Highly Efficient *p*-Toluenesulfonic Acid-Catalyzed Alcohol Addition or Hydration of Unsymmetrical Arylalkynes

Nathanaël Olivi, Emmanuel Thomas, Jean-François Peyrat, Mouâd Alami,* Jean-Daniel Brion

Laboratoire de Chimie Thérapeutique, BioCIS – CNRS (UMR 8076), Université Paris Sud XI, Faculté de Pharmacie, rue J. B. Clément 92296 Châtenay-Malabry Cedex, France
Fax +33(1)46835828; E-mail: mouad.alami@cep.u-psud.fr
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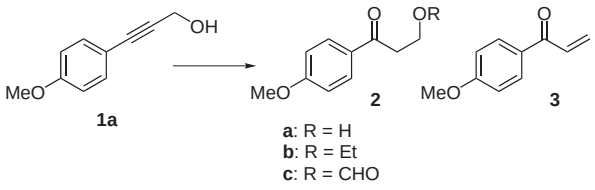
Abstract: Under a catalytic amount of PTSA in aqueous or alcoholic media, activated unsymmetrical arylalkynes **1** undergo regioselective water or alcohol addition to afford successfully carbonyl compounds **2** in good to excellent yields. This new environmentally metal-free procedure, which afforded only Markovnikov adducts, is characterized by the mildness of acidic conditions and the excellent regio- and chemoselectivity.

Key words: unsymmetrical arylalkyne, hydration, PTSA, ketone, alcohol addition, water

The direct addition of O-H bonds to alkynes, known as hydration, is one of the most simple and powerful tools to convert alkynes into carbonyl compounds.[1] Toward this end, a large number of metal-catalyzed methods has been developed. The older catalyst was mercury(II) salt[2] which allows hydration of alkynes in very good yields. However, the necessity of a stoichiometric amount of toxic mercury(II) and/or the strongly acidic conditions do not meet the contemporary requirement against hazardous reagents. In recent years, considerable effort has been expended to extend the hydration reaction to applications in fine chemicals, and to use new metal-transition catalysts, including Ru, Rh, Pd, Pt and Au.[3] All these catalysts have been used for the hydration of alkynes in moderate to good yields, however, the use of expensive metal-transition catalysts limits the exploitation of these methods. Therefore, a metal-free hydration of alkynes has been developed under acidic conditions[4] including concentrated sulfuric acid, formic acid and catalytic Brønsted acid such as trifluoromethanesulfonic acid or trifluoromethanesulfonimide.[5] While these reactions are suitable methods in the case of robust substrates, many of them either require harsh conditions (large excess of strong acid, long reaction times) or are particularly limited to terminal alkynes and/or display low selectivity when sensitive functional groups are present on the alkynes. To perform selective hydration of alkyne compounds on functionalized fragile substrates, the discovery and development of environmentally friendly procedures remain as intriguing challenges.

We report herein a metal-free procedure for the synthesis of carbonyl compounds which involves an efficient *p*-toluenesulfonic acid-catalyzed water or alcohol addition to activated unsymmetrical aryl-alkynes **1** in aqueous or alcoholic media. This new environmentally friendly procedure, which allows the formation of the corresponding ketones in good to excellent yields, is characterized by the mildness of reaction conditions, inexpensive reactants and the excellent functional group tolerance.

At first, we studied the *p*-toluenesulfonic acid-catalyzed hydration of 3-(4-methoxyphenyl)prop-2-yn-1-ol (**1a**) as a model system. The required arylalkynes **1** were readily prepared by Pd-catalyzed Sonogashira–Linstrumelle (SL) coupling reaction.[6] Substrate **1a**, bearing a free hydroxyl group was chosen so as to illustrate the advantages of the use of PTSA in terms of yield, catalytic efficiency and chemoselectivity of the procedure in comparison with other literature conditions.[4,5] Table 1 summarizes the results of these studies (Equation 1).



Equation 1

Table 1 Effect of Acid Mediated Hydration of Arylalkyne **1a**

Entry	Reactants	Yield (%)[a]	Product
1	PTSA (20 mol%), H_2O,[b] 100 °C, 12 h	75	**2a**
2	PTSA (20 mol%), EtOH,[c] 78 °C, 5 h	94	**2b**
3	CH_3SO_3H (20 mol%), EtOH,[c] 78 °C, 18 h	85	**2b**
4	CF_3COOH (30 mol%), EtOH,[c] 78 °C	0	–[d]
5	HCOOH, 100 °C, 5 h	50[e]	**2c**
6	CF_3SO_3H (20 mol%), H_2O[b]–dioxane, 100 °C, 4 h	60[e]	**3**
7	H_2SO_4 (65%), 20 °C, 2 h	0	–[e]

[a] Yield of isolated product.
[b] Deionized water was used.
[c] Commercially absolute EtOH was used.
[d] Exclusively starting material was recovered.
[e] No starting material was recovered.

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The use of PTSA monohydrate (20 mol%) in water allows hydration of **1a** in a 75% isolated yield; the reaction was completed within twelve hours at 100 °C (Table 1, entry 1). Since the water adds to the triple bond in accordance with Markovnikov's rule, 4-hydroxy-1-(4-methoxyphenyl)-1-propan-1-one (**2a**) was obtained as the only product in this reaction. Performing the reaction of **1a** in ethanolic media assisted both etherification of free hydroxyl group and carbonyl formation producing carbonyl ether compound **2b** in an excellent isolated yield (94%, entry 2). Changing the catalyst from PTSA to methanesulfonic acid resulted in a similar yield but in longer reaction times (entry 3), whereas no reaction occurred in the presence of trifluoroacetic acid (entry 4). It should be noted that the presence of PTSA catalyst is essential in aqueous or ethanolic media. In its absence no reaction has been observed. With formic acid as a solvent according to the conditions described by Shvo,[4c,d] alkyne **1a** undergoes after hydrolysis both hydration and formylation of the alcohol function and produced the corresponding ketone **2c** in only 50% yield (entry 5). The use of trifluoromethanesulfonic acid (20 mol%) under the recent report of Shirakawa's conditions[5] resulted in hydration of **1a** followed by elimination of water to give exclusively unsaturated ketone **3** in 60% yield (entry 6). Finally, when performing the hydration of **1a** in the presence of sulfuric acid[4a] no carbonyl compounds could be detected in the resulting crude polymers mixture (entry 7). Thus, the results of Table 1 unambiguously demonstrate that the use of PTSA in the hydration of arylalkynol compounds compares favorably with the previous acid mediated hydration reaction.

We next investigated the scope and limitations of this new friendly reaction using various kinds of unsymmetrical arylalkynes **1**. As shown in Table 2, the PTSA-catalyzed reaction is also effective in the case of arylalkynes **1b** and **1c** bearing longer alkynol chains (entries 1 and 2). The latter reacts more slowly as 36 hours are required to achieve complete conversion of the substrate. More importantly, etherification of the free hydroxyl group is not observed in this case. Another arylalkyne, **1d**, bearing *para* electron-donating groups such as amine, leads to similar results (entry 3). The reaction was also successful from unsymmetrical arylalkyne **1e**, which contains a hexynyl side chain (entry 4); the yield of the corresponding ketone **2g** remains high, although a longer reaction time was needed. Reaction from arylalkyne **1f** having a secondary propargylic alcohol provided the expected carbonyl ether **2h** in an excellent isolated yield (91%, entry 5). Under these conditions, tertiary propargyl alcohol **1g** leads in 73% yield to the corresponding conjugated ketone **2i**, well known as the Rupe's rearrangement[8] adduct (entry 6).

As shown in Table 2, the reaction rate proved to be dependent significantly on the steric and electronic nature of the substrate. Thus, arylalkynes **1h** and **1i** bearing in the *ortho* position of the aromatic ring an electron-donating substituent such as a methoxy group reacted as well and produced the corresponding ketones in good yields (entries 7 and 8). Owing to their bulkiness, they require, however, longer reaction times and in the case of **1i**, 1.2 equivalents of PTSA are needed to achieve complete conversion of **1i**. However, no reaction was observed from arylalkynes **1j** and **1k** as well as from terminal alkyne **1l** where the phenyl ring is not activated by an electron-donating group in the *ortho* or *para* position (entries 9–11). Finally, unsymmetrical diarylalkynes such as **1m** leads regioselectively to the formation of ketone **2o** in which the carbonyl function was proximal to the electron-rich phenyl ring (entry 12).

Table 2 PTSA-Catalyzed Synthesis of Various Carbonyl Compounds

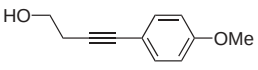
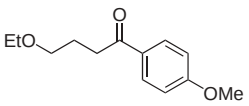
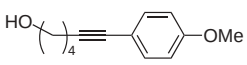
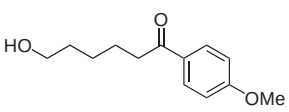
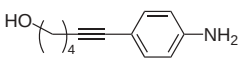
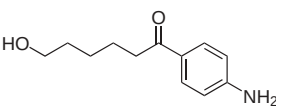
Entry	Alkyne **1**[a]	Solvent[b] Time Temp	Product **2**[c]	Yield[d] (%)
1	 **1b**	EtOH 24 h 78 °C	 **2d**	85
2	 **1c**	EtOH 36 h 78 °C	 **2e**	90
3	 **1d**	EtOH 6 h 78 °C	 **2f**	78

Table 2 PTSA-Catalyzed Synthesis of Various Carbonyl Compounds (continued)

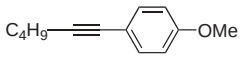
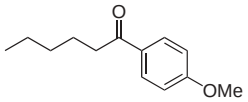
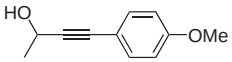
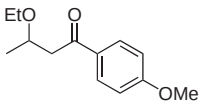
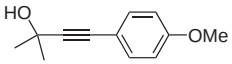
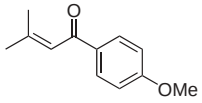
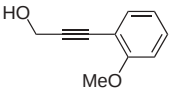
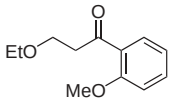
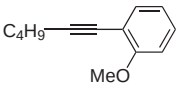
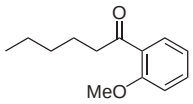
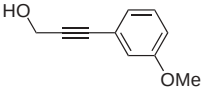
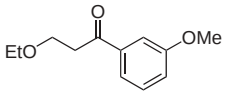
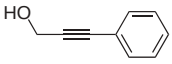
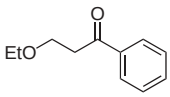
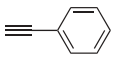
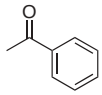
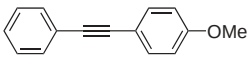
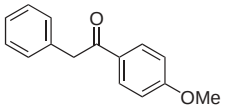
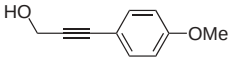
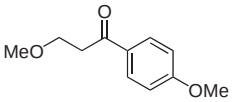
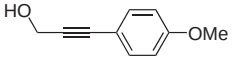
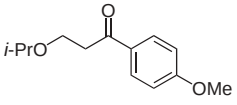
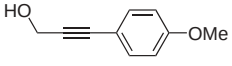
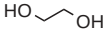
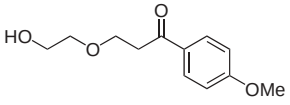
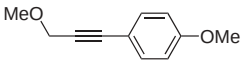
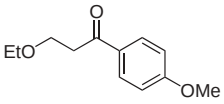
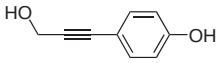
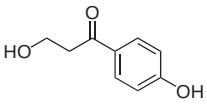
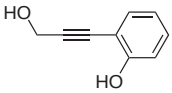
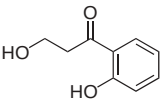
Entry	Alkyne **1**[a]	Solvent[b] Time Temp	Product **2**[c]	Yield[d] (%)
4	 **1e**	EtOH 60 h 78 °C	 **2g**	81
5	 **1f**	EtOH 24 h 78 °C	 **2h**	91
6	 **1g**	EtOH 10 h 78 °C	 **2i**	73
7	 **1h**	EtOH 144 h 78 °C	 **2j**	73
8	 **1i**	EtOH 144 h 78 °C	 **2k**	80[e]
9	 **1j**	EtOH 72 h 78 °C	 **2l**	0[f]
10	 **1k**	EtOH 72 h 78 °C	 **2m**	0[f]
11	 **1l**	EtOH 72 h 78 °C	 **2n**	0[f]
12	 **1m**	EtOH 72 h 78 °C	 **2o**	80
13	 **1a**	MeOH 6 h 65 °C	 **2p**	98
14	 **1a**	*i*-PrOH 7 h 82 °C	 **2q**	66
15	 **1a**	 17 h 100 °C	 **2r**	33

Table 2 PTSA-Catalyzed Synthesis of Various Carbonyl Compounds (continued)

Entry	Alkyne **1**[a]	Solvent[b] Time Temp	Product **2**[c]	Yield[d] (%)
16	 **1n**	EtOH 8 h 100 °C	 **2b**	90
17	 **1o**	H_2O[g] 8 h 100 °C	 **2s**	79
18	 **1p**	H_2O[g] 12 h 100 °C	 **2t**	73

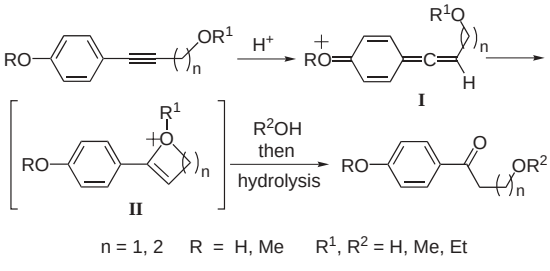
[a] Prepared according to ref.[6]
[b] Commercially absolute EtOH was used as a solvent.
[c] All new compounds exhibited satisfactory spectral properties. For a general procedure, see ref.[7]
[d] Isolated yield.
[e] 1.2 equiv of PTSA were used.
[f] In the presence of a catalytic or a slight excess (1.2 equiv) of PTSA, exclusively starting material was recovered.
[g] Deionized water was used.

As the etherification process keeps an unexpected result in this new procedure, we managed to study the relation between solvent and etherification reaction. In alcoholic media such as methanol or 2-propanol (entries 13 and 14) the ether derivatives **2p** and **2q** corresponding to the solvent used were formed in 98% and 66% yields, respectively, whereas, in ethylene glycol mono-etherification occurs smoothly and the ketone **2r** was obtained in moderate yield (33%, entry 15). Moreover, The PTSA-catalyzed reaction from arylalkyne **1n** bearing a methyl ether function resulted in a *trans*-etherification process furnishing the ethyl ether derivative **2b** in 90% yield (entry 16). Finally, several attempts were made in water to avoid etherification process. Under these conditions, hydration reactions occurred efficiently in good yields and free hydroxyl group remained unchanged (entries 17 and 18).

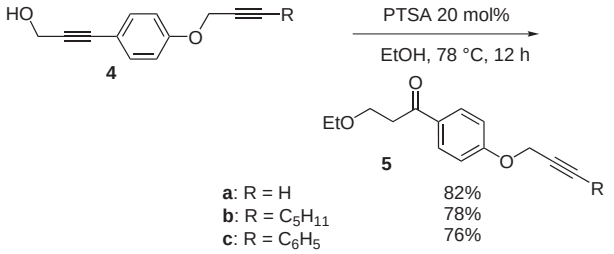
According to these results (entries 1, 5, 7, 13–18), it seems that the PTSA-catalyzed reaction was clearly hetero atom-assisted. Substrates having a propargylic or homopropargylic function could provide a four or a five membered cyclic oxonium intermediate **II** which could result from an intramolecular oxygen atom-addition (Scheme 1). Further nucleophilic ring-opening by alcoholic or aqueous media gives after hydrolysis the carbonyl compound. The formation of the intermediate **II** in this PTSA-catalyzed reaction was either supported by ether formation (entries 1, 5, 7, 13–15) and *trans*-etherification process (entry 16). We can notice that from substrates **1c** and **1d** having longer alkynol chain (n = 4, entries 2, 3) direct alcoholic media addition[9] on **I** is preferred in comparison with thermodynamically disfavored 7-membered cyclic oxonium intermediate formation, keeping free hydroxyl group unchanged.

The ketone formation from substrates **1e**, **1i** and **1m** would also result from alcoholic media addition and subsequent enol ether species hydrolysis. To support this assumption an experiment was carried out. When performing the PTSA-catalyzed reaction from **1e** in methanolic or ethanolic media, attempts isolation of enol ether intermediate before hydrolysis were unsuccessful. However, when 2-propanol was used as solvent the corresponding enol ether adduct was isolated together with the carbonyl derivative **2g**.

The requirement for an electron-donating substituent in the aryl ring imparts additional chemoselectivity to this new procedure and must especially underlined. Thus, terminal alkynes as well as aliphatic and non-activated arylalkynes did not react under the reaction conditions used before. Three examples of selective PTSA-catalyzed reactions of functionalized unsymmetrical arylalkynes **4** are depicted below (Equation 2).



Scheme 1 Proposed mechanism for the PTSA-catalyzed reaction



Equation 2

In conclusion, a novel and reliable procedure for the synthesis of aromatic ketones was achieved via *p*-toluenesulfonic acid-catalyzed reaction of unsymmetrical arylalkynes in alcoholic or aqueous media. This mild and selective protocol allows the alcohol addition or the hydration reaction to occur in the presence of free hydroxyl group and non-activated carbon-carbon triple bond, which is a valuable advantage over previously reported methods. Further investigation of the scope and synthetic application of this environmentally friendly procedure is under way and will be reported in due course.

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(7) **Typical Procedure for the PTSA-Catalyzed Hydration of Unsymmetrical Arylalkynes:** To a stirred solution of **1a** (162 mg, 1 mmol) in 2 mL of absolute EtOH, was added *p*TSA monohydrate (38 mg, 0.2 mmol). The mixture was heated at reflux for 5 h, diluted with H_2O and extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuo, the crude product was purified by column chromatography on silica gel (CH_2Cl_2) to afford 196 mg (94%) of **2b** as a yellow oil. 3-Ethoxy-1-(4-methoxyphenyl)propan-1-one (**2b**): ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.89 (2 H, d, *J* = 8.9 Hz), 6.87 (2 H, d, *J* = 8.9 Hz), 3.79 (2 H, t, *J* = 6.8 Hz), 3.78 (3 H, s), 3.47 (2 H, q, *J* = 7.0 Hz), 3.14 (2 H, t, *J* = 6.7 Hz), 1.14 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 196.7, 163.3, 130.2, 130.0, 113.5, 66.3, 65.8, 55.2, 38.4, 14.9. 1-(4-Aminophenyl)-6-hydroxyhexan-1-one (**2f**): ^{1}H NMR (270 MHz, CD_3OD): δ = 7.75 (2 H, d, *J* = 8.8 Hz), 6.63 (2 H, d, *J* = 8.8 Hz), 3.55 (2 H, t, *J* = 6.4 Hz), 2.87 (2 H, t, *J* = 7.6 Hz), 1.80–1.20 (6 H, m). ^{13}C NMR (67.5 MHz, CD_3OD): δ = 201.5, 153.6, 132.1, 126.8, 114.3, 62.3, 38.6, 33.5, 26.7, 26.1. 1-(2-Methoxyphenyl)hexan-1-one (**2k**): ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.61 (1 H, dd, *J* = 7.6 Hz, *J* = 1.8 Hz), 7.45–7.30 (1 H, m), 7.00–6.85 (2 H, m), 3.84 (3 H, s), 2.92 (2 H, t, *J* = 7.5 Hz), 1.75–1.55 (2 H, m), 1.35–1.25 (4 H, m), 0.87 (3 H, t, *J* = 6.9 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 202.9, 158.1, 132.8, 129.9, 128.7, 120.4, 111.4, 55.2, 43.5, 31.4, 23.9, 22.3, 13.7.

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