Tetrahedron Letters 50 (2009) 3786–3789

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

TfOH-catalyzed allylation of alkynes with cyclic Baylis–Hillman alcohols

Chen Wu, Li Liu *, Dong Wang, Yong-Jun Chen *

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

ARTICLE INFO

Article history:
Received 10 February 2009
Revised 31 March 2009
Accepted 3 April 2009
Available online 9 April 2009

Keywords:
Baylis–Hillman alcohols
Alkynes
TfOH
Ketones
Allylation

ABSTRACT

The substitution reaction of cyclic Baylis–Hillman alcohols with arylacetylenes was achieved under the catalysis of TfOH in nitromethane. The γ,δ-unsaturated ketones were obtained in moderate to good yields.

The chemical behavior of alkynes is one of the most important and useful subjects in organic chemistry.[1] The terminal alkyne could be used as a nucleophile in addition reactions with various electrophiles such as carbonyl compounds and imines, as well as Michael acceptors.[1,2] The direct reaction of terminal alkynes with alcohols should be another attractive process for C–C bond formation and the only byproduct is water. However, the catalytic nucleophilic substitution of alcohols with terminal alkynes is rarely reported.[3] In most cases, terminal alkynes should be transformed to metal alkynides such as alkynylboron and alkynyllithium.[4] A pioneering work on the reaction of terminal alkynes with alcohols is the $CpRu(PPh_3)_2Cl$-catalyzed reconstitutive condensation of acetylenes and allyl alcohols reported by Trost and co-workers. β,γ-Unsaturated ketones were obtained via ruthenium-vinylidene intermediates.[5] On the other hand, under the catalysis of CpRu(cod)Cl, the reaction provided γ,δ-unsaturated ketones in a totally different reaction pathway by the addition of the alkene bond of allylic alcohol to alkynes.[6] In the case of palladium catalysis, allylation of alkynes with allyl alcohols provided substituted 1,4-dienes.[7] Recently, Iron(III) was used as the catalyst for the reaction of benzylic alcohols with aryl alkynes and substituted aryl ketones were obtained in moderate yields.[8] It was noteworthy that different catalytic systems afford different products for the allylation of alkynes. Development of new efficient catalysts to explore the versatility of the reaction between alkynes and allylic alcohols is still desirable.

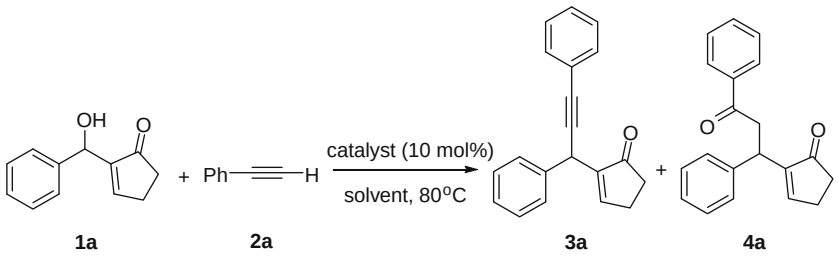
Baylis–Hillman adducts, bearing both allylic hydroxyl group and Michael acceptor moiety, have been illustrated as valuable starting materials for the synthesis of heterocycles and many biologically active molecules.[9] Herein, we wish to describe an efficient Brϕnsted acid-catalyzed allylation of terminal alkynes with Baylis–Hillman alcohols to produce γ,δ-unsaturated ketones.

Initially we investigated the reaction of cyclic Baylis–Hillman alcohol **1a** derived from cyclopentenone with phenylacetylene **2a** catalyzed by Lewis acid (Scheme 1). In the presence of 10 mol % $In(OTf)_3$, two products were obtained: 2-(1,3-diphenylprop-2-ynyl)cyclopent-2-enone **3a** and 2-(3-oxo-1,3-diphenylpropyl)cyclopent-2-enone **4a** as the relative hydration product in 18% and 24% yields, respectively (Table 1, entry 1). No Michael addition product was observed. Under the catalysis of AgOTf, the reaction provided similar results (entry 2). However, when AgOTf combined with a base such as $^{i}Pr_2NEt$ was used as the catalytic system, which could be used in the addition reactions to activate the alkynes, the reaction did not occur (entry 3).[2] With $Sc(OTf)_3$ catalysis, the reaction provided a better yield of **4a** (40%) and the same yield of **3a** (18%) (entry 4).

When $MeNO_2$ was used as the solvent, the total yield of **3a** and **4a** was increased under the catalysis of $Sc(OTf)_3$ or $Hf(OTf)_4$ (entries 5 and 7).[10] Whereas $FeCl_3{\cdot}6H_2O$ provided only moderate yields (**3a** + **4a** = 53%) (entry 7).[8] Fortunately, when TfOH was used as a catalyst, the reaction was complete in 10 min to provide 10% **3a** and 68% **4a**, and then prolonging the reaction time to 1 h affor-

* Corresponding authors. Tel.: +86 10 62554614; fax: +86 10 62554449 (Y.-J.C.).
E-mail addresses: lliu@mail.iccas.ac.cn (L. Liu), yjchen@mail.iccas.ac.cn (Y.-J. Chen).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.012



1a 2a 3a 4a

Scheme 1.

Table 1
Allylation of phenylacetylene **2a** with cyclic Baylis–Hillman alcohols **1a**[a]

Entry	Catalyst	Solvent	*t* (h)	Yield[b] of **3a** (%)	Yield[b] of **4a** (%)
1	$In(OTf)_3$	Toluene	12	18	28
2	AgOTf	Toluene	12	18	24
3	AgOTf $^iPr_2NEt$[c]	Toluene	12	0	0
4	$Sc(OTf)_3$	Toluene	12	18	40
5	$Sc(OTf)_3$	$MeNO_2$	12	18	55
6[d]	$FeCl_3{\cdot}6H_2O$	$MeNO_2$	5	10	43
7	$Hf(OTf)_4$	$MeNO_2$	1	13	64
8	TfOH	$MeNO_2$	10 min	10	68
9	TfOH	$MeNO_2$	1	0	76
10	—	$MeNO_2$	12	0	0

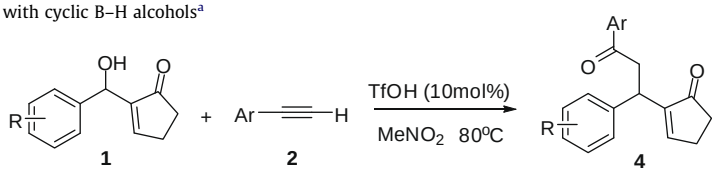
[a] Reactions were carried out on a 0.2 mmol scale in 2 mL of solvent, molar ratio of alcohols/phenylacetylene = 1:2.
[b] Isolated yield.
[c] $^iPr_2NEt$ 20 mol %.
[d] Reaction conditions see Ref. 8.

ded **4a** in 76% yield (entries 8 and 9). In the absence of the catalyst, no reaction occurred (entry 10).

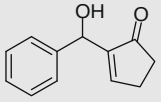
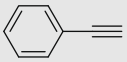
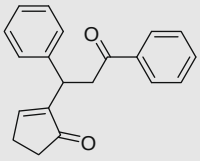
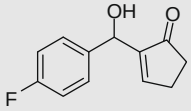
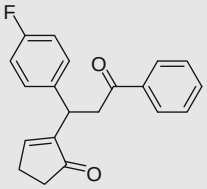
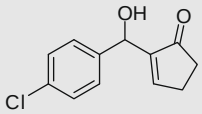
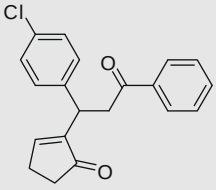
As shown in Table 2, various substituted Baylis–Hillman alcohols **1** could react with aryl alkynes **2** under the catalysis of TfOH in nitromethane at 80 °C. The ketone products **4** were obtained in moderate to good yields.[11] The reaction showed exclusively α-regioselectivity, no γ-allylic substitution products were observed. Under the optimized reaction conditions, alkyne-substituted products **3** were not isolated. Electronic effect of substituted phenyl acetylene is not distinct (Table 2, entries 7–9). In the reaction of 1,4-diethynylbenzene **2d** with **1a**, mono-substituted product **4j** was isolated in 48% yield (Table 2, entry 10).

Though in the model reaction, direct substituted product **3a** and relative hydration product **4a** were isolated, the reaction pathway is still not clear. One of the possible reaction pathways could be considered for the formation of alkenyl cation by regioselective nucleophilic attack of phenylacetylene on allylic cation

Table 2
TfOH-catalyzed reaction of arylacetylenes with cyclic B–H alcohols[a]

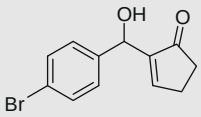
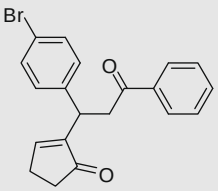
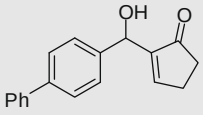
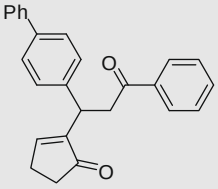
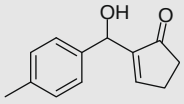
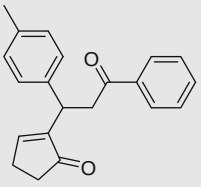
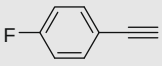
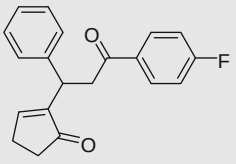
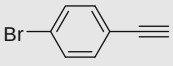
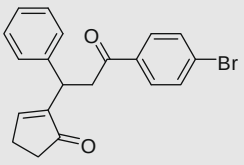
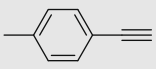
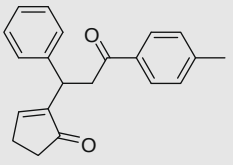
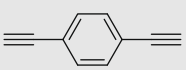
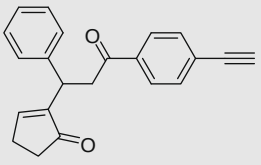


1 2 4

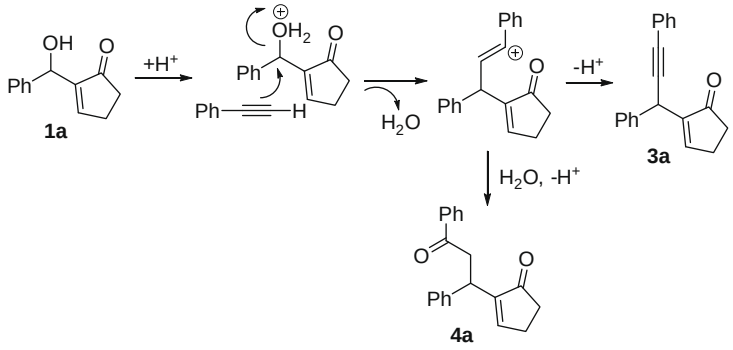
Entry	B–H alcohols	Alkynes	Products	Yield[b] (%)
1	 **1a**	 **2a**	 **4a**	76
2	 **1b**	**2a**	 **4b**	73
3	 **1c**	**2a**	 **4c**	74

(*continued on next page*)

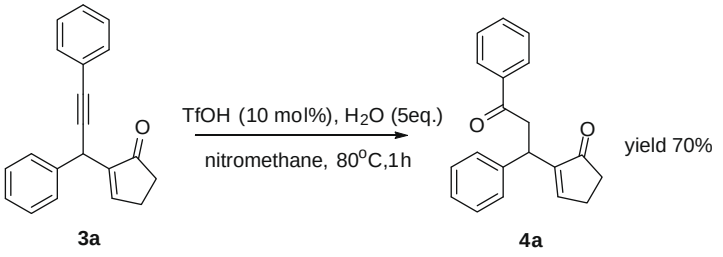
Table 2 (*continued*)

Entry	B–H alcohols	Alkynes	Products	Yield[b] (%)
4	 **1d**	**2a**	 **4d**	70
5	 **1e**	**2a**	 **4e**	64
6	 **1f**	**2a**	 **4f**	59
7	**1a**	 **2b**	 **4g**	73
8	**1a**	 **2a**	 **4h**	67
9	**1a**	 **2c**	 **4i**	64
10	**1a**	 **2d**	 **4j**	48

[a] Reactions were carried out on a 0.2 mmol scale in 2 mL of nitromethane for 1 h at 80 °C, molar ratio of alcohols/phenylacetylene = 1:2.
[b] Isolated yield.



Scheme 2. Proposed reaction pathway.



Scheme 3. Coversion of alkyne **3a** to ketone **4a**.

of Baylis–Hillman adduct, and then followed either by the selective hydration of alkenyl cation to generate the γ,δ-unsaturated ketone **4a** or by deprotonation to provide alkyne-substituted product **3a**. The plausible mechanism was illustrated in Scheme 2. However, ketone **4a** could also be generated by the hydration of compound **3a**.[12] The conversion of alkyne-substituted product **3a** to ketone product **4a** was further proved. When **3a** was treated with 10 mol % TfOH in $MeNO_2$ in the presence of water (5 equiv) at 80 °C for 1 h, **4a** was obtained in 70% yield (Scheme 3). The hydration of compound **3a** could not be catalyzed by $PdCl_2$ in MeCN–H_2O which had been used in the hydration of internal alkynes.[13]

In conclusion, the reaction of cyclic Baylis–Hillman alcohols with arylacetylenes was achieved under the catalysis of TfOH in nitromethane. The reaction provided γ,δ-unsaturated ketones in moderate to good yields via regioselective nucleophilic attack of terminal alkynes at α-position of Baylis–Hillman alcohols, followed by the in-site hydration.

Acknowledgments

We thank the National Natural Science Foundation of China (Nos. 20632010, 20872141) and the Chinese Academy of Sciences for financial support.

References and notes

1. (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979; (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.
2. Chen, L.; Li, C. J. *Adv. Synth. Catal.* **2006**, *348*, 1459.
3. Leadbeater, N. E. *J. Org. Chem.* **2001**, *66*, 7539.
4. Kabalka, G. W.; Yao, M. L.; Borella, S. *Org. Lett.* **2006**, 879.
5. (a) Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, 7809; (b) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, 5579; (c) Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, 5416; (d) Trost, B. M.; Flygare, J. A. *J. Org. Chem.* **1994**, 1078.
6. (a) Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, 10402; (b) Derien, S.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1994**, 2551; (c) Derien, S.; Jan, D.; Dixneuf, P. H. *Tetrahedron* **1996**, 5511.
7. Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945.
8. Jana, U.; Biswas, S.; Maiti, S. *Eur. J. Org. Chem.* **2008**, 5798.
9. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Basavaiah, D.; Rao, A. J.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581; (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; (d) Shi, Y. L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.
10. Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340.
11. *Typical procedure for the allylation of terminal alkynes with cyclic Baylis–Hillman alcohols catalyzed by TfOH*: To a stirred solution of 2-(hydroxy(phenyl)-methyl)cyclopent-2-enone **1a** (0.2 mmol) in nitromethane (2 mL) were added phenylacetylene **2a** (0.4 mmol) and TfOH (0.02 mmol). The resulting reaction was then heated to 80 °C and monitored by TLC. On cooling to room temperature, saturated $NaHCO_3$ (10 mL) was added and the organic layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 4/1) to afford the γ,δ-unsaturated ketone **4a** and the phenylacetylene-substituted product **3a**.
Compound **3a**: mp 83–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.50–7.44 (m, 4H), 7.34–7.21 (m 6H), 4.96 (s, 1H), 2.64–2.59 (m, 2H), 2.48–2.42 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.76, 159.32, 146.83, 139.46, 131.70, 128.59, 128.23, 128.07, 127.78, 127.11, 123.28, 88.95, 83.56, 34.91, 34.25, 26.40; IR (KBr) 3038, 2908, 1703, 1490, 757, 694 cm^{-1}; HRMS: *m/z* calcd for $C_{20}H_{16}O$: 272.1201; found, 272.1204.
Compound **4a**: mp 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.92 (d, *J* = 7.2 Hz, 2H), 7.56–7.51 (t, *J* = 7.2 Hz, 1H), 7.45–7.40 (t, *J* = 7.2 Hz, 2H), 7.30–7.25 (m, 5H), 7.22–7.19 (m, 1H), 4.48–4.43 (td, *J* = 7.1 Hz, 0.7 Hz, 1H), 3.86–3.77 (dd, *J* = 17.0 Hz, *J* = 7.3 Hz, 1H), 3.51–3.43 (dd, *J* = 17.0 Hz, *J* = 7.3 Hz, 1H), 2.54–2.52 (m, 2H), 2.41–2.37 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 208.51, 197.91, 158.66, 148.05, 141.97, 136.88, 133.05, 128.58, 128.10, 127.86, 126.71, 42.54, 38.31, 35.10, 26.42; IR (KBr) 3046, 2914, 1694, 1448, 1237, 1205, 1001, 752, 698 cm^{-1}; HRMS: *m/z* calcd for $C_{20}H_{18}O_2$: 290.1307; found, 290.1310.
12. Hintermann, L.; Labonne, A. *Synthesis* **2007**, *8*, 1121.
13. Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816.