ORGANIC LETTERS

2008
Vol. 10, No. 9
1783−1785

Novel One-Pot Approach to Synthesis of Indanones through Sb(V)-Catalyzed Reaction of Phenylalkynes with Aldehydes

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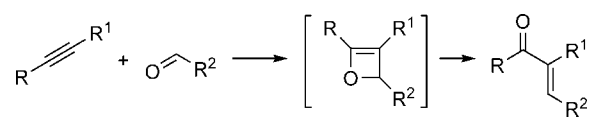
Received March 10, 2008

ABSTRACT

Catalytic SbF_5 and the use of EtOH as an additive efficiently converted a mixture of phenylalkynes and aldehydes to indanone compounds in one pot, and the reaction stereoselectively afforded the corresponding 2,3-disubstituted indanones as a single *trans*-isomer.

1-Indanone compounds are important synthetic intermediates for pharmaceutical agents and biologically active compounds,[1] and there are numerous methods available for the preparation of 1-indanones.[2] One-pot approaches for the synthesis of indanones via Nazarov cyclization[3] of phenyl alkenyl ketone intermediates have been known as convenient methods, while the procedures often required stoichiometric amounts of promoters[4,5] and organometallics.[6] The formation of conjugated enones from alkyne and aldehyde by formal alkyne−carbonyl metathesis has received attention because of the atom-economical process alternative to the Wittig reaction (Scheme 1).[7,8] Although alkyne−carbonyl metathesis is promoted by miscellaneous Lewis acids and Brønsted acids,[9,10] to the best of our knowledge, a one-pot approach to the catalytic formation of indanones by a reaction of alkyne and aldehyde has yet to have been achieved.[11] We

Scheme 1. Alkyne−Carbonyl Metathesis



(1) For examples: (a) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817–1828. (b) Bogeso, K. P.; Arnt, J.; Frederiksen, K.; Hansen, H. O.; Hyttel, J.; Pedersen, H. *J. Med. Chem.* **1995**, *38*, 4380–4392. (c) Sugimoto, H. *Pure Appl. Chem.* **1999**, *71*, 2031–2037. (d) Guillon, J.; Dallemagne, P.; Leger, J.-M.; Sopkova, J.; Bovy, P. R.; Jarry, C.; Rault, S. *Bioorg. Med. Chem.* **2002**, *10*, 1043–1050.

(2) For a recent summary of the synthesis of 1-indanones, see: Wessig, P.; Glombitza, C.; Muller, G.; Teubner, J. *J. Org. Chem.* **2004**, *69*, 7582–7591.

(3) For review: Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.

(4) Examples of Knoevenagel condensation−Nazarov cyclization: (a) Satori, G.; Bigi, F.; Maggi, R.; Bernardi, G. L. *Tetrahedron Lett.* **1993**, *34*, 7339–7342. (b) Bhattacharya, A.; Segmuller, B.; Ybarra, A. *Synth. Commun.* **1996**, *26*, 1775–1784. (c) Lawrence, N. J.; Armitage, E. S. M.; Greedy, B.; Cook, D.; Ducki, S.; McGown, A. T. *Tetrahedron Lett.* **2006**, *47*, 1637–1640. (d) Cui, H.-F.; Dong, K.-Y.; Zhang, G.-W.; Wang, L.; Ma, J.-A. *Chem. Commun.* **2007**, 2284–2286.

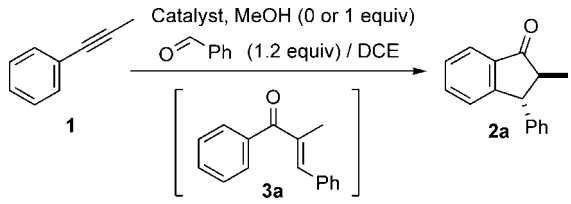
(5) Examples of Friedel−Craft acylation−Nazarov cyclization: (a) Dietrich, U.; Hackmann, M.; Rieger, B.; Klinga, M.; Leskela, M. *J. Am. Chem. Soc.* **1999**, *121*, 4348–4355. (b) Jaroch, S.; Hölscher, P.; Rehwinkel, H.; Sülzle, D.; Burton, G.; Hillmann, M.; McDonald, F. M. *Bioorg. Med. Chem.* **2002**, *12*, 2561–2564. (c) Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 4312–4315.

10.1021/ol800539a CCC: $40.75
Published on Web 04/09/2008

herein report the stereoselective synthesis of 2,3-disubstituted indanones through the SbF_5-catalyzed reaction of phenylalkyne derivatives with aldehydes.

At the outset, we focused our efforts on the screening of catalysts (10−20 mol %) for the formation of indanone **2a** in the reaction of phenylalkyne **1** with benzaldehyde (1.2 equiv) in 1,2-dichloroethane (DCE, Table 1). Although

Table 1. Screening of Catalyst Systems for the Formation of **2a**[a]



	MeOH (none)			MeOH (1 equiv to **1**)		
	yield (%)[b]			yield (%)[b]		
Catalyst (mol % to **1a**)	**2a**	**3a**	**1**	**2a**	**3a**	**1**
$AgSbF_6$ (10)	20	4	–	46	–	–
BF_3·OEt_2 (20)	21	26	7	27	44	20
TfOH (20)	39	6	–	53	–	–
In $(OTf)_3$ (10)	–	20	–	61	–	–
Sc $(OTf)_3$ (10)	21	41	6	35	40	–
Yb $(OTf)_3$ (10)	–	–	–	4	–	48
Cu $(OTf)_2$ (10)	8	37	–	13	39	–
SbF_5 (10)	8	31	–	61[c]	–	–
$SbCl_5$ (10)	–	19	55	2[c]	72	8

[a] Reaction conditions: 90 °C, 18−22 h. [b] Determined by ^{1}H NMR analysis using toluene as an internal standard. [c] 90 °C, 4 h.

previously reported catalysts have brought about good results for the formation of conjugated enones,[7−10] **2a** was obtained in low yields even at 90 °C for 18−22 h (left column, Table 1). On the other hand, an addition of alcohol (1 equiv to **1**) exerted a remarkable effect on the formation of **2a** (right column, Table 1). In particular, by the use of SbF_5 in the presence of MeOH, the desired reaction stereoselectively proceeded at 90 °C within 4 h to give **2a** as a single *trans*-isomer[12]in 61% yield.

We next investigated the additive effect of alcohol (1 equiv to **1**) in the reaction of **1** with benzaldehyde (1.2 equiv) in the presence of SbF_5 (10 mol %) at 90 °C for 2 h in DCE (Figure 1). Compared with the fluorinated alcohol or aprotic polar additive, EtOH turns out to be an efficient additive. Thus, in the presence of EtOH, **1** was consumed at 90 °C within 2 h to give **3a** in 76% yield with complete *trans*-selectivity.[13]

Under the optimized conditions, the present catalytic system could be applied to the reaction of substituted alkyne compounds **1**, **4**, and **6** with various aldehydes (Table 2). Thus, many aldehydes successfully reacted with alkyne **1**, **4**, and **6** to give the corresponding indanone products in moderate to high yields. In all cases, complete *trans*-selectivities were observed. The reaction of terminal alkyne

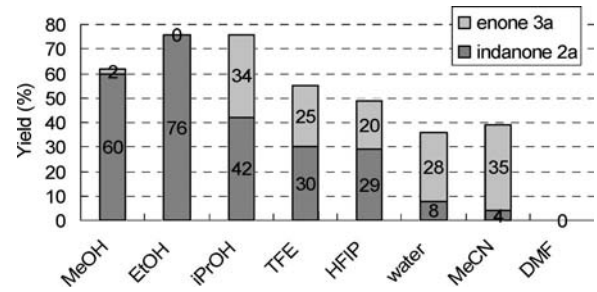
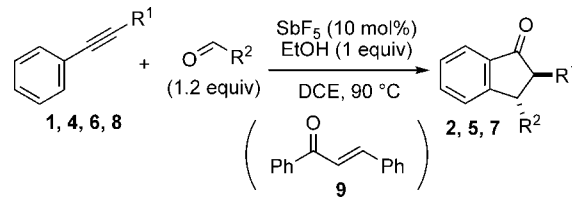


Figure 1. Effect of protic or aprotic polar additive (1 equiv to **1**) in the SbF_5(10 mol %)-catalyzed reaction of **1** benzaldehyde (1.2 equiv) at 90 °C for 2 h in DCE. (Yields of **2a** and **3a** were determined by ^{1}H NMR.) TFE, 2,2,2-trifluoroethanol; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol.

8, however, did not yield indanone but enone **9**.[14] It should be mentioned that the use of $PhCH(OEt)_2$ instead of benzaldehyde showed a rather lower yield of **2a**, regardless of the presence of EtOH (Table 2). Although propiophenone (**10**), propiophenone diethylacetal (**11**), or α-ethoxy-*β*-methylstyrene (**12**) would be expected as an intermediate from alkyne **1** and EtOH, the use of the compounds instead of **1** brought about inferior results (see Supporting Information).

The reaction of phenylalkyne **1** with benzaldehyde at a lower temperature (60 °C, 1 h) by the present catalytic system afforded the enone **3a** in 92% yield (Scheme 2). **3a** could be converted into the corresponding indanone **2a** under similar conditions at 90 °C within 2 h in good yield with excellent selectivity (Scheme 2). Therefore, we believe that the one-pot formation of **2a** from **1** and aldehyde would

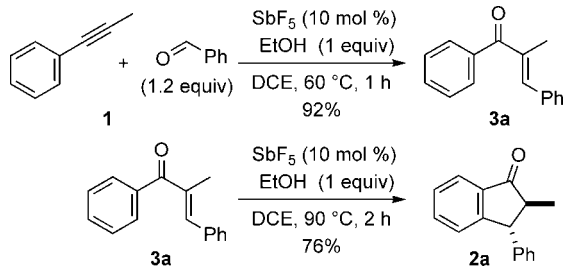
Table 2. Formation of Indanones by SbF_5-EtOH-Catalyzed Reaction of Phenylalkynes with Aldehyde[a]



alkyne/R^1	R^2CHO	time (h)	product/%[b]	
1/Me	PhCHO	2	**2a**	78
	$PhCH(OEt)_2$	7	**2a**	55 (54[c])
	*t*BuCHO	8	**2b**	89
	EtCHO	22	**2c**	75
	CyCHO	72	**2d**	72
4/*n*Bu	PhCHO	4	**5a**	78
	*t*BuCHO	10	**5b**	82
	Ph $(CH)_2$CHO	22	**5c**	66
	*i*PrCHO	96	**5d**	38 (63[d])
6/Ph	PhCHO	22	**7a**	59
	MeCHO[e]	48	**7b**	45
8/H	PhCHO	48	**9**	60

[a] CyCHO: cyclohexanecarboaldehyde. [b] Isolated yield. [c] EtOH was absent. [d] SbF_5: 20 mol %. [e] 3 equiv.

Scheme 2



consist of (i) the formal alkyne−carbonyl metathesis between both substrates and (ii) Nazarov cyclization of phenyl alkenyl ketone intermediates. Although the precise role of EtOH is less clear, one of the possibilities would be the generation of the protic catalyst SbF_5•EtOH.[15]

To gain a qualitative understanding of the activation of alkyne **1** and benzaldehyde by the present catalytic system, we carried out NMR studies using SbF_5•10EtOH (a 1:10 mixture of SbF_5 and EtOH). The ^{13}C NMR spectrum (75 MHz) of a 1:1 mixture of **1** and benzaldehyde in the presence of 10 equiv of EtOH in $(CD_2Cl)_2$ at room temperature showed that the signals of the sp-carbons (δ 81.32, 87.73) of **1** scarcely shifted (δ 81.34, 87.69) and the carbonyl-carbon (δ 193.78) of benzaldehyde shifted to a lower field (δ 194.20). In the case of the mixture of **1**, aldehyde, and a stoichiometric amount of SbF_5•10EtOH (**1**/benzaldehyde/SbF_5/EtOH = 1:1:1:10), the slight shift of sp-carbons of **1** to a higher field (δ 81.12, 87.58) and the shift of carbonyl-carbon to a lower field (δ 194.31) were observed.[16] A similar observation has been reported in the Ag(I)-catalyzed reaction of alkyne and aldehyde.[8] Thus, the present catalytic system would preferentially activate aldehyde rather than alkyne to bring about the formation of **3a**.

In conclusion, we developed a highly stereoselective one-pot synthesis of *trans*-2,3-disubstituted indanone derivatives from phenylalkynes with aldehydes. The use of EtOH as an additive was found to be essential for the SbF_5-catalyzed formation of indanone derivatives. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

Acknowledgment. This work was supported by a Grant-in-Aid for Young Scientists (B), MEXT Japan (No. 17790021). A generous donation of HFIP by Central Glass Co., Ltd., is gratefully acknowledged.

Supporting Information Available: Experimental procedures and physical data for **2a**−**2d**, **3a**, **5a**−**5c**, and **7a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In the $GaCl_3$-mediated reactions of phenylalkynes with aldehydes, 3-chloro-1,2-dialkyl-1*H*-indene derivatives were obtained as byproducts (4−22%). See: Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 1613–1615.

(12) It is one of the possibilities that small amounts of *cis*-indanone included in the initially formed diastereomer mixtures would be isomerized to *trans*-isomer. See: Touron, P.; Laude, B. C. R. *Acad. Sci. Ser. C* **1979**, *289*, 53.

(13) Addition of 1 equiv of EtOH to **1** ended with an optimum amount for the formation of **2a** (see Supporting Information).

(14) Nazarov cyclization of chalcone (**9**) also did not proceed under the identical conditions. Generally, **9** required more harsh conditions than 2-substituted enones. See: Koltunov, K. Y.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391.

(15) Il'in, E. G.; Nazarov, A. P.; Buslaev, Y. A. *Dokl. Akad. Nauk SSSR* **1979**, *249*, 1149–1152.

(16) By NMR studies using various equivalents of SbF_5•10EtOH (0.1, 0.3, 0.5, 1 equiv to **1**), we found that the change in chemical shift of **1** and benzaldehyde depends on an amount of SbF_5•10EtOH. Thus, it is suggested that SbF_5•10EtOH would induce an activation of **1** and/or benzaldehyde.