Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 397–400
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Tributylphosphine-catalyzed reaction of ethanethiol with alkynyl ketones

Shen Zhao [a], Qing Fa Zhou [a,*], Jia Zhi Liu [a], Wei Fang Tang [a], Tao Lu [a,b,**]

[a] *Department of Organic Chemistry, China Pharmaceutical University, Nanjing 210009, China*
[b] *Key Laboratory of Drug Quality Control and Pharmacovigilance, China Pharmaceutical University, Ministry of Education, Nanjing 210009, China*

Received 9 July 2010
Available online 17 January 2011

Abstract

A stereoselective and effective method for the synthesis of vinyl thioethers has been developed. This method is based on the Michael addition of ethanethiol to various alkynyl ketones using 10 mol% of tributylphosphine as catalyst. Most of alkynyl ketones react with ethanethiol in this system to yield mainly *Z*-isomer of vinyl thioether adducts, only in one case mainly *E*-isomer of vinyl thioether adducts was observed.

Keywords: Tributylphosphine; Synthesis; Alkynyl ketones; Michael addition; Vinyl thioether

Organocatalysis is emerging as a rapidly growing field of organic chemistry due to the advantages of efficiency, operational simplicity, mild reaction conditions and environmentally benign nature compared with metal complex-catalysis [1]. Among them nucleophilic catalysis *via* conjugate addition of N- and P-nucleophile displays an important subset of organocatalytic reactions, such as the Morita–Baylis–Hillman condensation [2], isomerization of alkynyl ketones [3], nucleophilic additions to α,β-unsaturated systems [4], [3 + 2] cycloadditions [5], [4 + 2] cycloadditions [6], dehydrogenative coupling reaction of carboxylic acids with silanes [7], ring-opening reaction of epoxides and aziridines [8], allylic amination [9].

Sulfur-containing compounds are both important intermediates in organic synthesis [10] and exhibit a wide range of pharmaceutical uses. For example, the dihydrobenzoxanthiin is a selective estrogen receptor modulator [11], and diltiazem is used as a calcium channel blocker in the treatment of hypertension [12]. Thus, many ways have been developed for the synthesis of organosulfur compounds. These include metal-catalyzed coupling reaction [13], acids-catalyzed or promoted reaction [14], electrochemical reaction [15]. Michael addition of thiols to electron-deficient alkynes represents an attractive route for the direct synthesis of vinyl thioethers [16]. However, even though there have been several reports on the regioselective synthesis of vinyl thioethers in the presence of N-catalyst or inorganic base, few examples of synthesis of vinyl thioethers in the presence of phosphine Lewis base have been reported, to the best

* Corresponding author.
** Corresponding author at: Department of Organic Chemistry, China Pharmaceutical University, Nanjing 210009, China.
E-mail addresses: zhouqingfa@cpu.edu.cn (Q.F. Zhou), lut163@163.com (T. Lu).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.11.007

1a **2a**

Scheme 1.

Table 1
Reaction of 1,3-diphenylprop-2-yn-1-one (**1a**) and ethanethiol under various conditions.

Entry	Base (mol%)	Solvent	Time (h)	*Z/E* selectivity (%)[a]	Yield of **2a** (%)[b,c]
1	Ph_3P (10)	CH_2Cl_2	96	73/27	17
2	(n-Bu)$_3$P (10)	CH_2Cl_2	0.25	68/32	99
3	(n-Bu)$_3$P (10)	CH_2Cl_2	1.5	87/13	99[d]
4	Et_3N (10)	CH_2Cl_2	48	86/14	96
5	Pyridine (10)	CH_2Cl_2	96	–	Trace
6	(n-Bu)$_3$P (10)	Et_2O	96	85/15	79
7	(n-Bu)$_3$P (10)	THF	96	64/36	20
8	(n-Bu)$_3$P (10)	Toluene	3	87/13	89
9	(n-Bu)$_3$P (10)	EA	2.5	82/18	95
10	(n-Bu)$_3$P (10)	Acetone	2.5	85/15	99
11	(n-Bu)$_3$P (10)	MeOH	24	88/12	59
12	(n-Bu)$_3$P (10)	CH_3CN	96	–	Trace

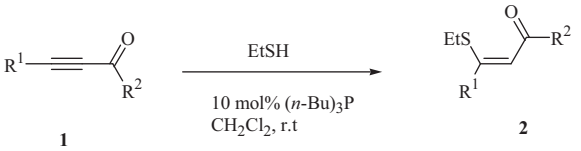
[a] *Z/E* selectivity was estimated by crude ^{1}H NMR determination.
[b] Yield after purification by silica gel column chromatography.
[c] Unless otherwise noted, reactions were carried out at room temperature.
[d] Reaction was carried out at 0 °C.

of our knowledge, in literature [17]. Here, we wish to report a facile method for the synthesis of vinyl thioethers through the Michael addition of thiols to electron-deficient alkynes by use of tributylphosphine as catalyst with good to excellent chemical yields and regioselectivity (Scheme 1).

We first chose 1,3-diphenylprop-2-yn-1-one (**1a**) and ethanethiol as the standard substrate to search for potential catalyst and suitable reaction conditions and the results are shown in Table 1. It was observed that poor yield was obtained when PPh_3 (10 mol%) was applied as a nucleophilic promoter and the reaction was carried for 96 h at room temperature in dichloromethane solution. A diastereomeric ratio of 73:27 was observed in favor of the *Z*-isomer. The configuration of the double bond of carbon and carbon in **2a** was determined by its ^{1}H-NOESY NMR spectrum, from which no NOE effect was found between the signals of vinyl proton and methylene protons in *Z*-isomer, whereas NOE effect was observed between the signals of vinyl proton and methylene protons in *E*-isomer. However, the yield and the degree of diastereoselective induction increased greatly from 17 to 99% and 75:25 to 85:15 when tributylphosphine ((n-Bu)$_3$P) was used as a catalyst. At lower temperature (0 °C), better diastereoselectivity was observed. Then we tested amines such as triethylamine and pyridine; triethylamine could effectively catalyze the action, but pyridine was not adapted to the above reaction. Moreover, among the solvents we examined, CH_2Cl_2 was proved to be the optimum solvent, and the yield of product decreased significantly when another solvent such as THF or MeOH was used. Therefore, it seems to us that the best reaction condition is to carry out this reaction in CH_2Cl_2 with (n-Bu)$_3$P as a catalyst at room temperature [18].

With these results in hand, a variety of alkynyl ketones were first submitted to the reaction; the results are summarized in Table 2. It was observed that all of electron-deficient internal alkynes react with ethanethiol in this system to yield mainly *Z*-isomer of vinyl thioether adducts and afford the corresponding products with good to excellent yields under the optimized condition. The substituents on the phenyl ring of the electron-deficient internal alkynes have obvious effect on the yields of the reaction. For example, the reaction of 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-one or 1,3-diphenylprop-2-yn-1-one, under the conditions described, gave the corresponding products **2e** and **2a** in 97% and 99% yields, respectively. However, the substituents on the phenyl ring of the electron-deficient internal

Table 2
Reaction of Alkynyl ketones **1** with ethanethiol



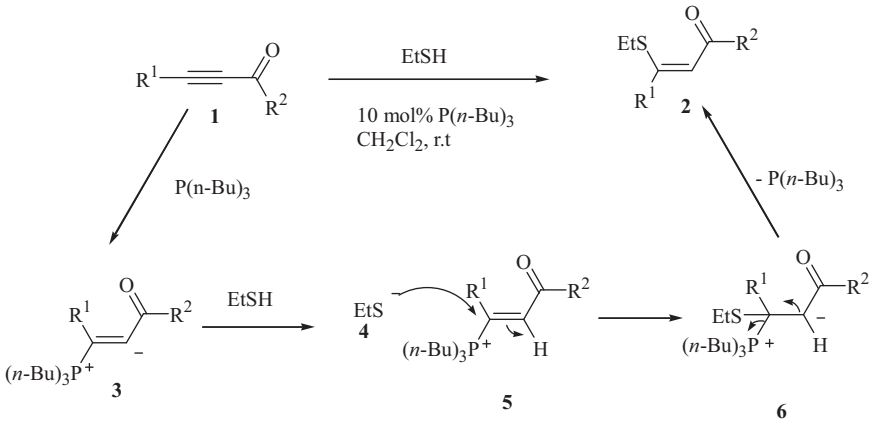
Entry	R^1	R^2	Time (minute)	Product	*Z/E* selectivity (%)[a]	Yield of **2** (%)[b]
1	Ph	Ph	15	**2a**	67/33	99
2	Ph	*p*-F-Ph	15	**2b**	67/33	99
3	Ph	*p*-Cl-Ph	15	**2c**	87/13	99
4	Ph	*p*-Br-Ph	40	**2d**	71/29	99
5	Ph	*p*-NO_2-Ph	15	**2e**	79/21	97
6	Ph	*m*-NO_2-Ph	20	**2f**	71/29	80
7	Ph	*p*-MeO-Ph	60	**2g**	68/32	96
8	Ph	*p*-MeS-Ph	60	**2h**	74/26	96
9	Ph	3,4-$(MeO)_2$-Ph	90	**2i**	73/27	99
10	Ph	2,3,4-$(MeO)_3$-Ph	60	**2j**	85/15	88
11	Ph	4-pyridine	10	**2k**	69/31	99
12	H	Ph	35	**2l**	81/19	90
13	H	*o*-Cl-Ph	15	**2m**	18/82	76

[a] *Z/E* selectivity was estimated by crude ^{1}H NMR determination.
[b] Yield after purification by silica gel column chromatography.

alkynes only have slightly effect on the stereoselectivity. Electron-deficient terminal alkynes with ethanethiol also proceeded smoothly to generate the corresponding products with good yields (Table 2, entries 12–13). For example, when 1-phenylprop-2-yn-1-one was tested in the conditions described, the product of vinyl thioether was formed in 90% yield with a *Z/E* selectivity ratio of 81:19, which was based on crude ^{1}H NMR analysis.

A proposed mechanism for this reaction was outlined in Scheme 2 based on the previous investigation. Initially, tributylphosphine act as nucleophilic promoter to initiate the reaction and produces a zwitterionic intermediate **3**, which then deprotonates ethanethiol to form the corresponding intermediates **4** and **5**. Subsequent Michael addition of **4** to **5** give intermediate **6**, which then eliminate tributylphosphine to afford the final product.

In summary, we have developed a stereoselective and effective method for the synthesis of vinyl thioethers through the conjugate addition of thiols to alkynyl ketones catalyzed by tributylphosphine in mild condition.



Scheme 2.

Acknowledgment

We are grateful for the financial support from National Natural Science Foundation of China (No. 30973609).

References

[1] (a) X. Lu, C. Zhang, Z. Xu, Acc. Chem. Res. 34 (2001) 535;
(b) H. Georger, Chem. Rev. 103 (2003) 2795.
[2] (a) A.G.M. Barrett, A.S. Cook, A. Kamimura, Chem. Commun. (1998) 2533;
(b) M. Shi, L.H. Chen, C.Q. Li, J. Am. Chem. Soc. 127 (2005) 3790.
[3] (a) B.M. Trost, T. Schmidt, J. Am. Chem. Soc. 110 (1988) 2303;
(b) D. Ma, Y. Lin, X. Lu, Y. Lu, Tetrahedron Lett. 29 (1988) 1045;
(c) Q.F. Zhou, F. Yang, Q.X. Guo, S. Xue, Chin. Chem. Lett. 18 (2007) 1029.
[4] (a) B.M. Trost, G.R. Dake, J. Am. Chem. Soc. 119 (1997) 7595;
(b) C. Zhang, X. Lu, Synlett (1995) 645.
[5] (a) C. Zhang, X. Lu, J. Org. Chem. 60 (1995) 2906;
(b) Z. Xu, X. Lu, Tetrahedron Lett. 38 (1997) 3461;
(c) Z. Xu, X. Lu, J. Org. Chem. 63 (1998) 5031.
[6] Y.S. Tran, O. Kwon, J. Am. Chem. Soc. 129 (2007) 12632.
[7] G.B. Liu, H.Y. Zhao, T. Thiemann, Adv. Synth. Catal. 349 (2007) 807.
[8] (a) R.H. Fan, X.L. Hou, L.X. Dai, J. Org. Chem. 67 (2002) 5295;
(b) R.H. Fan, X.L. Hou, J. Org. Chem. 68 (2003) 726.
[9] C.W. Cho, J.R. Kong, M.J. Krische, Org. Lett. 6 (2004) 1337.
[10] (a) F. Bossert, Angew. Chem. Chem., Int. Ed. 4 (1965) 879;
(b) W.D. Rudorf, A. Schierhorn, M. Augustin, Tetrahedron 35 (1979) 551;
(c) T. Nishio, Y. Omote, Synthesis (1980) 390;
(d) O.D. Lucchi, V. Lucchini, C. Marchioro, J. Org. Chem. 51 (1986) 1457.
[11] T.A. Blizzard, F. DiNinno, H.Y. Chen, Bioorg. Med. Chem. Lett. 15 (2005) 3912.
[12] C. Mordant, C. Caño de Andrade, R. Touati, Synthesis (2003) 2405.
[13] (a) G.H. Posner, P.W. Tang, J. Org. Chem. 43 (1978) 4131;
(b) S. Murahashi, M. Yamamura, K. Yanagisawa, J. Org. Chem. 44 (1979) 2408;
(c) K. Takagi, Chem. Lett. (1987) 2221.
[14] (a) N. Srivastava, B.K. Banik, J. Org. Chem. 68 (2003) 2109;
(b) M.M. Alam, R. Varala, S.R. Adapa, Tetrahedron Lett. 44 (2003) 5115;
(c) S.K. Garg, R. Kumar, A.K. Chakraborti, Tetrahedron Lett. 46 (2005) 1721.
[15] (a) O. Arjona, F. Iradier, R. Medel, J. Org. Chem. 64 (1999) 6090;
(b) M.T. Omar, M.N. Basyouni, Bull. Chem. Soc. Jpn. 47 (1974) 2325;
(c) R. Medel, M.I. Monterde, J. Plumet, J. Org. Chem. 70 (2005) 735;
(d) C. Reuter, F. Vögtle, Org. Lett. 2 (2000) 593.
[16] (a) O. Arjona, F. Iradier, R. Medel, J. Org. Chem. 64 (1999) 6090;
(b) M.T. Omar, M.N. Basyouni, Bull. Chem. Soc. Jpn. 47 (1974) 2325;
(c) R. Medel, M.I. Monterde, J. Plumet, J. Org. Chem. 70 (2005) 735.
[17] J. Inanaga, Y. Baba, T. Hanamoto, Chem. Lett. (1993) 241.
[18] Typical procedure: a solution of alkynones (0.3 mmol), ethanethiol (0.33 mmol), and (n-Bu)$_3$P (0.03 mmol) in 2 mL of CH_2Cl_2 was stirred at room temperature. After the reaction was completed as monitored by TLC, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (15:1–10:1 PE-EtOAc) to afford the corresponding pure product.