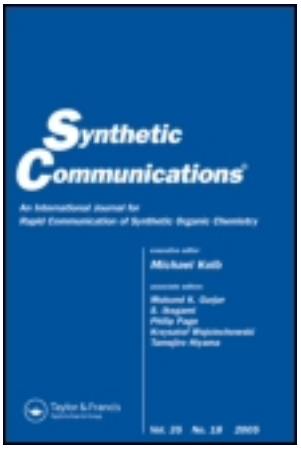

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Versatile Methodology to Hydrate Alkynes, in the Presence of a Wide Variety of Functional Groups, with Mercury(II) p-Toluensulfonamidate, Under Catalytic, Mild, and Neutral Conditions

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VERSATILE METHODOLOGY TO HYDRATE ALKYNES, IN THE PRESENCE OF A WIDE VARIETY OF FUNCTIONAL GROUPS, WITH MERCURY(II) *P*-TOLUENSULFONAMIDATE, UNDER CATALYTIC, MILD, AND NEUTRAL CONDITIONS

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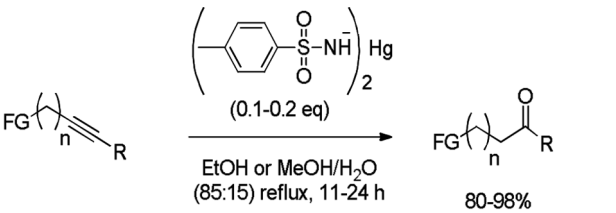
GRAPHICAL ABSTRACT



FG: -N_3, -Cl, -CN, -OH, -COOMe
-COMe, -Cyclic ketone
-OMe, -OEt, -OBn, Cyclic ether
-$CH(OMe)_2$, -OMEM,
-H, -Alkyl, -Alkenyl, -Alkynyl, -Aryl

R: H, Alkyl, Ph, Alkynyl

Abstract *A method to generate carbonylic compounds from alkynes under mild and neutral conditions, with excellent functional group compatibility and good yields, is described. Hydration takes place under catalytic conditions by using 0.1 to 0.2 equivalents of the easily available and inexpensive mercury(II)* p-*toluensulfonamidate in a hydroalcoholic solution. After use, the catalyst is rendered inert and/or recycled.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Acetylene; carbonylic compounds; catalyst; hydration; mercury(II) *p*-toluensulfonamidate; regioselectivity; stereoselectivity

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INTRODUCTION

The addition of water to alkynes to obtain carbonyl compounds is a very useful reaction in organic chemistry.[1] The traditional methods based on mercury(II) catalysts[2] hydrate internal and terminal alkynes to give the Markovnikov adduct. Usually acid is required to form the carbonyl product in typical methods. The use of an acid considerably reduces the functional group compatibility and narrows the scope of the methodology. When using a buffered system such as mercury(II) triflate–N,N,N′,N′-tetramethylurea (TMU) complex,[3] good functional group compatibility is observed except for substrates containing acetal or benzyl groups.[4]

Other methods have been reported that use catalysts based on gold(I),[5] gold (III),[6] platinum(II),[7] palladium(II),[8] rhodium (III),[9] and ruthenium(II)[10] to form the anti-Markovnikov product. These are very efficient catalysts but their main disadvantage is the cost of the catalysts based on noble metals.

This article reports a catalytic method under neutral conditions based on the inexpensive reagent mercury(II) *p*-toluensulfonamidate.[11] The efficiency of this reagent in the hydration of terminal alkynes has been proven, under stoichiometric conditions, for the total synthesis of 1,7-epoxycyclononanes,[12] affording intermediate diketones in excellent yields (Table 1). Under these reaction conditions, polymerization and epimerization of the substrates (especially at the α position of ketones) were avoided due the neutral and mild conditions used.

Herein we report that mercury(II) *p*-toluensulfonamidate is a highly effective and inexpensive catalyst with an excellent functional group tolerance for the hydration of terminal and internal alkynes, even with acetal or benzyl substrates. Preparation of mercury(II) *p*-toluensulfonamidate is six times cheaper than $Hg(OTf)_2 \cdot TMU$ and approximately 100 times lower in cost than Au(I) or Au(III) catalysts. Furthermore we report the chemoselective hydration of the most accessible alkyne group in some dialkyne substrates. On the other hand, the use of small catalytic amounts of this catalyst, together with its inertization and/or recovery, avoids possible toxic and/or environmental impacts.

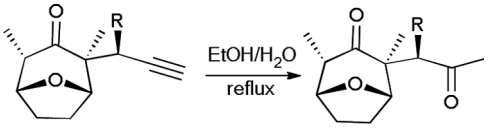
RESULTS AND DISCUSSION

In our initial assays, we worked under stoichiometric conditions of $Hg(TsNH)_2$ with the 8-oxabicyclo[3.2.1]octane substrates (Table 1). The main characteristic of these substrates is the presence of a protected propargylic alcohol group and one stereocenter in α to the carbonyl group (on C-3), sensitive to epimerization.

Upon treatment of **1** with 1.3 eq. of mercury(II) sulfonamidate in a (85:15) mixture of ethanol–water as a solvent for 24 h, the dicarbonyl product **2** was obtained in quantitative yield. It is important to note that the benzyl group (Table 1, entry 1) does not cleave at all upon the hydration reaction. Also the acetalic group methoxymethyl remains stable (Table 1, entry 4). Thus, the sensitive substrate **7** that contains the acetalic protecting group methoxymethyl (OMEM) was converted into **8** in quantitative yield.

The methoxy and ethoxy substrates **3** and **5** also afforded the hydration products **4** and **6** with good yields. Finally, the hydration reaction of **9** also gave the carbonylic product **10** with good yield.

Table 1. Hydration of terminal alkynes of 1,7-epoxycyclononane substrates with $Hg(TsNH)_2$ under stoichiometric conditions (1:1.3 eq.)



Entry	R group	Substrate	Time (h)	Product	Yield (%)[a,b,c]
1	OBn	**1**	24	**2**	92–100
2	OMe	**3**	23	**4**	85
3	OEt	**5**	18	**6**	85
4	OMEM	**7**	24	**8**	98
5	H	**9**	24	**10**	85

[a]Isolated yields.
[b]The reaction yields are quantitative by NMR or GC (using internal standard).
[c]Conversion in all cases is 100%.

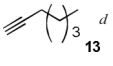
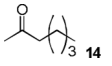
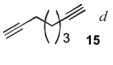
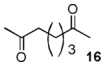
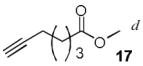
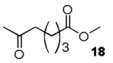
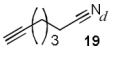
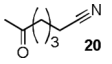
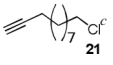
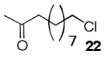
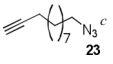
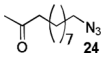
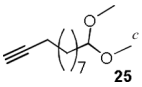
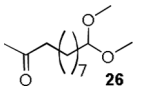
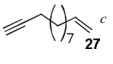
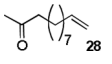
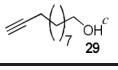
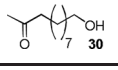
In all these reactions the epimerization product at the α carbons of both ketone groups, in the final product, was not observed. However, this problem was detected previously by us working with other hydration methods that need the use of an acid (i.e., $HgSO_4/H_2SO_4$). Moreover, by working with $Hg(TsNH)_2$ under neutral conditions the R group at the propargylic position was not cleaved at all.

The next step in our project was to investigate how the reaction took place under catalytic conditions and the functional group compatibility (Table 2). Phenylacetylene **11** reacted under catalytic conditions, using 0.1 eq of $Hg(TsNH)_2$, to form acetophenone **12** in excellent yield, which indicates that the electron delocalization of the triple bond towards the aromatic ring does not interfere in the reaction. Hydration of 1-heptyne **13** to afford 2-heptanone **14** demonstrates that the reaction works with good yield for substrates with alkyl linear chains. A dialkyne substrate **15** was also dihydrated with 0.17 eq. into 2,7-octadienone **16**. Methyl ester **17**, nitrile **19**, and chloride **21** groups did not interfere with the catalytic cycle and completely converted into the ketone products **18, 20**, and **22**, respectively.

Because of the poor solubility of substrates **23** and **27** in methanol, the reactions were carried out in (85:15) ethanol–water as a solvent. The hydration of both products gave **24** and **28** in good yields. The dimethoxyacetal substrate **25** was efficiently converted into product **26**, without observing any degree of hydrolysis of this acid-sensitive group, under these mild neutral conditions. Finally, alcohol **29** was converted into the ketone **30** in good yield, and no anchimeric influence of the hydroxyl group was observed on the yield and regioselectivity of the reaction.

Most of substrates (Table 2) also reacted with mercury(II) *p*-toluensulfonamidate under stoichiometric conditions (1:1.3 eq.), with similar reaction times, conversions, and yields. The reaction also converted substrates with internal C≡C bonds into carbonyl compounds (Table 3). Because of the characteristics of the catalyst, the selective hydration of the terminal alkyne group in front of the internal triple bonds is accomplished, under reflux conditions, on substrates in which one of the C≡C bonds is sterically hindered. This steric-controlled chemoselectivity could be of interest in synthetic organic chemistry.

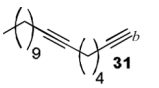
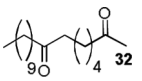
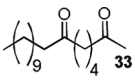
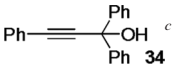
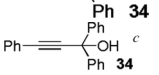
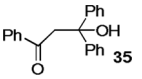
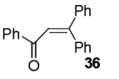
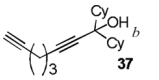
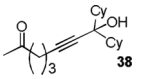
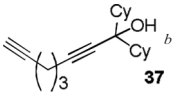
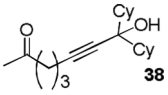
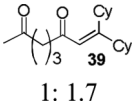
Table 2. Chemoselective hydration of alkynes having different functional groups using catalytic amounts of $Hg(TsNH)_2$

Entry	Substrate	Conditions	Product	Eq. $Hg(TsNH)_2$ (mmol/mmol of substrate)	Conversion (%)	Yield (%)[a,b,c]
1	 11	$MeOH/H_2O$ Reflux, 20 h	 12	0.10	100	80[c]
2	 13	$MeOH/H_2O$ Reflux, 14 h	 14	0.20	100	78[c]
3	 15	$MeOH/H_2O$ Reflux, 39 h	 16	0.17	100	82[c]
4	 17	$MeOH/H_2O$ Reflux, 22 h	 18	0.11	100	98
5	 19	$MeOH/H_2O$ Reflux, 21 h	 20	0.08	100	93
6	 21	$MeOH/H_2O$ Reflux, 20 h	 22	0.11	100	88
7	 23	$EtOH/H_2O$ Reflux, 66 h	 24	0.10	100	80
8	 25	$MeOH/H_2O$ Reflux, 48 h	 26	0.21	100	85
9	 27	$EtOH/H_2O$ Reflux, 24 h	 28	0.20	100	80
10	 29	$MeOH/H_2O$ Reflux, 38 h	 30	0.20	100	93

[a]Isolated yields (by column chromatography).
[b]The reaction yields are quantitative by NMR and GC (using internal standard).
[c]The reactions have been performed several times at different scales (20–300 mg), showing robustness. However, a loss of mass has been observed in the case of low-boiling products during workup, especially for those products that form azeotropes with the solvents. Alternative isolation procedures for these products are described in the experimental section.
[d]Commercially available substrates.
[e]Synthesized substrates.

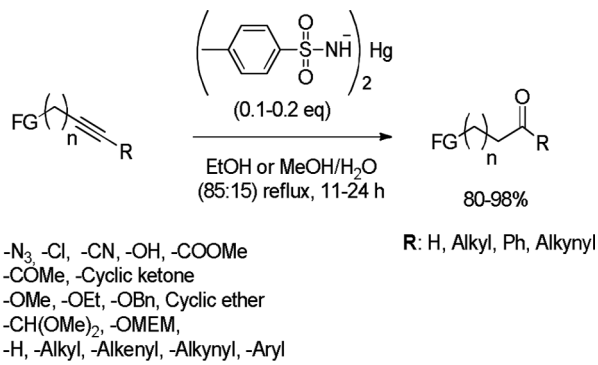
The nonhindered dialkyne substrate **31** was used as a standard substrate and it was hydrated under catalytic conditions to afford the dicarbonyl products **32** and **33** in a 1:1 ratio. In this case, as expected, no chemoselectivity was observed, and both C≡C bonds were hydrated, but with complete regioselectivity for the terminal C≡C bond. 1,1,3-Triphenylpropargyl alcohol **34** did not react under reflux of solvent even with 1.3 eq. of mercury(II) *p*-toluensulfonamidate, even for long reaction times, because of the steric hindrance around the C≡C bond. The reaction conditions were forced by using microwave irradiation and then the hydration took place regioselectively, by insertion of the hydroxyl group on the carbon atom α to the aromatic ring. Product **35** and the dehydration product **36** were obtained (in a ratio of 1:6), because **35** is a β-hydroxyketone that dehydrates to afford the highly conjugated α,β-unsaturated ketone **36**.

Table 3. Chemoselective hydration catalyzed by $Hg(TsNH)_2$ of dialkynes having two differently hindered C≡C bonds

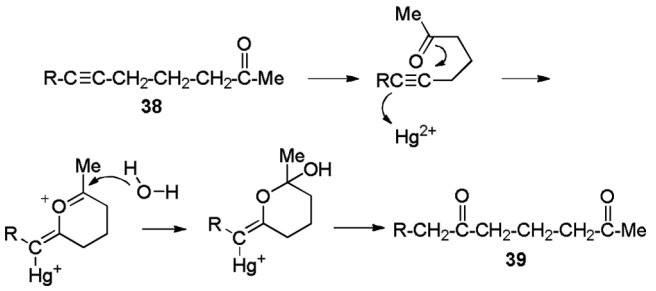
Entry	Substrate	Conditions	Product **1**	Product **2**	Eq. $Hg(TsNH)_2$	Conversion (%)	Yield (%)[a]
1	 **31**[b]	$EtOH/H_2O$ Reflux, 16 h	 **32**	 **33** 1:1	0.2	100	95
2	 **34**[c]	$MeOH/H_2O$ Reflux, 24 h	—	—	1.3	0	—
3	 **34**[c]	$MeOH/H_2O$, microwave, 130 °C, 8 bar, 27 h	 **35**	 **36** 1:6	0.2	96	93
4	 **37**[b]	$MeOH/H_2O$ Reflux, 24 h	 **38**	—	0.2	82	80
5	 **37**[b]	$MeOH/H_2O$, microwave, 130 °C, 8 bar, 20 h	 **38**	 **39** 1: 1.7	0.2	100	98

[a]Isolated yields (by column chromatography).
[b]Synthesized substrates.
[c]Commercially available substrates.

Then, this hydration methodology was studied for substrate **37**, a diacetylene having a terminal -C≡CH bond and a hindered -C≡C-CR_3 triple bond. This study was performed under two different reactions conditions: a) Under reflux of solvent, only the methyl ketone was obtained and the internal triple bond was not hydrated at all, affording **38** in 80% yield. No other products were detected by NMR or gas chromatogrphy (GC), which demonstrates *chemoselective discrimination*. (b) Under microwave conditions, substrate **37** was completely converted; 62% of the substrate was dihydrated and formed the 1,5-dicarbonylic compound **39**, which lost the



Scheme 1. General overview of the alkyne hydration with mercury(II) *p*-toluensulfonamidate under mild and neutral conditions.

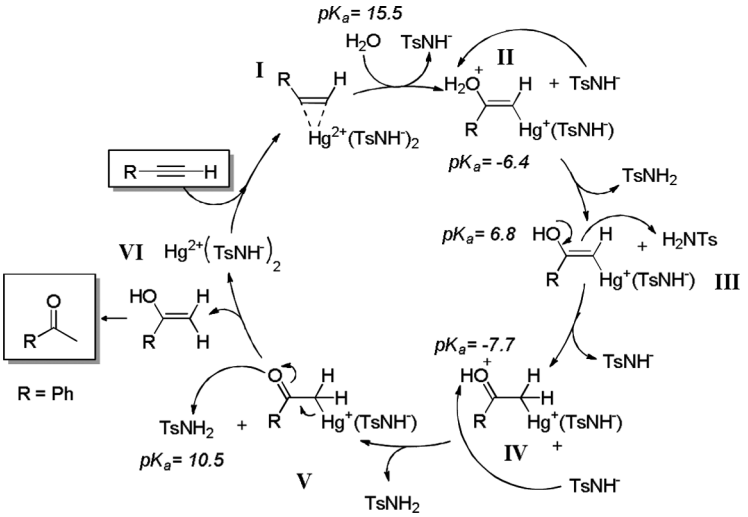


Scheme 2. Proposed mechanism for the regioselective formation of 1,5-diketones by anchimeric assistance of the initially formed carbonyl group.

alcohol group. The reaction also afforded the monohydrated product **38** in 36% yield. In this case, an unexpected regioselective hydration of the internal alkyne was observed, and a 1,5-dicarbonyl compound was obtained, instead of a 1,6-diketone, which is the product expected from the usual hydration mechanism, because of the insertion of the Hg-ligand entity on the less hindered acetylenic carbon (Scheme 2).[13,14]

The explanation for this result could be based on the fact that the hydration of the terminal alkyne is faster than that of the internal one, and thus the product **38** is obtained as a reaction intermediate. In a second step, 1,5-dicarbonyl compound **39** is formed instead of the 1,6-diketone by the anchimeric assistance of the initially formed carbonyl group, according to a mechanism previously reported[15] (Scheme 2).

The general reaction mechanism proposed (Scheme 3) consists of a catalytic cycle.[16] The first step is the coordination of Hg(II) to the triple bond **(I)** followed by the addition of water to the carbon, which better supports the partial



Scheme 3. Proposal of a catalytic cycle for the hydration process.

positive charge **(II)**, avoiding interactions of the R group with the Hg-ligand entity.

Then the β-hydroxyethynyl-mercury intermediate **(III)** is formed, which after a proton exchange forms the oxonium cation **(IV).** Intermediate **(IV)** could afford the α-mercuriated carbonyl compound **(V)**, which has been characterized by x-ray diffraction analysis in previous studies.[13]

CONCLUSIONS

We may conclude that we have developed a catalytic method of hydrating terminal and internal triple bonds under mild and neutral conditions. The hydration reaction with mercury(II) *p*-toluensulfonamidate does not cleave the acid-sensitive groups: dimethoxyacetal, benzyl, and propargylic methoxymethyl, methoxy and ethoxy groups. The reaction conditions are compatible with a wide variety of other functional groups as azides, alcohols, nitriles, esters, ketones, or terminal double bonds. These neutral conditions also avoid epimerization of enolizable substrates. This catalytic approach and the recovery of the insoluble mercury by-products by filtration or centrifugation considerably minimize the environmental and safety impacts of the process.

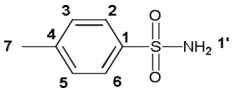
Last but not least, this methodology is also much more economical than other hydration reactions of C≡C triple bonds. Further efforts are under way in our laboratory to study the reaction under conditions very different from those reported here and using much smaller amounts of catalysts.

EXPERIMENTAL

NMR spectra were recorded on a Varian Inova 300 and/or a Mercury 400 apparatus. Chemical shifts (δ) are expressed in parts per million (ppm) versus tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Nicolet 6700 fourier transform (FT)–IR by film, KBr pellet, or ATR (attenuated total reflectance) methods. Mass spectrometry was performed on a Hewlett-Packard 5890 apparatus, generally under a CI (chemical ionization) method using NH_3 or CH_4 or by direct insertion under electron impact at 70 eV and 150 °C. The elemental analyses were obtained in a Fisons elemental analyzer, model Na-1500. The samples were previously pyrolized at 1000 °C under an oxygen atmosphere, and the contents of carbon and hydrogen were determined by evaluation of the combustion gases by gas chromatography using a flame ionization detector. All solvents were dried according to standard procedures and distilled prior to use. All other major chemicals were obtained from commercial sources and used without further purification. Gas chromatography was perfomed by using a Shimatzu AOC-20i apparatus with a capilary column HP-5 crosslinked 5% Ph-Me-siloxane(L = 30 m, ($\phi_i = 0.32$ mm, film thickness = 0.25 μm) under the following experimental conditions: $T_i = 35$ °C, $t_i = 1$ min, rate = 5 °C/min, $T_f = 250$ °C, $t_f = 5$ min, split 1:100; gas brands and preasures are He = 5.5 bar (Linde, Helio 5.0), air = 3 bar (Linde, Aire Sintético), $H_2 = 3$ bar (Linde, H_2 5.0).

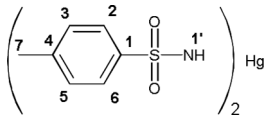
Preparation of Catalyst

Preparation of *p*-toluensulfonamide.



Commercial tosyl chloride (117.73 g, 0.61 mol) dissolved in acetonitrile (590 mL) was slowly added to a magnetically stirred solution of ammonium hydroxide (197 mL, 3.09 mol) under an Ar atmosphere. The reaction mixture was stirred for 30 min. After completion of the reaction, the excess of ammonium hydroxide was neutralized by using concentrated HCl. Then, the solvent was evaporated, and a white solid was formed. The solid was washed with water (to remove NH_4Cl) and dried under vacuum, affording pure product as white solid (87.78 g, 83%). Mp: 137–138 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.82 (d, $J = 8.1$ Hz, 2H, H2, H6), 7.32 (d, $J = 8.1$ Hz, 2H, H3, H5), 4.72 (br s, 2H, H1′), 2.44 (s, 3H, H7).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 143.71 (C4), 139.03 (C1), 129.70 (C3,C5), 126.44 (C2,C6), 21.51 (C7). IR (KBr) ν: 3329 (N-H, st), 3232 (N-H, st), 3017 (Csp^2-H, st), 2919 (Csp^3-H, st), 1911–1793 (comb), 1588 (N-H, δ), 1322 (S=O, st as), 1015 cm^{-1}. MS [DIP-EI, 70 eV, 150 °C, m/z (%)]: 171 (M^+, 40), 169 (M^+-H, 10), 156 (M^+-Me, 16), 155 (M^+-NH_2, 50), 91 (M^+-SO_2NH_2, 100), 65 (43). HRMS: Calcd. for $C_7H_9NO_2S$: 171.03540. Found: 171.03536.

Preparation of mercury(II) *p*-toluensulfonamidate.



p-Toluensulfonamide (29.66 g, 173.2 mmol) and HgO (18.28 g, 83.1 mmol) were ground together in a mortar to get a very fine and homogeneous powder. The mixture was placed in a crucible and warmed up to 200 °C in an oven for 1.5 h. The mixture was stirred with a glass bar every 15 min. Once the orange color of HgO disappeared, the reaction was complete. The crucible was cooled down to room temperature and the solid was transferred to a round-bottomed flask fitted with a reflux condenser. EtOH (150 mL) was added, and the solution was refluxed for 30 min to dissolve unreacted *p*-toluensulfonamide excess. Then the mixture was filtered when hot. After lixiviation, the resulting residue was dried in a desiccator containing phosphorus pentoxide for 1 day to obtain pure product as a white solid (36.12 g, 89%). Mp: 249.8–250.7 °C (in closed capillary tube, previously purged with Ar). IR (KBr): 3307 (N-H, st), 3036-3024 (Csp^2-H, st), 2978 (Csp^3-H, st), 1910–1652 (comb), 1276 (S=O, st, as), 1139 (S=O, st, sym), 945 (S-O, st), 812 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.68 (d, $J = 8.0$ Hz, 4H; H2, H6, H2′, H6′), 7.34 (d, $J = 8.0$ Hz, 4H; H3, H5, H3′, H5′), 2.35 (s, 6H, H7 and H7′). Calcd. for $C_{14}H_{16}HgN_2O_4S_2$: C, 31.08; H, 2.98; N, 5.18; S, 11.85%. Found: C, 31.11; H, 3.01; N, 5.15; S, 11.83%.

Hydration Procedures

Procedure for the hydration reaction with mercury(II) *p*-toluensulfonamidate under stoichiometric conditions. To a stirred suspension of mercury(II) *p*-toluensulfonamidate (892 mg, 1.65 mmol) in a mixture of MeOH–H_2O (85:15) (30 mL) under Ar atmosphere, methyl hept-6-ynoate **(17)** (178 mg, 1.27 mmol) in the same solvent system (5 mL) was added. The mixture was warmed up to reflux of solvent and stirred for 13 h.

Procedure for the hydration reaction with mercury(II) *p*-toluensulfonamidate under catalytic conditions. To a stirred solution of mercury(II) *p*-toluensulfonamidate (16.4 mg, 0.03 mmol) in a mixture of MeOH–H_2O (85:15) (20 mL) under Ar atmosphere and warmed up to reflux, 11-chloroundec-1-yne **(21)** (51 mg, 0.28 mmol) in the same solvent system (5 mL) was added. The mixture was stirred under reflux of solvent for 20 h.

Workup Procedures

Usual workup procedure for isolation of low-boiling-point products. To a stirred solution of mercury(II) *p*-toluensulfonamidate (225 mg, 0.42 mmol) in a mixture of MeOH–H_2O (85:15) (50 mL), 1-heptyne **(13)** (200 mg, 2.08 mmol) in the same solvent system (10 mL) was added, under an Ar atmosphere. The mixture was warmed up to reflux of solvent and stirred under these conditions for 14 h. After completion of the reaction (control by TLC, CG), the mixture was cooled down to room temperature and the mercury(II) catalyst precipitated with an aqueous 10% (w/w) solution of $(NH_4)_2S$ (0.6 mL). The precipitate of HgS was removed by centrifugation. Then, the mother liquor was extracted with *n*-pentane (×6), the organic layers were combined together, dried over $MgSO_4$, and filtered. Pentane was removed by slow simple distillation at atmospheric pressure, using a Vigreux column, affording pure product **(14)**(186.2 mg, 78%).

Usual workup for high-boiling-point products. To a stirred solution of mercury(II) *p*-toluensulfonamidate (74.4 mg, 0.14 mmol) in a mixture of MeOH–H_2O (85:15) (40 mL), 5-hexynenitrile **(19)** (165 mg, 1.72 mmol) in the same solvent system (6 mL) was added, under an Ar atmosphere. The mixture was warmed up to reflux of solvent and stirred under these conditions for 21 h. After completion of the reaction (control by TLC, CG), the crude mixture was cooled down to room temperature and an aqueous 10% (w/w) solution of $(NH_4)_2S$ (0.2 mL) was added. The resulting mixture was filtered through a short column of silica gel and alumina (1:1) to remove HgS, which at the end was collected and processed properly. The hydro-alcoholic solution was concentrated to remove alcohol (MeOH or EtOH), and the resulting residue was dissolved in Et_2O. The ethereal solution was extracted with NaOH (2 M) (×3). The aqueous layers were combined and extracted again with diethyl ether. The organic layers were combined together, extracted with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was then submitted to a flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate (or diethyl ether) of increasing polarity, obtaining with H/AcOEt 50:50 pure product **(20)** (178.4 mg, 93.3%).

SUPPORTING INFORMATION

Synthetic procedures for the acetylenic substrates and complete spectroscopic characterization of acetylenes and their hydration products are included in the Supplementaly Material (S1), available online. In addition, copies of ^{1}H NMR, ^{13}C NMR, and IR spectra of acetylenic substrates and hydration products are included also as Supplementarly Material (S2) and are available at the Web page of this journal.

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