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Efficient catalytic transition-metal-free conditions for nucleophilic addition of arylacetylenes to aromatic ketones

Junfeng Liu, Jin Lin, Ling Song *

Fujian Institute of Research on the Structure of Matter, Chinese Academy of Science, Fuzhou 350002, China

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ABSTRACT

A mild, efficient, and transition-metal-free method for nucleophilic addition of arylacetylenes to diverse aromatic ketones, using catalytic amount of tetrabutylammonium chloride as a promoter and solid KOH as a base in THF, was developed to afford aromatic tertiary propargylic alcohols with high and excellent yields. Aliphatic ketones also gave satisfactory results.

Introduction

Alkynylation reactions of carbonyl compounds that generate propargylic alcohols are among the most important family of carbon–carbon bond-forming reactions. Moreover, propargylic alcohols are important intermediates for the synthesis of natural products and pharmaceuticals.[1] A common approach used to produce these substances involves nucleophilic addition of terminal alkynes to carbonyl compounds, promoted by stoichiometric or excess amounts of organometallic bases (e.g., organolithium) to generate the reactive acetylide anions.[2,3] Although catalytic amount of transition metals has also been employed as promoters for addition reactions that lead to the generation of aliphatic and aromatic propargylic alcohols,[2,4–8] the high cost of the reagents and the difficulty of removing trace quantities of metals serve as critical limitations for these methods.

In order to circumvent these drawbacks, silylated propargyl alcohol derivatives are formed through metal-free nucleophilic additions of silylacetylenes to carbonyl compounds.[9] Although propargyl alcohols can be generated by simple hydrolysis of the products, this method is not straightforward and has only very limited success for aromatic ketones.

Several catalytic non-transition-metal methods have also been developed for the direct alkylation addition of terminal alkynes to carbonyl compounds. Using catalytic amount bases KOH,[10] *t*BuOK,[11] and CsOH,[12] only aliphatic carbonyl compounds can be efficiently transformed into the corresponding propargylic alcohols. The first organocatalytic addition reactions of terminal alkynes with carbonyl compounds, using benzyltrimethylammonium hydroxide as the catalyst, were described by Saito and his co-workers in 2003.[13] Aliphatic and alicyclic carbonyl substrates react satisfactorily under these conditions but their aromatic counterparts participate in low yielding addition reactions. Kondo and his co-workers developed another strategy for this process that utilizes tert-Bu-P4 base as a catalyst in DMSO.[14] Quantitative yields of alkynylated products were observed, but the investigated substrates were limited to pivalaldehyde and acetone. In 2005, Schreiner and his co-workers used 20 mol % tetrabutylammonium bromide (TBAB) in PhF/aqueous NaOH two-phase system as a catalyst for addition reactions of terminal alkynes with aliphatic carbonyl compounds,[15] which furnished alkynylated products in high yields, but the reaction of phenylacetylene with aromatic aldehydes and ketones produced poor yields. Although the catalytic transition-metal-free methods mentioned above show to be efficient for alkynylation reactions of aldehydes and aliphatic ketones with terminal alkynes, an efficient catalytic strategy for alkynylating aromatic ketones with terminal alkynes has not yet been devised.

Wang and his co-workers reported a new technique for performing solvent-free alkynylation reactions of aromatic ketones with terminal alkynes that rely on the use of 18-crown-6 and ball-milling condition with solid KOH as the base.[16] Unfortunately, stoichiometric amounts of 18-crown-6 are necessary in order to promote complete reactions. Considering earlier observations which demonstrate that quaternary ammonium salts serve as

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* Corresponding author. Tel./fax: +86 591 8372 0913.
E-mail address: songling@fjirsm.ac.cn (L. Song).

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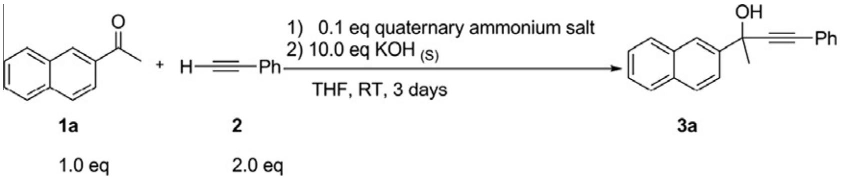
Table 1
Effect of different quaternary ammonium salts as phase-transfer catalyst for nucleophilic addition of phenylacetylene to 2′-acetonaphthone (**1a**)

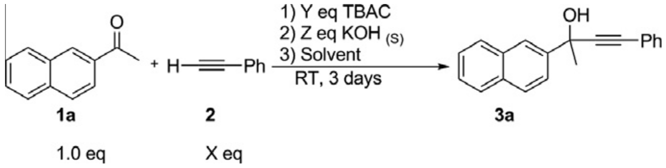


Entry	Quaternary ammonium salt[a]	Yield[b](%)
1	TBAF	66
2	TMAF	53
3	**TBAC**	**69**
4	TBAB	63
5	HTAB	56
6	TBAI	64

[a] TBAF, tetrabutylammonium fluoride; TMAF, tetramethyla-mmonium fluoride, 1.0 M in THF; TBAC, tetrabutylammonium chloride; TBAB, tetrabutylammonium bromide; HTAB, (1-hex-adecyl) trimethylammonium bromide; TBAI, tetrabutylammoni-um iodide.

[b] Isolated yield.

Table 2
Screening reaction conditions of TBAC-catalyzed addition of phenylacetylene to 2′-acetonaphthone (**1a**)



Entry	X equiv of **2**	Y equiv of TBAC	Z equiv of base	Solvent	Yield[a] (%)
1	2.0	0.1	10.0 KOH	Toluene	15
2	2.0	0.1	10.0 KOH	Et_2O	57
3	2.0	0.1	10.0 KOH	CH_3CN	5
4	2.0	0.1	10.0 KOH	THF	69
5	2.0	0.1	10.0 KOH	DMSO	–[b]
6	2.0	0.05	10.0 KOH	THF	53
7	**4.0**	**0.1**	**10.0 KOH**	**THF**	**82**
8	4.0	0.1	10.0 KOH	THF	71[c]
9	4.0	0.1	5.0 KOH	THF	55
10	4.0	0.1	10.0 NaOH	THF	35
11	4.0	0.1	10.0 $CsOH\cdot H_2O$	THF	22
12	4.0	0.1	10.0 K_2CO_3	THF	11

[a] Isolated yield.

[b] No product was detected.

[c] 2 days.

effective phase-transfer catalysts for reactions involving inorganic bases in organic solvents,[17] we envisaged that catalytic quantities of these salts might also assist solid KOH participated alkynylation reactions of aromatic ketones with terminal alkynes carried out in organic solvents. Herein, we report our recent studies on developing a mild and efficient transition-metal-free strategy for alkynylating aromatic ketones with phenylacetylene. The effort, which led to the discovery that tetrabutylammonium chloride (TBAC) with solid KOH suspended in THF is an ideal catalyst system for this process, is described below.

Result and discussion

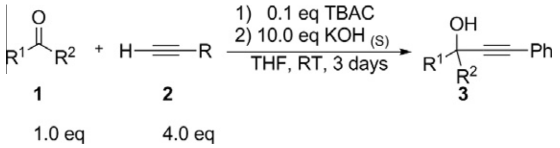
Initially, the nucleophilic addition reaction between phenylacetylene and 2′-acetonaphthone (**1a**) was explored utilizing 10 mol % TBAB and solid KOH suspended in THF at room temperature. This process was observed to produce the corresponding adduct **3a** in 63% yield (Table 1, entry 4). Encouraged by this finding, we next evaluated the effectiveness of various quaternary ammonium salts as phase-transfer catalysts for this process. Among these salts, possessing different alkyl chain lengths and counter anions (Table 1), tetrabutylammonium fluoride (TBAF), and tetrabutylammonium bromide (TBAB) promoted the reaction with higher yields (Table 1, entry 1 and 4), in contrast to tertramethylammonium fluoride (Table 1, entry 2), (1-hexadecyl)trimethylammonium bromide (Table 1, entry 5). The results show that tetraalkylammonium salts with a medium alkyl chain length are better catalysts for this process than those with shorter or longer alkyl chains. No significant difference in product yield was observed when the addition reaction was catalyzed by using tetraalkylammonium salts with different halide ions (Table 1, entry 1, 3, 4 and 6), but the reaction using TBAC gave a slightly higher yield (69% yield).

Further studies were carried out to determine the optimal conditions for the TBAC-catalyzed reaction of phenylacetylene (**2**) and 2′-acetonaphthone (**1a**) (Table 2). Using KOH as the base, the reaction in THF led to 69% yield of **3a** (Table 2, entry 4), which contrasts to the lower 57%, 15%, and 5% yields for the processes carried out in Et_2O, toluene, and CH_3CN (Table 2, entries 1–3), respectively. Using DMSO as the solvent, no alkynylated product was generated and the ketone was decomposed (Table 2, entry 5). Decreasing the amount of TBAC from 0.1 to 0.05 equiv resulted in a decrease in the yield of the addition product from 69% to 53% (Table 2, entry 6). However, the yield of the process increased from 69% to 82% when the amount of phenylacetylene was raised from 2.0 to 4.0 equiv (Table 2, entry 7). Shorting the reaction time from 3 to 2 days also decreased the yield of **3a** to 71% (Table 2, entry 8). When $CsOH\cdot H_2O$ was employed as the base, reaction in THF led to only 22% yield of **3a**, and using NaOH and K_2CO_3 led to low yields as well (Table 2, entries 10–12). As the data obtained from this survey show, 10 mol % of TBAC in the presence of 4.0 equiv of phenylacetylene using 10 equiv solid KOH as the base and THF as the solvent at room temperature for 3 days are ideal conditions for the addition reaction (Table 2, entry 7).

Employing the optimized conditions described above, addition reactions of various aromatic ketones with phenylacetylene were carried out. The results of these processes, summarized in Table 3, show that these processes take place efficiently to generate adducts in good to excellent yields. For example, the reaction of phenylacetylene with acetophenone (**1b**) produced propargylic alcohol **3b** in 80% yield (Table 3, entry 2), which contrasts with

Table 3

Reactions of ketones with alkynes using TBAC as the catalyst and solid KOH as the base



Entry	Ketone (R^1, R^2)	R	Product	Yield[a] (%)	Lit. yield[b] (%)
1	**1a** (2-Naph, Me)	–Ph	**3a**	82	/
2	**1b** (Ph, Me)	–Ph	**3b**	80	38[c], 35[d]
3	**1c** (Ph, CF_3)	–Ph	**3c**	–[e]	/
4	**1d** (4-$NO_2C_6H_4$, Me)	–Ph	**3d**	–[e]	/
5	**1e** (4-$CF_3C_6H_4$, Me)	–Ph	**3e**	88	/
6	**1f** (4-ClC_6H_4, Me)	–Ph	**3f**	86	/
7	**1g** (4-FC_6H_4, Me)	–Ph	**3g**	81	/
8	**1h** (4-$MeOC_6H_4$, Me)	–Ph	**3h**	45[f]	/
9	**1i** (3-$CF_3C_6H_4$, Me)	–Ph	**3i**	83	
10	**1j** (3-ClC_6H_4, Me)	–Ph	**3j**	82	/
11	**1k** (3-BrC_6H_4, Me)	–Ph	**3k**	81	/
12	**1l** (3-$MeOC_6H_4$, Me)	–Ph	**3l**	78	/
13	**1m** (1-Naph, Me)	–Ph	**3m**	65	/
14	**1n** (2-$CH_3C_6H_4$, Me)	–Ph	**3n**	33	/
15	**1o** (Ph, Et)	–Ph	**3o**	79	/
16	**1p** (Ph, Ph)	–Ph	**3p**	99	/
17	**1q** (Ph, 4-FC_6H_4)	–Ph	**3q**	98	/
18	**1r** (3-Pyridyl, Me)	–Ph	**3r**	85	/
19	**1s** (*n*Pr, Me)	–Ph	**3s**	94	/
20	**1t** (Et, Et)	–Ph	**3t**	95	81[c], 70[g]
21	**1u** (-$(CH_2)_5$-)	–Ph	**3u**	93	95[c],88[d], 88[h]
22	**1v** (Ph, Me)	–2-Thiophenyl	**3v**	77	/
23	**1w** (Ph, Me)	–nC_4H_9	**3w**	—[e]	/

[a] Isolated yield.
[b] Other transition-metal-free catalytic methods.
[c] See Ref. 13.
[d] See Ref. 15.
[e] No product was detected.
[f] Isolated yield in 6 days.
[g] See Ref. 11a.
[h] See Ref. 12.

the outcomes of reactions performed by using other transition-metal-free catalytic methods that afforded the adducts in only 38%[13] and 35%[15] yields. Reactions of aliphatic ketones with phenylacetylene employing the optimized conditions also proceeded smoothly giving adducts in >90% yield, that are either similar to or higher than those reported transition-metal-free catalytic methods[11a,12,13,15] (Table 3, entries 19–21). Alkynylation of acetophenone (**1b**) with aromatic 2-ethynylthiophene, led to high yield as well (Table 3, entry 22), but no product was detected with aliphatic 1-hexyne (Table 3, entry 23).

Further investigations demonstrated that substituent effects influence the yields of tertiary propargylic alcohols formation in the alkynylation reactions of aromatic ketones. The data in Table 3 show that a substituent with positive substituent constant σ value, which has electron-withdrawing ability, enhances the reactivity of acetophenone, whereas a substituent with negative substituent constant σ value, which has electron-donating ability, has the opposite effect.[18] These phenomena were demonstrated by the comparative yields of reactions of acetophenone (**1b**) and its 4-trifluoromethyl (**1e**) and 4-mexthoxy (**1h**) analogs with phenylacetylene which took place in respective yields of 80%, 88%, and 45% (Table 3, entries 2, 5 and 8). Compared to the negative σ value at *p*-position, methoxy substituent at *m*-position has positive value and the alkynylation reaction of 3-methoxyacetophenone (**1h**) with phenylacetylene took place in 78% yield. However, 4-nitroacetophenone and α,α,α-trifluoroacetophenone which have very strong electron-withdrawing groups, were decomposed under our conditions. In addition, alkynylation reactions of the more sterically hindered 1′-acetonaphthone (**1m**) and *o*-methylacetophenone (**1n**) with phenylacetylene gave products in only 65% and 33% yields, respectively (Table 3, entries 13 and 14). Finally, addition reactions of non-enolizable aromatic ketones, such as benzophenone (**1p**) and 4-fluorobenzophenone (**1q**), occurred smoothly and gave excellent product yields (Table 3, entries 16 and 17).

Conclusion

In conclusion, the effort described above has led to the development of a mild and efficient method for alkynylation of a diverse array of aromatic ketones with arylacetylenes. By using catalytic amount of tetrabutylammonium chloride as a promoter and solid KOH as a base in THF, these processes took place in high yields under transition-metal-free condition. Aliphatic ketones also gave satisfactory results under these conditions. An asymmetric version of our method is currently undergoing development.

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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.2012.02.058.

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