Organocatalytic Alkynylation of Aldehydes and Ketones under Phase-Transfer Catalytic Conditions

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Keywords: Alkynylation / C–C coupling / Organocatalysis / Phase-transfer catalysis / Propargylic alcohols

We developed alkynylations of various aldehydes and ketones under practical phase-transfer conditions at room temperature. The straightforward methodology combines one-pot synthesis and simple workup with good to excellent yields for propargylic alcohols derived from aliphatic aldehydes and ketones. Even aromatic aldehydes and ketones could be transformed to the corresponding propargylic alcohols in somewhat lower yields. The yield depending on the amount of PT catalyst and NaOH concentration was also determined.

Introduction

The nucleophilic addition of alkynes to aldehydes and ketones is an essential organic C–C coupling reaction that provides propargylic alcohols as versatile intermediates for organic synthesis.[1,2] Metal-catalyzed additions of alkynes to carbonyl compounds with stoichiometric amounts of organometallics (e.g., organolithium, Grignard reagents) are typically employed. Only a few reports demonstrate the catalytic activation of an alkyne derivative and subsequent addition to a carbonyl compound.[3–7] These alternative routes involve either acid-base reactions of strong alkaline bases, or transition metal complexes with the deployed alkyne. Virtually none of the published protocols are universally applicable to aliphatic as well as aromatic aldehydes and ketones. Using potassium *tert*-butoxide, only aliphatic ketones can be transformed to the corresponding propargylic alcohols with moderate to good yields,[7] whereas alkynylations, using zinc reagents, are limited to aldehydes, but give good to excellent yields.[5,6,8] $CsOH{\cdot}H_2O$ as the base can be used to transform aliphatic aldehydes and ketones into the resulting ynols also with good to excellent yields.[4] While zinc derivatives in conjunction with chiral ligands affect enantioselective alkynylations, reactions with alkali or earth alkali bases generally cannot be conducted in a stereoselective fashion.

A possible way to overcome these limitations has been the use of a nonmetallic ammonium base (triton B) as catalyst by Saito and coworkers: a variety of aldehydes and ketones were transformed into propargylic alcohols with moderate to good yields; propargylic alcohols derived from aromatic aldehydes showed significant base-catalyzed rearrangement to the respective chalcones.[3] As the in situ preparation of ammonium bases should simplify this procedure by not having to use DMSO as the solvent (from which the dimsyl anion may be generated in situ) and by having a straightforward two-phase separation, we envisioned a phase-transfer catalytic (PTC) protocol for this reaction.

Results and Discussion

The use of strong alkaline bases for the title reaction is not new. The original report on this type of transformation – often referred to as the "Favorskii reaction"– utilizes KOH.[9,10] This reaction does not involve an acid–base equilibrium involving a potassium acetylide; the reaction is assumed to proceed through the formation of a potassium hydroxide–acetylene complex.[10] Knochel et al. showed that the more soluble $CsOH{\cdot}H_2O$ can also be utilized.[4] Neither approach utilizes the PTC concept, and NaOH was deemed unsuitable as the base for this purpose.[10] Since we did not foresee any obvious problems with the use of NaOH as the inorganic base, in combination with a tetraalkyl ammonium salt as the PT catalyst, we put our proposal to test. Utilizing a two-phase system consisting of an aqueous sodium hydroxide layer, an organic layer with fluorobenzene and a quaternary ammonium salt as the PT catalyst, we developed a mild and efficient method for the organocatalytic alkynylation of a variety of aliphatic aldehydes and ketones (Scheme 1).

The two-phase reaction conditions with relatively low base concentration in the organic layer reduce the formation of by-products resulting from aldol condensations or Cannizzaro reactions. Various aliphatic aldehydes as well as ketones (**1a**–**1f**) react cleanly with different alkynes (**2a**–**2c**) to give the corresponding propargylic alcohols (**3a**–**3k**, Table 1). Two slightly different methods A and B were em-

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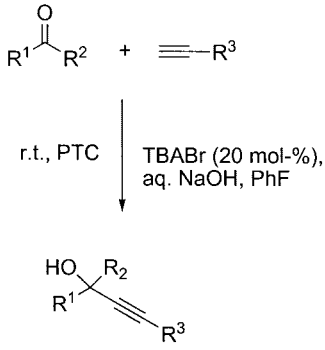
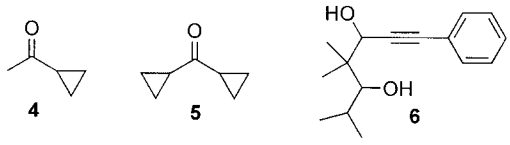
 DOI: 10.1002/ejoc.200500064



Scheme 1. General alkynylation conditions.

ployed; method A is typically used for aliphatic carbonyl compounds and acetophenones, whereas method B is more advantageous for aromatic aldehydes.

Generally, the propargylic alcohols derived from aliphatic aldehydes and ketones with phenylacetylene were obtained in good yields; methods A and B gave similar results. As expected, aliphatic aldehydes react faster than aliphatic ketones; non-enolizable **1d** was converted fully after 24 h (at 100% catalyst loading). Even enolizable carbonyl compounds showed no significant aldol condensation, with isobutyraldehyde being the only exception where we could isolate a by-product, identified as **6** (Scheme 2) in negligible amounts (≈ 3%). Deactivated cyclopropyl ketones (**4** and **5**) showed little (20%) or no conversion, respectively.

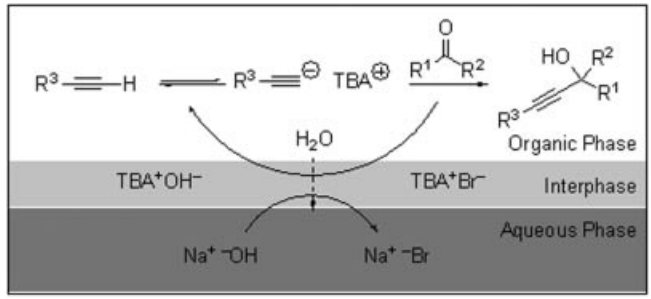


Scheme 2. Deactivated cyclopropyl ketones and by-product.

THP-protected propargylic alcohols as the alkyne component can also be utilized but give somewhat lower yields (entries 7–9). The resulting protected ynols with an additional functional group are also useful building blocks for organic synthesis. 1-Hexyne reacted slightly more effectively (entries 10 and 11).

Aromatic ketones and aldehydes gave propargylic alcohols in moderate yields (entries 12–14), although this is not a problem of reactivity. Rather we found that under these conditions significant amounts of polymers and unidentified and inseparable by-products form.

Surprisingly little is known about phase-transfer catalytic mechanisms, probably owing to the fact that multicomponent mixtures are difficult to analyze.[13–16] As a working mechanistic hypothesis, we refer to Scheme 3 that shows the deprotonation of the alkyne, coordination to the PT-catalyst, and subsequent reaction with the carbonyl compound. With the available data we cannot distinguish between extraction and interphase mechanisms. The carbanion-ammonium ion pairs were also proposed in the reactions with triton B;[3] our present work lends further evidence to this mechanistic suggestion. We therefore addressed two key factors, namely the concentration dependence of the PTC-catalyst and base in these reactions.

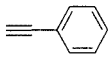
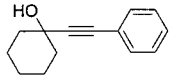
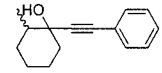
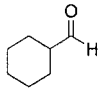
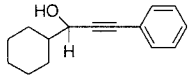
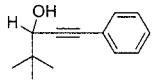
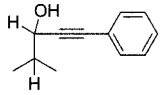
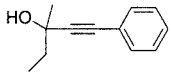
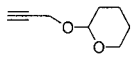
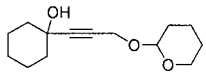
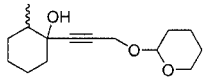
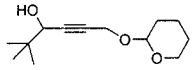
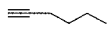
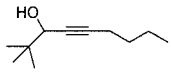
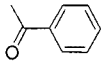
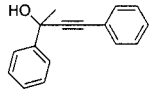
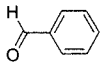
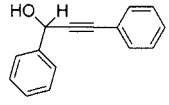
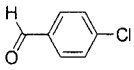
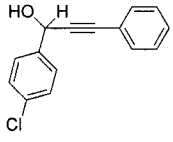


Scheme 3. Proposed PTC alkynylation mechanism.

The model reaction of cyclohexanone and phenylacetylene (entry 1) was optimized by varying parameters such as catalyst concentration (Figure 1, left), concentration of sodium hydroxide (Figure 1, right), reaction time, solvent, ratio of carbonyl compound and alkyne, and mode of addition. Using dichloromethane instead of fluorobenzene for entry 1 gave only 25% of **3a**. Fluorobenzene and toluene are suitable solvents for PTC reactions.[17] In our experience, the higher dipole moment of fluorobenzene facilitates the extraction of the ammonium compound into the organic phase; it also does not display many of the typical side reactions often observed in dichloromethane. Figure 1 (left) demonstrates that the overall reaction *is* phase-transfer catalytic: while a minimum concentration of about 10 mol-% is required for satisfactory yields within 24 h, it is noteworthy that the reactions do run to completion at any catalyst concentration (at the expense of longer reaction times). Apparently up to a catalyst concentration of about 10–15 mol-% the rate-limiting step is the transport of OH into the organic phase promoted by the PT catalyst. Higher catalyst concentrations result in a change of mechanism; the rate-limiting step is now likely to be the nucleophilic addition of the acetylide anion to the carbonyl compound. From this point on an increase of catalyst concentration has only little effect.

A practical protocol therefore utilizes 15–20 mol-% PTC-catalyst and adjustable reaction times. As the in situ generation of the ammonium hydroxide takes place in form of equilibrium reactions at the phase boundary (Scheme 3),[18] its relative concentration in the organic phase depends on the absolute concentration of aqueous sodium hydroxide. This is evident from the yield dependence of **3a** on the NaOH concentration (Figure 1, right) that must exceed 30 mass-% for an efficient reaction to occur. For this purpose we determined the pH and thus the relative concentration of hydroxide anions in the organic phase with a simple experiment. We simulated the reaction conditions by stirring 10 mL of fluorobenzene, 10 mL 50% aqueous sodium hydroxide, and 15 mmol of TBABr for two hours to reach equilibrium. Then we separated the organic layer and extracted the dissolved salts with 10 mL of distilled water. Measuring the pH (12.51–13.05 ± 0.05) and the volume of the resulting aqueous phase (including the former in-

Table 1. PTC/organocatalytic alkynylation of selected aldehydes and ketones.

Entry	Carbonyl compound		Alkyne		Product		Cond.[a] (time [h])	Yield of isolated product [%]
1		**1a**		**2a**		**3a**	A (96)	88
2		**1b**		**2a**		**3b**	A (96)	87[b]
3		**1c**		**2a**		**3c**	B (72)	78
4		**1d**		**2a**		**3d**	A (48)	92
5		**1e**		**2a**		**3e**	A (48)	52
6		**1f**		**2a**		**3f**	A (96)	65
7		**1a**		**2b**		**3g**	A (96)	51
8		**1b**		**2b**		**3h**	A (96)	50
9		**1d**		**2b**		**3i**[11]	A (72)	72
10		**1d**		**2c**		**3j**	A (72)	57
11		**1a**		**2c**		**3k**	A (96)	53
12		**1g**		**2a**		**3l**	A (48)	35
13		**1h**		**2a**		**3m**[12]	B (36)	30
14		**1i**		**2a**		**3n**[12]	B (36)	31

[a] Method A: 7 mmol alkyne, 8.4 mmol carbonyl compound, 1.4 mmol [20 mol-%] TBABr; method B: 14 mmol alkyne compound, 7 mmol carbonyl compound, 1.4 mmol [20 mol-%] TBABr. For details see experimental section. [b] 1:1 mixture of diastereomeric propargylic alcohols.

terphase) and conversion to the volume of OH^- gave an average relative concentration of $c[OH^-]$ = 0.11 mol/L. These experiments were repeated three times.

The hydroxide anion is much more basic in the organic phase than in water. Whereas an aqueous solution of NaOH (1 mol/L) deprotonates weak acids up to p*K*a ≈ 14–15, the "naked" hydroxide ion is, owing to loss of its solvating water molecules, highly activated: extracted into the organic phase it is able to deprotonate reactants up to a p*K*a of about 35![17] Consequently alkynes with p*K*a ≈ 22–26

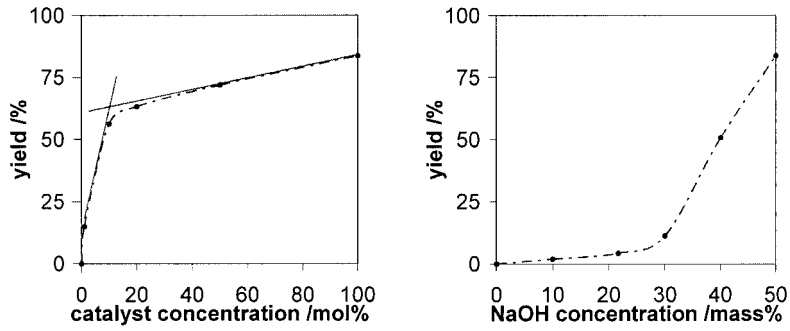


Figure 1. (left) Yields of **3a** vs. concentration of phase-transfer catalyst TBABr [*x* mol-%]; 50 mass-% NaOH; reaction time 24 h. (right) Yields of **3a** vs. NaOH concentration [*y* mass-%]; 100 mol-% catalyst; reaction time 24 h.

(phenylacetylene: 23.2–23.7[19]) are easily converted into their corresponding anions that can subsequently act as nucleophiles. This remarkably behaviour of OH^- is driven to extreme in PTC halogenation reactions of alkanes, where it functions even as electron donor, i.e., as a reduction agent.[17,20–22]

Conclusions and Outlook

We present a mild and effective organocatalytic PTC protocol for the alkynylation of various aldehydes and ketones. Best results are obtained for aliphatic ketones and non-enolizable aldehydes; the alkyne component can be varied widely and can be aromatic or aliphatic. As the coordination between the PT-catalyst and the carbanion is implied in this and other PTC reactions, we also hope to develop stereoselective alkynylations.[23–25] Experiments in this direction are currently under way and will be reported in due course.

Experimental Section

All chemicals were purchased from Acros Organics, Aldrich, and Lancaster in highest purities available; liquid aldehydes were freshly distilled through a 10 cm Vigreux column prior use, solid aldehydes were used without further purification. Reactions were monitored with a HP 5890 GC spectrometer with a HP 5971 mass selective detector. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AM 400 spectrometer using TMS as internal standard; chemical shift values are given in ppm. IR spectra were measured with a Bruker IFS 25 spectrometer. Elemental analysis (CHN) was determined with a Carlo Erba EA 1106.

Method A: To an intensively stirred solution of 7 mmol alkyne compound, 8.4 mmol carbonyl compound and 1.4 mmol (20 mol-%) TBABr in 5 mL of fluorobenzene, 5 mL of aqueous sodium hydroxide (50%) was added. After stirring for the corresponding reaction time mentioned in Table 1, 10 mL of water were added and the phases were separated. The organic layer was washed with water and brine and subsequently dried over anhydrous sodium sulphate. Filtration from the drying agent and removal of the solvent by distillation left in all cases a colored mixture of product, reactant and PT catalyst. The product was isolated by high-vacuum distillation or column chromatography (SiO_2/EtOAc/hexane, 1:3) to give the propargylic alcohols as colorless solids or colorless to slightly yellowish oils. All propargylic alcohols prepared are known in the literature.

Method B: To an intensively stirred mixture consisting of 14 mmol alkyne compound, 1.4 mmol (20 mol-%) TBABr, 3 mL of fluorobenzene and 5 mL of aqueous sodium hydroxide (50%), a solution of 7 mmol carbonyl compound in 2 mL of fluorobenzene was added over a period of 2 hours via an addition funnel. Reaction time and workup are identical to method A.

Side product (new compound):

4,4,6-Trimethyl-1-phenylhept-1-yne-3,5-diol (6): Colorless solid, m.p. 98.5 °C, R_f = 0.23 (ethyl acetate/hexane, 1:3), 3% isolated product. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 2 H, CH), 7.32 (m, 3 H, CH), 4.55 (s, 1 H, CH), 3.57 (d, J = 2.3 Hz, 1 H, CH), 2.73 (br. s, 2 H, OH), 2.03 (m, 1 H, CH), 1.17 (s, 3 H, CH_3), 1.05 (d, J = 6.8 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.97 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 128.4, 128.3, 122.6, 88.4, 86.2, 82.3, 73.3, 43.1, 29.5, 23.2, 21.7, 16.4, 16.2 ppm. IR (KBr): $\tilde{\nu}$ = 3236.3, 2964.3, 2360.9, 1597.0, 1490.8, 1332.8, 1045.8 cm^{-1}. $C_{16}H_{22}O_2$: calcd. C 78.01, H 9.00; found C 77.86, H 9.18.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie.

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Received: January 26, 2005
Published Online: April 25, 2005

