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Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

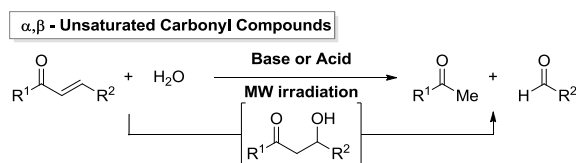
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Microwave-assisted, Tetrabutylammonium hydroxide Catalysed 1,4-Addition of Water to α,β -Unsaturated Ketones and α,β -Ynones in Aqueous Solution

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Microwave-assisted, tetrabutylammonium hydroxide catalysed 1,4-addition reactions of water to α,β -unsaturated ketones and α,β -ynones take place efficiently in water. Reactions of the resulting β -hydroxy ketones lead to the formation of either C-C bond cleavage or annulation products.

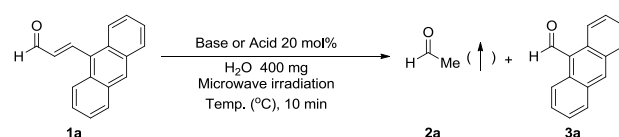
Recently, green chemistry has become an interesting topic in organic synthesis because reactions which adhere to green principles have many benefits, such as reduced chemical wastes, use of benign solvents, and enhanced efficiencies and atom economy.¹ Especially important is that the use of green solvents leads to minimization or elimination of environmental pollutants. As a result, many attempts have been made to develop solvent free processes² or to use non-traditional solvents like ionic liquids³ and supercritical fluids.⁴ Among the most eco-friendly solvents is water because it is inexpensive, non-toxic, non-corrosive, and non-flammable.⁵ To carry out efficient organic reactions in water, a solvent with a high dielectric constant, microwave irradiation is often employed as the heating source.⁶ Microwave-assisted processes typically have reduced reaction times and higher efficiencies owing to the fact that heat is delivered directly at the molecular level.



Scheme 1 The reactions of α,β -unsaturated compounds via β -hydroxy ketone by base or acid catalyst under microwave irradiation

With green chemistry principles in mind, we have devised a new method for carrying out 1,4-addition reactions of water to α,β -unsaturated ketones and α,β -ynones. The processes utilize H_2O as the solvent and MW irradiation as the heat source. Moreover, retro-aldol reactions of the resulting β -hydroxy ketone occur to generate C-C bond cleavage or annulation products.⁷ Specifically, secondary C-C double bond cleavage reactions of adducts derived from α,β -enones and -enals⁸ occur through base catalysed retro-aldol fragmentation (Scheme 1). In addition, multi-substituted phenols⁹ are generated through reactions of α,β -ynones in the presence of β -diketones via a base-triggered cascade involving Robinson annulation.

Table 1 Microwave-assisted C-C double bond cleavage by various base or acid in aqueous conditions ^a



Entry	Acid/Base	Temp.(°C)	GC yield of 3a (%)
1	NaOH	130	9
2	NaOH ^b	130	73
3	TBA-OH	130	76
4	K ₂ CO ₃	130	Trace (< 5)
5	Amberlyst A26(base)	130	Trace (< 5)
6	HCl	130	No reaction
7	Molecular sieve	130	No reaction
8	Phosphotungstic acid	130	No reaction
9	Amberlyst 16(acid)	130	No reaction
10	TBA-OH	150	> 99

^a Reaction conditions: 3-(Anthracen-9-yl)acrylaldehyde (0.2 mmol), NaOH, TBA-OH, K₂CO₃ and HCl (20 mol%), Amberlyst A26, Molecular sieve, Phosphotungstic acid and Amberlyst 16 (100 mg), H_2O (400 mg), reaction time (10 min). ^b using TBA-Cl (tetrabutylammonium chloride) as PTC (phase transfer catalyst).

3-(Anthracen-9-yl)acrylaldehyde (**1a**) was selected as the model substrate to explore features of the MW-assisted reactions of α,β -enals (Table 1). Reaction of **1a** (0.4 mmol) in water under the various acid and base catalysts (20 mol%) were carried out for 10 min. Although acetaldehyde (**2a**) and anthracene-9-carbaldehyde (**3a**) are both formed in these reactions, the yield of only **3a** could be determined because of the volatility of **2a**. Reaction of **1a** at 130 °C in aqueous solution containing NaOH gives **3a** in a 9% yield (GC analysis, Table 1, entry 1). With addition of NaOH with TBA-Cl (tetrabutylammonium chloride, 20 mol%) as phase transfer catalyst, yield of **3a** increased dramatically to 73% (entry 2). On the basis of this result, when tetrabutylammonium hydroxide (TBA-OH) is used to promote this process at 130 °C, the yield of **3a** is 76% (entry 3). TBA-OH (tetrabutylammonium hydroxide) acts as dual-role of base catalyst for H₂O nucleophile and phase transfer catalyst. Other acid and base catalysts, such as K₂CO₃, amberlyst, phosphotungstic acid, and molecular sieves, are not effective in promoting the addition reaction (entries 4-9). In contrast, when the temperature is 150 °C and 20 mol% of TBA-OH is present, **3a** is formed in a >99% GC yield (entry 10). The results demonstrate that the C-C double bond cleavage reaction of **1a** is highly efficient when TBA-OH is employed as the catalyst and microwave irradiation is employed as the heat source.

Table 2 Microwave-assisted C-C double bond cleavage of various α,β -unsaturated carbonyl compounds by TBA-OH catalyst in water

Entry	1	Isolated yield of 3 (GC %)
1		93 (> 99)
2		91 (96)
3		60 (69)
4		51 (55)
5		91 (97)

^a Reaction condition: α,β -unsaturated carbonyl compounds (0.2 mmol), TBA-OH (20 mol%), H₂O (400 mg), microwave (M.W.) 150 °C, 10 min.

To explore the substrate scope of this process, reactions of other α,β -enals and α,β -enones **1** were carried out (Table 2). In each case, the corresponding carbonyl product **3** is generated in

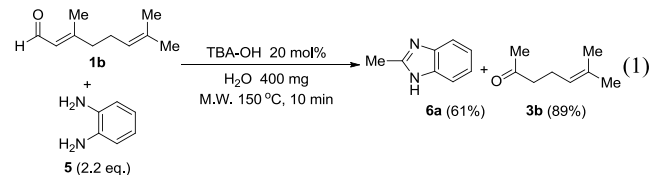
moderate to high isolated yields (51-93%) with the volatile products **2** produced in each process not being analyzed. Even the β -alkyl substituted α,β -enal **1b** participates in this C-C double bond reaction to give **3b** in a 91% isolated yield (entry 2). However, α -methyl substituted α,β -enal **1d** undergoes the cleavage reaction only inefficiently 51% (entry 4).

Table 3 The formation of benzimidazole derivatives via trapping of aldehyde by benzene-1,2-diamine ^a

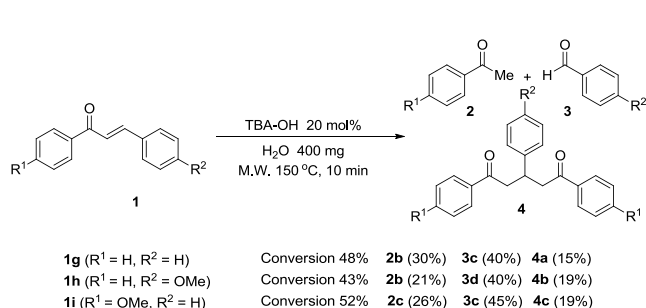
Entry (1)	α,β -Unsaturated compounds R ² R ³	Conversion (C-C double bond cleavage)	Isolated yield (%) 6 7
1 (1a)	H	> 99	62 (6a) 58 (7a)
2 (1c)	H	> 99	63 (6a) 48 (7b)
3 (1d)	CH ₃	> 99	70 (6b) 60 (7b)
4 ^b (1f)	<i>n</i> -C ₅ H ₁₁	94	61 (6c) 50 (7b)

^a Reaction condition: α,β -unsaturated carbonyl compounds (0.2 mmol), benzene-1,2-diamine (2.2 eq.), TBA-OH (20 mol%), H₂O (400 mg), microwave (M.W.) 150 °C, 10 min. ^b Using 4 equiv. of benzene-1,2-diamine.

Aldehydes generated from cleavage reactions of α,β -enals **1** are readily trapped by using benzene-1,2-diamine (**5**) to produce the corresponding benzimidazoles, **6** and **7** (Table 3). In these cases, even the volatile aldehyde products of the cleavage reaction, such as acetaldehyde, are trapped to give readily isolated imidazoles **6a** (entries 2-4). For example, microwave irradiation of an aqueous solution of 3-(anthracen-9-yl)acrylaldehyde (**1a**) in the presence of TBA-OH and **5** at 150 °C for 10 min leads to formation of benzimidazole **6a** and **7a** in respective 62% and 58% isolated yields (Table 3, entry 1).

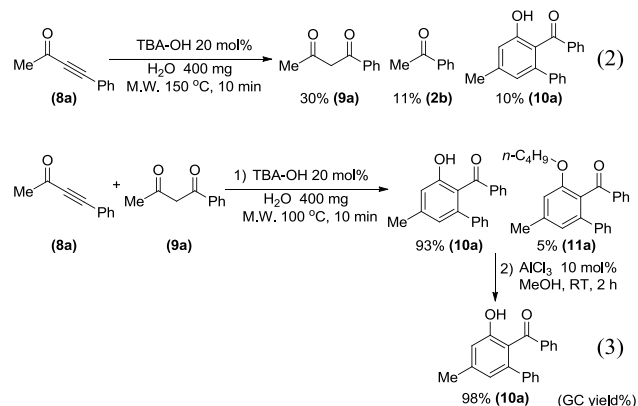


Especially interesting is the reaction of citral **1b** under these conditions in that it produces 2-methylimidazole **6a** (61%) and ketone **3b** (89%) (eq. 1). Thus, because ketones in the presence of **5** are not readily converted to imidazoles, the secondary derivatization technique serves as a convenient method to separate ketones and aldehydes formed in these reactions.

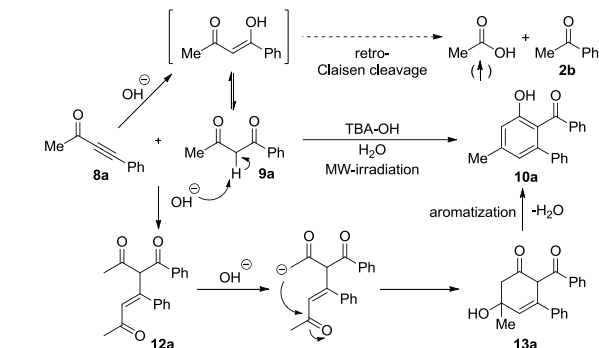


Scheme 2 Base catalysed reaction of chalcone derivatives

The reaction of chalcone (**1g**) in an aqueous solution containing TBA-OH is intriguing in that it produces the secondary conjugate addition product **4a** (15%) along with the expected C-C bond cleavage products, acetophenone (**2b**, 30%) and benzaldehyde (**3c**, 40%) (Scheme 2). 1,5-Diketone **4a** is likely formed in this reaction by 1,4-addition reaction of **1g** with the enolate anion derived by TBA-OH deprotonation of the initially generated methyl ketone **2b**. Other chalcone derivatives, **1h** and **1i**, display similar reactivity profiles.



α,β -Unsaturated ynones are another family of interesting substrates for the 1,4-addition reaction (eq. 2). This is exemplified by MW-assisted reaction of 4-phenylbut-3-yn-2-one (**8a**). Specifically, treatment of **8a** in an aqueous solution containing 20 mol% TBA-OH results in the formation of a mixture of 1,3-diketone **9a** (30%), acetophenone (**2b**, 11%), and substituted phenol **10a** (10%). The structure of **10a** was determined by using COSY, HMBC, HSQC 2D NMR spectroscopy (See the ESI[†]). In addition to this result, the microwave-assisted reaction of **8a** with **9a** by TBA-OH catalyst in aqueous condition produced a mixture of substituted phenol **10a** (93%) and *o*-alkylated phenol **11a** (5%), generated by butylation of **10a** with TBA-OH. The *o*-alkylated phenol **11a** was converted into substituted phenol **10a** by 10 mol% of AlCl₃ in MeOH for 2 h (eq. 3).¹⁰ It is reasonable to speculate that the 1,3-diketone **9a** is generated by 1,4-addition of water followed by tautomerization (Scheme 3). And **2b** comes from **9a** by retro-Claisen cleavage.¹¹ In addition, phenol derivative **10a** is likely formed by Robinson annulation between 1,3-diketone **9a** with ynone **8a** occurring via intermediates **12a** and **13a**. To

Scheme 3 Plausible mechanism of multi-substituted phenol by Michael addition reactions of diketone toward α,β -unsaturated ketone

confirm this proposal, a mixture of **8a** and **9a** in H₂O was MW-heated at 100 °C for 10 min in the presence of TBA-OH followed by treatment with AlCl₃ in MeOH. This process led to formation of **10a** in a 90% (Table 4, entry 1). The generality of the MW-assisted reactions of α,β -unsaturated ynones, which take place much more efficiently than those induced by using

Table 4 The synthesis of multi-substituted phenol from alkyne and 1,3-diketone with base catalyst^a

Entry	α,β -unsaturated ynone	R ³ R ⁴	Isolated yield (%)	
			10	
1	R ¹ = Me R ² = Ph (8a)	R ³ = COMe R ⁴ = C(=O)Ph (9a)	90 (10a)	
2	(8a)	R ³ = COMe R ⁴ = COMe (9b)	46 (10b)	
3	(8a)	R ³ = C(=O)Ph R ⁴ = C(=O)Ph (9c)	79 (10c)	
4 ^b	R ¹ = Ph R ² = Ph (8b)	(9a)	79 (10d)	
5	(8b)	(9b)	57 (10e)	
6	R ¹ = Ph R ² = <i>n</i> -C ₄ H ₉ (8c)	(9a)	83 (10f)	
7	(8c)	(9b)	55 (10g)	

^a Reaction condition: 1) α,β -unsaturated carbonyl compounds (0.2 mmol), 1,3-diketone compounds (1.1 eq.), TBA-OH (20 mol%), H₂O (400 mg), microwave (M.W.) 100 °C, 10 min, 2) AlCl₃ (10 mol%), MeOH (400 mg), room temperature, 2 h. ^b microwave (M.W.) 100 °C, 30 min.

conventional heating,¹² was demonstrated by the examples displayed in Table 4 (entries 2-7). And they produced 2,3,5-trisubstituted phenols in good to moderate yields.

Conclusions

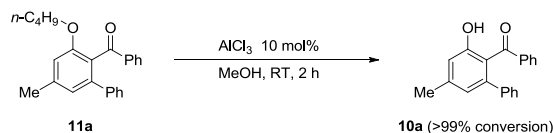
In the effort described above, we developed an eco-friendly, TBA-OH catalysed, microwave-assisted method for efficient 1,4-addition of water to α,β -unsaturated ketones and α,β -ynones. The observed C-C double bond cleavage reactions of α,β -enones and annulation reactions of α,β -ynones take place with high efficiencies in pure aqueous solutions. Efforts directed at developing applications of this 'Green Chemistry' method to the synthesis of important targets are progressing.

Acknowledgements

This work was supported by a grant from the National Research Foundation of Korea (NRF) (2011-0016830).

Notes and references

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Graphic Abstract

