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Rapid microwave assisted hydration of internal arylalkynes in the presence of PTSA: an efficient regioselective access to carbonyl compounds

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Abstract—A metal-free procedure for the regioselective hydration of internal arylalkynes under microwave irradiation is described. The reaction promoted by PTSA takes place rapidly in EtOH and regioselectively afforded in good yields various carbonyl compounds **2**.

The direct addition of O–H bonds to alkyne compounds, known as hydration, is one of the most simple and powerful tools to convert alkynes into carbonyl compounds, which are of great interest in organic synthesis.[1] Usually, this transformation requires the use of toxic mercury(II) salts[2] or expensive metal-transition catalysts[3] (Ru, Rh, Pt, etc.). Other alternatives require the presence of very strong acids[4] (H_2SO_4, HCOOH, TfOH), which could not be compatible in terms of selectivity in the case of functionalized substrates. Moreover, such conditions do not fulfil the contemporary requirements against the use of dangerous reagents.

Recently we reported a new and efficient acid-catalyzed hydration of various unsymmetrical arylated alkynes **1**.[5] The process consists in carrying out the reaction in boiling aqueous or alcoholic media in the presence of a catalytic amount (20 mol %) of *p*-toluenesulfonic acid (PTSA). This new friendly procedure, which is characterized by the mildness of reaction conditions, inexpensive reactants and the excellent functional group tolerance, allows the formation of the corresponding ketones in good to excellent yields from various internal alkynes. Activated arylalkynol substrates bearing a *para* σ-electron-donating group on the aromatic ring undergo regioselective water or alcohol addition (Markovnikov's rule) to afford carbonyl compounds within 6–24 h. However, this new regioselective hydration suffers from the following limitations: (i) under similar conditions, arylalkylalkynes were found to be less reactive than their propargylic homologues and 60 h were necessary to complete the reaction, (ii) hydration of arylalkynol substrates with an *ortho* σ-electron-donating substituent required longer reaction times due to their bulkiness (144 h) and finally, (iii) no reaction occurred from non-activated arylalkynes where the aryl ring is not activated by an electron-donating group in the *ortho* or *para* position even after prolonged reaction times.

To circumvent these limitations, we envisioned that microwave irradiation (MWI) could enhance this process and expand the chemistry scope. Microwave-assisted reactions have been widely recognized as an efficient synthetic tool and its benefits have been well documented.[6] Thus, the use of microwave irradiation was found to accelerate a wide variety of transformations and allowed significant improvements in yield and substrate scope. Vasudevan et al.[7] reported very recently a fast microwave promoted hydration of alkynes in superheated water (200 °C). While this reaction is a suitable method, it was exclusively described in the case of terminal alkynes. Consequently, in order to

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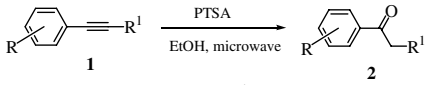
extend the substrate scope and to reduce the reaction times of the *p*-toluenesulfonic acid-catalyzed hydration of internal arylalkynes, we undertook to investigate this reaction under MWI. The results of this study are now reported.

Initial efforts focused on optimizing microwave conditions for the formation of ketone **2a** using 20 mol % of PTSA in EtOH, based on prior investigations of conventional thermal conditions.[5] We found that complete conversion of arylalkyne **1a** with a *para* σ-electron-donating group was observed at 120 °C within 30 min and the corresponding ketone **2a** was obtained in an 85% isolated yield. For comparison, under conventional thermal conditions in refluxing ethanol, an 81% yield was obtained but within 60 h.[8] In 30 min, alkyne **1b** with an *ortho* σ-electron-donating substituent was successfully hydrated and yields as well as conversions increased with higher reaction temperatures. Complete conversion was observed at 170 °C[9] (Table 1 compare entries 2, 3 and 4) and ketone **2b** was isolated in an excellent yield (92%, entry 4).

Next, the effects of microwave irradiation time, temperature and the amount of PTSA on the efficiency and the yield were briefly investigated in the case of non-activated arylalkyne **1c**. No reaction occurred at 120 °C within 30 min even when performing the hydration reaction in the presence of a stoichiometric amount of PTSA (entry 5). However, increasing the temperature up to 170 °C, the reaction rates and yield were considerably enhanced to afford an 89% yield of the expected ketone **2c** (entry 8). Similarly, low reactive *meta*-substituted arylalkylalkyne **1d** was transformed into **2d** but in a moderate 60% yield (entry 9). It should be noted by comparison that no reaction occurred from **1c** or **1d** under the traditional thermal conditions (78 °C, 72 h, oil bath), even with a more reactive unsubstituted arylalkyne having a propargylic alcohol.[5] More interestingly, we were pleased to observe that activated diarylalkyne **1e** could be rapidly and successfully transformed into its corresponding ketone **2e** under microwave heating. Though 72 h were needed to achieve complete conversion under classical heating, we noticed a significative benefit to use MWI (entries 10 and 11). Thus, in the presence of a stoichiometric amount of PTSA at 120 °C, **2e** was isolated with a nearly quantitative 96% yield (entry 12).

Table 1. Optimization of the PTSA promoted hydration of arylalkynes[10] **1** under MWI



a: R = *p*-OMe $R^1 = C_4H_9$
b: R = *o*-OMe $R^1 = C_4H_9$
c: R = H $R^1 = C_4H_9$
d: R = *m*-OMe $R^1 = C_4H_9$
e: R = *p*-OMe $R^1 = C_6H_5$

Entry	PTSA (equiv)	Alkyne	*T* (°C)	Time (min)	Conv.[a] (%)	Yield of **2**[b] (%)
1	0.2	**1a**	120	30	100	85
2	0.2	**1b**	120	30	40	nd
3	0.2	**1b**	150	30	85	nd
4	0.2	**1b**	170	30	100	92
5	1.0	**1c**	120	30	0	0
6	0.2	**1c**	160	30	9	nd
7	1.0	**1c**	160	30	50	35
8	1.0	**1c**	170	30	100	89
9	1.0	**1d**	170	30	71	60
10	0.2	**1e**	120	30	68	nd
11	0.2	**1e**	140	30	79	nd
12	1.0	**1e**	120	30	100	96

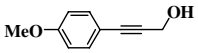
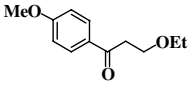
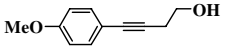
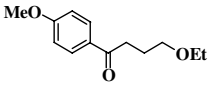
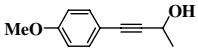
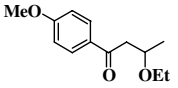
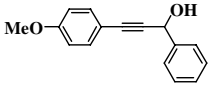
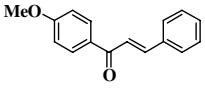
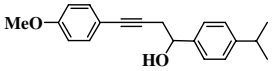
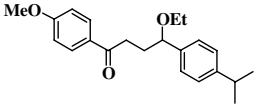
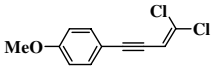
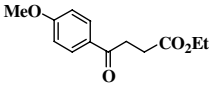
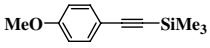
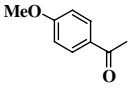
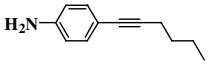
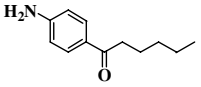
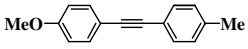
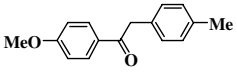
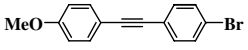
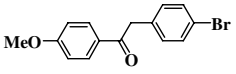
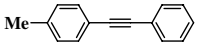
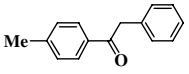
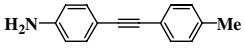
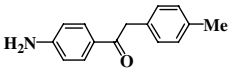
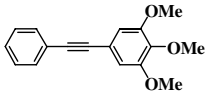
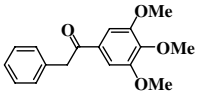
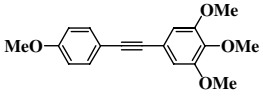
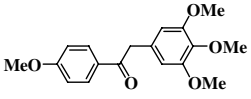
[a] The conversion was measured by ^{1}H NMR analysis and is based on remaining alkyne.
[b] Isolated yields.

We next investigated the scope and limitation of this hydration reaction with PTSA under MWI using a variety of internal alkynes. The results of this study are reported in Table 2.

Firstly, we have applied this efficient process to several arylated propargylic or homopropargylic alcohols (entries 1–5). Thus by using 0.2 equiv of PTSA under MWI at 120 °C in ethanol (conditions A), we have observed for each substrate both the etherification of the free hydroxyl group and the regioselective hydration of the triple bond in good yields (51–98%). 1,1-Dichloroenyne **1k**, prepared from Sonogashira–Linstrumelle coupling using 1-bromo-2,2-dichloroethylene, was transformed into 1,4 ketoester **2k**. Under these conditions, hydration and alcoholysis of the vinyl chlorine bonds occurred and provided **2k** with a 51% isolated yield (entry 6). Under conditions A, silylated arylalkyne **1l** was efficiently transformed into 4-methoxyacetophenone **2l** after hydration and subsequent hydrolysis of the silylated moiety with a satisfactory 77% yield. One notes that under conventional heating, the PTSA process was not efficient to prepare acetophenones, the triple bond was recovered unchanged even after a prolonged reaction time. Arylalkyne **1m** bearing in the *para* position of the aromatic ring another electron-donating substituent, such as a NH_2 group, reacted as well and produced the corresponding ketone **2m** in good yield (91%, entry 8). According to this result, we suppose that the reaction proceeds via hydration of **1m** as its free amine (electron-donating group) rather than its corresponding ammonium (electron withdrawing group). Indeed, all attempts to perform the hydration of substrates having an electron withdrawing group (e.g., CO_2R and CN) failed and the starting materials were recovered unchanged.

Then, the PTSA-catalyzed hydration reaction of internal alkynes under MWI was evaluated with unsymmetrical diarylalkynes. In the presence of a stoichiometric amount of PTSA, we were pleased to observe at 120 °C that the substrate **1n** reacted to regioselectively give ketone **2n** in a good yield within 30 min, while 72 h were required under classical heating in refluxing ethanol. Hydration of halogenated **1o** was also examined under conditions A. Total conversion was observed after stirring for 1 h and **2o** was regioselectivity obtained in a good yield (98%).

Table 2. PTSA-promoted hydration of internal arylalkynes under MWI: synthesis of functionalized arylketones **2**

Entry	Alkyne **1**		Conditions	Ketone **2**	Yield[a] of **2** (%)
1		**1f**	A		**2f** 98
2		**1g**	A		**2g** 79
3		**1h**	A		**2h** 51[b]
4		**1i**	A		**2i** 90
5		**1j**	A		**2j** 69
6		**1k**	A		**2k** 51
7		**1l**	A		**2l** 77
8		**1m**	A		**2m** 91
9		**1n**	A		**2n** 97[c]
10		**1o**	A		**2o** 98[d]
11		**1p**	B		**2p** 80[e]
12		**1q**	B		**2q** 79
13		**1r**	C		**2r** 68
14		**1s**	C		**2s** 55[f]

Conditions A: 120 °C, 30 min, PTSA (0.2 equiv); B: 150 °C, 30 min, PTSA (1 equiv); C 170 °C, 30 min, PTSA (1 equiv).

[a] Isolated yields.

[b] 27% of the conjugated ketone (Rupe's rearrangement) were also isolated.

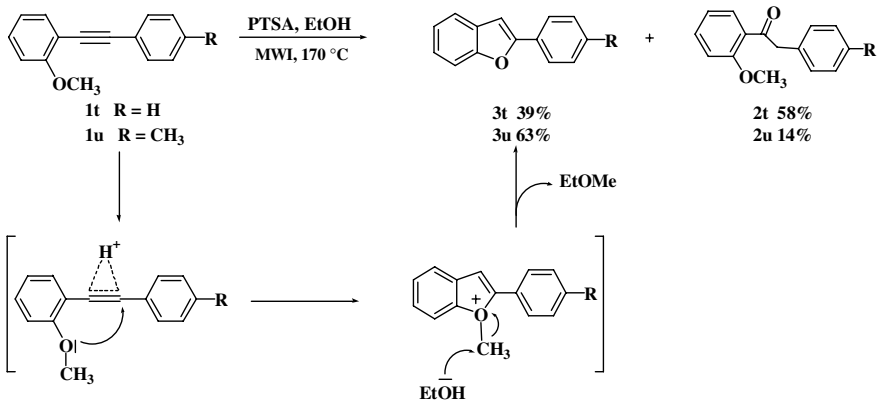
[c] Reaction was carried out using 1 equiv of PTSA.

[d] Reaction was run for 1 h (a 75% conversion was obtained within 30 min).

[e] Obtained as an inseparable 90/10 mixture with the other regioisomer.

[f] Obtained as an inseparable 87/13 mixture with the other regioisomer.

When diarylalkynes having a *para* Me- or NH_2-substituent were used, the above experimental conditions A were not appropriate and the starting materials were recovered together with the expected ketones **2p** and **2q**. Increasing gradually the temperature and the amount of PTSA (conditions B: 150 °C; 1 equiv), substrates **1p**



Scheme 1. Hydration of *ortho*-methoxydiarylalkynes **1** under microwaves irradiation: a plausible explanation of 2-arylbenzo[*b*]furans **3** formation.

and **1q** efficiently reacted to give their corresponding ketones with similar yields (entries 11 and 12). Surprisingly, the 3,4,5-trimethoxyaryl unit, which is frequently found in natural substances,[11] was found to disable the triple bond. To circumvent this, the reactional temperature was increased to 170 °C for 30 min (conditions C) and ketones **2r** and **2s** were regioselectivity obtained in good yields (entries 13 and 14).

Next, we studied the hydration of hindered diarylalkynes bearing in the *ortho* position a methoxy substituent (Scheme 1). Surprisingly, hydration of **1t** under conditions B afforded beside the expected arylketone **2t** (58%) a 39% yield of 2-phenylbenzo[*b*]furan **3t**. More interestingly, under these conditions, the *ortho* methoxytolylalkyne **1u** reacted to mainly give the 2-substituted benzo[*b*]furan **3u** (63%), together with a small amount (14%) of arylketone **2u** (Scheme 1). A plausible explanation for the obtention of 2-arylbenzo[*b*]furans **3** (unoptimized in the present study) is depicted in Scheme 1. The 2-arylbenzo[*b*]furan **3** formation could not be explained by the well known[12] intramolecular cyclization of 2-alkynylphenol derivatives. Indeed we never observed during this study any phenol formation resulting from the methoxy cleavage even at higher temperatures (see Table 2, entries 13 and 14), and 4-methylanisole itself did not react under these conditions.

Consequently, we suppose that in the presence of PTSA catalyst, the activated triple bond underwent regioselective 5-*endo*-dig-cyclization with the *ortho* methoxy substituent. Then, EtOH would cleave the oxonium species to afford 2-arylbenzo[*b*]furan derivatives **3**. This latest synthesis of 2-substituted-benzo[*b*]furans as well as its extension to the preparation of other heteroatom-containing cyclic compounds is already underway.

In summary, the purpose of this study was to expand the chemistry scope of the hydration of arylalkylalkynes as well as diarylalkynes under MWI. We have demonstrated the positive effect of the microwaves heating towards arylpropargylic alcohols, which could be hydrated with reduced reaction times (50 times faster than with conventional heating) under PTSA-catalysis. Furthermore, the present process was extended to the synthesis of various functionalized diarylketones starting from diarylalkynes with good outputs and by preserving some various functional groups. The experimental microwave experiments[13] described in this letter are well established and controlled to be safely and beneficially reported.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.155.

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