvent system. The beneficial effect of water as a solvent in the MBHR reaction is long known, however this was the first systematic study of a water/ionic liquid mixture under microwave irradiation (Discover Station, CEM Corporation, NC, USA). In this studies, as previously observed by Bhat in a solventless system, an impressive rate of acceleration was observed for the reaction between *p*-nitrobenzaldehyde and acrylonitrile catalyzed by DABCO. As pointed out by the authors, at room temperature the product **9** could not be detected even after 3 hours of reaction.

The addition of small amounts of ionic liquids (0.1 mL/5mL water) was also studied and found to be extremely beneficial in every case. Among the ionic liquids tested [bmim][PF_6] was found to be superior to [bmim][BF_4] in all cases, where the former afforded 70% decrease in reaction time (Table **4**).

When the reaction system was expanded to other aromatic aldehydes, even the less reactive aldehydes such as piperonal, furnished the adducts in moderate yields, (Entry 4 Table **5**).

The use of functionalized aldehydes, such as arylhydrazonals as the electrophilic component in the MBHR was recently studied by Al-Awadi and co-workers [40], leading to an efficient and simple route to dihydropyrazines. The authors have used an Explorer Microwave Synthesizer (CEM Corporation, NC, USA) to irradiate the reaction at 160°C for 5 min. The reaction yield ranged from good to excellent (Table **6**).

RECENT APPLICATION OF MICROWAVE IRRADIATION ON THE MORITA-BAYLIS-HILLMAN ADDUCTS

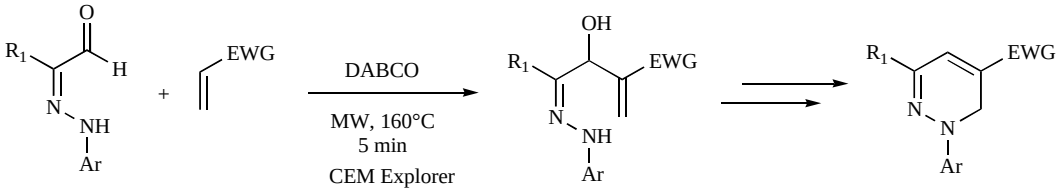
Due to the potential functionalization of adducts obtained from the MBHR and, as a consequence, of the synthetic importance of such adducts, an increasing number of examples of MW irradiation of the Morita-Bayllis-Hillman products have been published. In this section, examples comprising the last ten years (1999-2009) will be discussed.

Fisera and co-workers [41,42], in consecutive studies, investigated the effect of the addition of methylmagnesium bromide on the

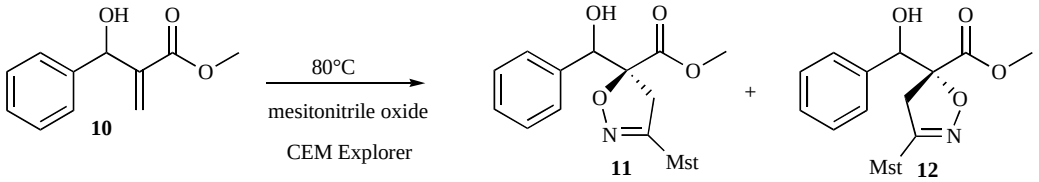
Table 5. De Souza and Co-Workers Results on the Morita-Baylis-Hillman Reaction Under Microwave Irradiation

Entry	Aldehyde	R_2	Time (min)	Conversion (%)
1	Benzaldehyde	CO_2CH_3	60	58
2	Benzaldehyde	$CO_2C(CH_3)_3$	60	40
3	4-F-Benzaldehyde	CN	60	62
4	Piperonal	CO_2CH_3	60	35
5	2-pyridinecarboxaldehyde	CO_2CH_3	40	78

Table 6. Al-Awadi and Co-Workers Results for the Morita-Baylis-Hillman Reaction of Arylhydrazonals Under Microwave Irradiation

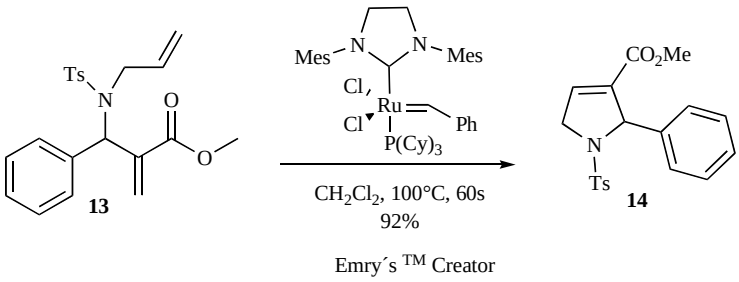


Entry	R_1	Ar	EWG	Yield (%)
1	CO_2Et	*p*-Cl-C_6H_4	CN	79
2	Furane-2-yl-methanone	C_6H_5	$COCH_3$	95
3	COC_6H_5	C_6H_5	$COCH_3$	92



*Mst = 2,4,6 trimethylphenyl

Scheme 3. Conventional and domestic microwave irradiation effect of the addition of methylmagnesium bromide on the stereoselectivity of reactions of mesitonitrile oxide with the Morita-Baylis-Hillman adducts.



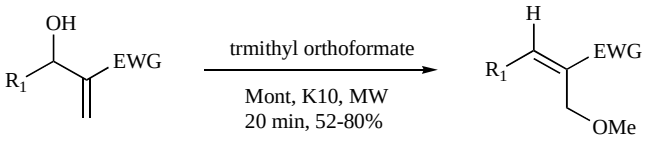
Scheme 4. Formation of 2,5-dihydropyrroles, from Morita-Baylis-Hillman adducts, using ring-closing metathesis reaction under microwave irradiation.

stereoselectivity of reactions of mesitonitrile oxide with the Baylis-Hillman adducts **10**, under conventional heating and by using of domestic microwave irradiation. The MW irradiation led to a significant improvement upon the reaction time and yield when compared to conventional heating (Scheme **3**). No influence on the reaction was detected.

In 2004, Adolfsson and co-workers [43] reported an efficient use of aza-Morita-Baylis–Hillman adducts for the formation of 2,5-dihydropyrroles **14** using a ring-closing metathesis reaction under microwave irradiation (sealed tube for 60s at 100°C, temperature control, fixed hold time off, normal absorption mode) using an Emry´s ™ Creator (Scheme **4**). Lamaty and co-workers [44] expanded the scope of this transformation in the same year with several aza-Morita-Baylis-Hillman derivatives.

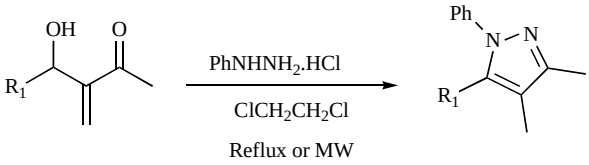
Montmorillonite-clay was used by Yadav and co-workers [45] on the stereoselective syntheses of aryl-substituted (*E*)- and (*Z*)-allyl iodides and bromides from Morita-Baylis-Hillman adducts and improved yields and enhanced rates have been achieved by employing microwave irradiation. The Shanmugan group, in three different articles, [46-48] studied the montmorillonite-K10 assisted isomerization of Morita-Baylis-Hillman adducts. The results obtained in this study showed that the combination of microwave irradiation and montmorillonite-K10 catalysis is an efficient protocol for the isomerization of Morita-Baylis-Hillman adducts (Table **6**).

Table 7. Montmorillonite-K10 Assisted Isomerization of Morita-Baylis-Hillman Adducts Under Microwave Irradiation



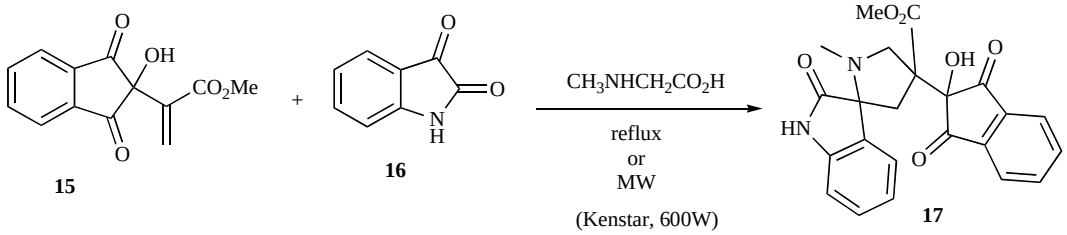
Entry	R_1	EWG	Time (min.)	Yield (%)
1	Ph	CO_2Et	20	74
2	Naphth-1-yl	CO_2Et	21	72
3	Naphth-1-yl	CN	23	60
4	4-Cl-Ph-	CO_2Et	19	62
5	4-Cl-Ph-	CN	20	52
6	4-Me-Ph-	CO_2Et	18	70
7	Naphth-2-yl	CN	22	63

Table 8. Conversion of Morita-Baylis-Hillman adducts into 1,5-diarylpyrazoles Under Microwave Irradiation



Entry	R_1	Conventional Heating		Microwave Irradiation (Domestic MW)	
		Time (min)	Yield (%)	Time (min)	Yield (%)
1	*p*-BrC_6H_4	450	70	2.5	80
2	*m*-$NO_2C_6H_4$	420	75	2	90
3	2-furyl	360	70	3	90

Table 9. Conversion of Morita-Baylis-Hillman Adducts into Functionalized Spiropyrrolidines/Pyrrolizidines



Method A (Conventional Heating)		Method C (Kenstar, 600W)	
Time	Yield (%)	Time	Yield (%)
3.0 h	51	5 min.	84

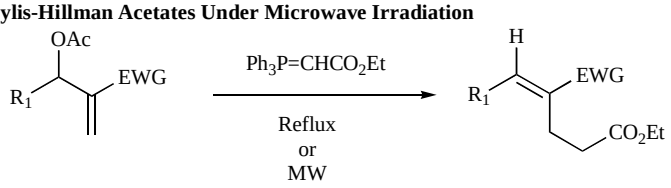
Isomerization of Morita-Baylis-Hillman adducts was also studied by Ravichandran [49] for the synthesis of methyl(2*E*)-2-methylalkyl-2-enoates under microwave irradiation. High yields and stereoselectivities were obtained in short reaction times.

The conversion of MBH adducts into 1,5-diarylpyrazoles under microwaves was investigated by Mamaghani and co-workers [50]. The comparison between conventional heating and microwave irradiation shows the improvement upon reaction time and yield (Table **7**).

Recently, Raghunathan and co-workers [51] reported their results on the solvent-free conversion of MBH adducts into functionalized spiropyrrolidines/pyrrolizidines, comparing the results under conventional heating and microwave irradiation. A remarkable example was the formation of the adduct oxindole spiro-(2.2´)-4´-methoxycarbonyl-4´-(2-hydroxy-indane-1,3-dione)-1-*N*-methyl pyrrolidine **17** from the reaction between the MBH adduct **15** of ninhydrin **16** and sarcosine. Rate and yield enhancement were obtained under microwave irradiation (5 minutes, 84%) when compared to conventional heating (Table **8**).

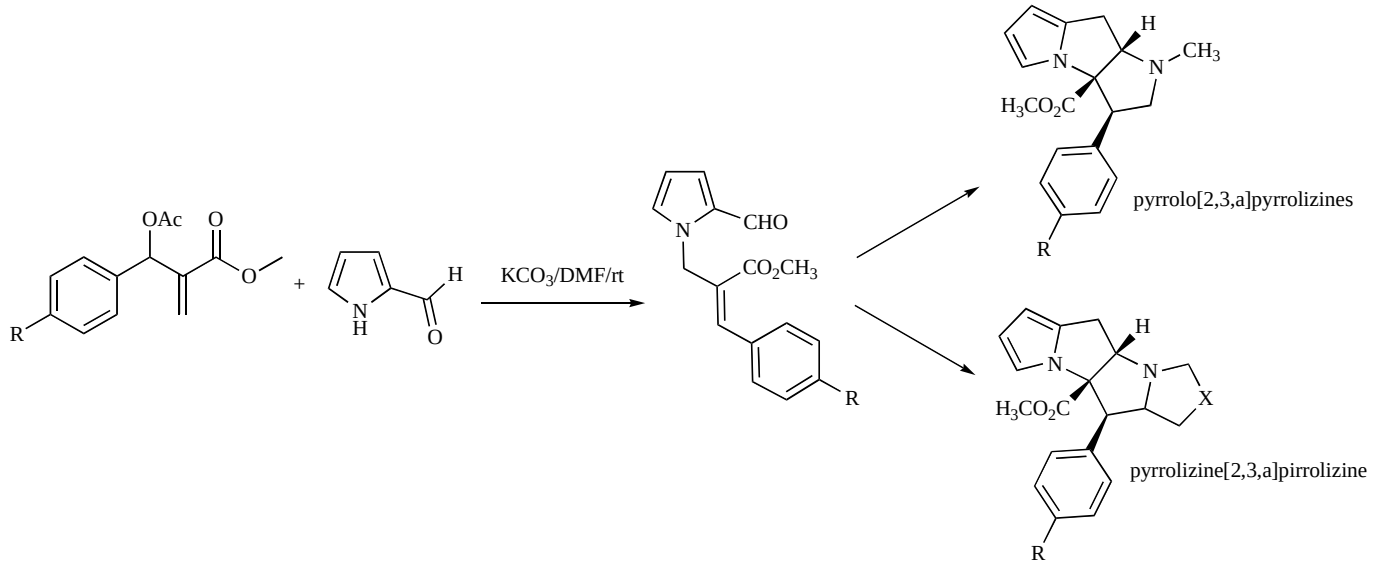
In 2007, a comparative study of conventional heating and microwave irradiation were performed by Yadav and co-workers [52] on the S_N2 substitution of Baylis-Hillman acetates. The results obtained led to an efficient protocol for 5-aryl-pentenoates with reduced reaction time and minimal thermal decomposition of the products when microwave irradiation is applied (Table **9**).

Table 10. S_N2 Substitution of Morita-Baylis-Hillman Acetates Under Microwave Irradiation



Entry	R_1	EWG	Conventional Heating		Microwave Irradiation (Domestic BMO-800T at 450W)	
			Time	Yield (%)	Time	Yield (%)
1	Ph	CO_2Et	12 h	85	3 min.	87
2	4-Cl-Ph	CO_2Et	10 h	86	3.0 min.	83
3	4-OMe-Ph	CN	18 h	90	2.5 min.	93
4	β-naftyl	CN	14 h	85	3.0 min.	88
5	Nonyl	CO_2Et	36 h	88	3.5 min.	90
6	Ethyl	CO_2Et	36 h	85	3.0 min.	87

Table 11. Results of Raghunathan and Coworkers on the Synthesis of pyrrolo[2,3,a]pyrrolizines and pyrrolizine[2,3,a]pirrolizine Derived from Morita-Baylis-Hillman Adduct



Entry	pyrrolo[2,3,a]pyrrolizines		pyrrolizine[2,3,a]pirrolizine		Conventional Heating		Microwave Irradiation (Domestic MW)	
	X	R	X	R	Time (h)	Yield %	Time (h)	Yield %
1	CH_2	H	-	-	2.0	65	3.5	85
2	CH_2	Cl	-	-	3.0	56	4.0	75
3	CH_2	Br	-	-	3.5	59	4.0	79
4	-	-	CH_2	H	2.0	55	2	87
5	-	-	CH_2	Cl	2.5	61	2.5	85
6	-	-	CH_2	Br	3.0	63	2.5	78
7	-	-	S	H	3.0	51	2	84
8	-	-	S	Cl	3.5	48	2.5	81
9	-	-	S	Br	4.0	48	2.5	78

In 2009, Raghunathan and coworkers [53] reported their results on the synthesis of pyrrolo[2,3,a]pyrrolizines and pyrrolizine[2,3,a]pirrolizine derived from Baylis-Hillman adduct through an intramolecular 1,3 dipolar cycloaddition, as depicted in Table **10**.

The results presented in Table **11** show a dramatic effect of the microwave irradiation on the yield of the reactions, with an equivalent decrease in the reaction time. The adducts were obtained in good to excellent yield with high diastereosselectivity. Unfortu-

nately, was no information with respect to the conditions used for the microwave irradiation were available.

FUTURE PROSPECTS AND CHALLENGES

In this review, we summarized the results of microwave irradiation applied to the Morita-Baylis-Hillman reaction, reported mainly within the last 15 years in approximately 50 publications. The synthetic potential of the Baylis Hillman adducts allied with the rate accelerating effects of microwaves opens a great opportunity for invention in organic synthesis. In most cases, domestic microwave equipment was used and comparative studies with microwave irradiation and conventional heating were performed. Despite this, it is quite clear from the growing number of emerging publications that microwave technology is a very valuable technique for organic synthesis.

ACKNOWLEDGMENTS

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