Stereoselective Synthesis of *E*-Vinyl Sulfides from Alkynes in Water under Neutral Conditions Using β-Cyclodextrin[1]

R. Sridhar, K. Surendra, N. Srilakshmi Krishnaveni, B. Srinivas, K. Rama Rao*

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500007, India
E-mail: drkrrao@yahoo.com

Received 16 July 2006

Abstract: This is the first example of stereoselective synthesis of *E*-vinyl sulfides in water in excellent yields by hydrothiolation of aromatic alkynes with thiophenols by anti-Markonikov addition in the presence of β-cyclodextrin. This protocol tolerates a wide variety of functional groups or substrates and does not require the use of transition-metal or base catalysts. β-Cyclodextrin can be recovered and reused for a number of runs without any loss of activity.

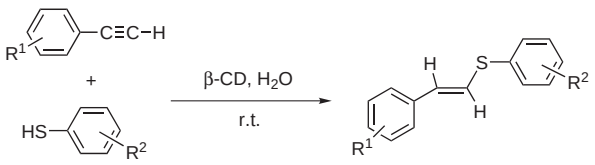
Key words: β-cyclodextrin, *E*-vinyl sulfides, aromatic alkynes, thiophenols, water

Hydrothiolation of alkynes is an important reaction, which produces vinyl sulfides of significant synthetic utility.[2] Vinyl sulfides have acquired special importance as intermediates in various synthetic transformations of natural products and biologically active compounds containing vinyl sulfide groups.[3] They have also been utilized as equivalents of enolate ions[4] and Michael acceptors.[5]

In view of unique applicability of vinyl sulfides in organic synthesis, their stereo- and regioselective synthesis has merited exploitation. Typical synthetic routes involve: (i) addition of thiols to alkynes under radical conditions to afford anti-Markonikov type vinylic sulfides as *E* and *Z* stereoisomeric mixture, (ii) transition-metal catalysis proceeding in *syn* fashion affording anti-Markonikov *E*-vinyl sulfides but with low regioselectivity in some cases[6–8] and, (iii) base-catalyzed addition of thiols to acetylene compounds mostly in *trans* fashion affording *Z*-vinylic sulfides.[9] The Wittig reaction has also been utilized in the synthesis of vinyl sulfides but this requires the use of strong bases and the synthesis of the appropriate Wittig reagent may be problematic.[10] However, these methodologies often have limited scope due to lack of regio- and stereoselectivity. Thus, there is a need to develop hydrothiolation reactions in water with a recyclable catalyst. The development of environmentally benign and clean synthetic procedures has become the goal of present-day organic synthesis.[11] Water as solvent has acquired significance since it is safe, economical and environmentally benign.[12] We report herein for the first time a novel and environmentally benign synthesis of *E*-vinyl sulfides in water with a recyclable catalyst via hydrothiolation of alkynes with thiophenols under neutral conditions catalyzed by cyclodextrin in water.

SYNLETT 2006, No. 20, pp 3495–3497
Advanced online publication: 08.12.2006
DOI: 10.1055/s-2006-956458; Art ID: D20606ST

Cyclodextrins catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Generally α-cyclodextrin can typically complex low molecular weight molecules or compounds with aliphatic side chains, whereas β-cyclodextrin can complex aromatics and heterocycles and γ-cyclodextrin can accommodate larger molecules such as macrocycles and steroids.[13,17b] Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[14] prompted us to attempt the addition of various thiols to alkynes under biomimetic conditions in the presence of β-cyclodextrin in water (Scheme 1).



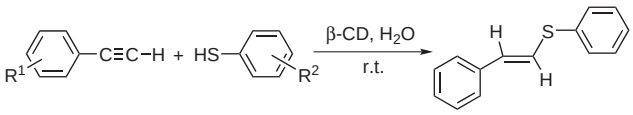
R^1 = H, Me, Br, Cl; R^2 = H, Me, OMe, Cl, Br

Scheme 1

In general, the reaction was carried out by the in situ formation of the β-cyclodextrin complex of the aryl alkynes in water followed by the addition of thiols and stirring at room temperature to give the corresponding *E*-vinyl sulfides in impressive yields (90–96%).[15] This represents the first practically feasible anti-Markonikov addition reaction of thiols with a variety of alkynes in water with high regio- and stereoselectivity. The reaction proceeds efficiently at room temperature without the need for any additional catalyst and goes to completion in a short time (4.0–4.5 h). This methodology is compatible with various substituted alkynes and thiols with different functionalities such as bromo, chloro, methyl and methoxy group, under mild reaction conditions (Table 1). No by-product formation was observed. These reactions are highly selective forming *E*-vinyl sulfides as the only product in excellent yields and the β-cyclodextrin can be easily recovered and reused. However, no reaction was observed when alkyl thiols (e.g., butane thiol) and alkyl alkynes (e.g., 1-octyne) were used. All the compounds were characterized spectroscopically and compared with the known compounds.[6a,8a,16] The catalytic activity of cyclodextrins for these anti-Markonikov additions is established by the fact that no reaction was observed in the absence of cyclodex-

trin. The reaction takes place with α-cyclodextrin as well with the same regioselectivity and stereochemistry; however, β-cyclodextrin was chosen as the catalyst since it is inexpensive and easily accessible.

Table 1 Hydrothiolation of Alkynes with Thiophenols in the Presence of β-Cyclodextrin in Water



Entry	R^1	R^2	Time (h)	Yield (%)[a,b]
1	H	H	4.0	96[c]
2	H	*o*-Me	4.5	92
3	H	*p*-OMe	4.5	94
4	H	*p*-Cl	4.0	95
5	H	*p*-Br	5.0	96
6	H	*p*-Me	5.0	94
7	*p*-Br	H	4.0	95
8	*p*-Br	*p*-Br	4.5	92
9	*p*-Br	*o*-Me	4.0	90
10	*p*-Me	H	4.5	94
11	*p*-Me	*p*-OMe	4.0	92
12	*p*-Me	*o*-Me	4.5	90
13	*p*-Me	*p*-Br	4.0	94
14	*p*-Cl	H	4.0	95

[a] All products were reported previously in literature.[6a,8a,16]
[b] Isolated yields.
[c] The catalyst was recovered and reused for five consecutive runs in this reaction without change in yield and purity.

The fact that these reactions do not take place in the absence of cyclodextrin in water indicates the essential role of cyclodextrin. Here the cyclodextrin appears to form an inclusion complex with the alkyne from the secondary face with the attack of thiophenol from the primary face. The hydrogen bonding of thiols with the cyclodextrin hydroxyls makes the S–H bond weaker, enhancing the nucleophilicity of sulfur and making it a better nucleophile towards addition to the triple bond of the alkyne at the terminal end in a *cis* fashion. This stereospecific *cis* nucleophilic addition across the triple bond leads to the formation of *trans* alkenes. Evidence for this mechanism was deduced from ^{1}H NMR spectroscopy, using phenylacetylene and thiophenol as representative examples. The ^{1}H NMR spectra (D_2O) of β-cyclodextrin, β-cyclodextrin–phenylacetylene complex and freeze-dried reaction mixture of the β-cyclodextrin–phenylacetylene complex with thiophenol after two hours were studied. A clear upfield shift of the H3 (δ = 0.01 ppm) and H5 (δ = 0.021 ppm) protons of the β-cyclodextrin in the β-cyclodextrin–phenylacetylene complex as compared to β-cyclodextrin were observed, indicating the formation of an inclusion complex of phenylacetylene with β-cyclodextrin from the secondary face. The spectrum of the reaction mixture of the β-cyclodextrin–phenylacetylene complex and thiophenol after two hours also showed an upfield shift of the H6 proton by 0.013 ppm indicating the complexation of thiophenol from the primary face of the cyclodextrin. These shifts are in the reported range for such complexes.[17] Thus, ^{1}H NMR studies indicate that supramolecular catalysis of the highly regio- and stereoselective addition of thiophenol to alkynes to form *E*-vinyl sulfides takes place in the β-cyclodextrin cavity with thiophenol at the primary face approaching the acetylene placed at the secondary face.

In summary, we have documented for the first time cyclodextrin-catalyzed synthesis of *E*-vinyl sulfides with high regio- and stereoselectivity from alkynes. These cyclodextrin-mediated water solvent reactions are very useful both from economical and environmental points of view. This reaction is simple with a recyclable catalyst and runs under relatively mild conditions, with shorter reaction times and high selectivities.

Acknowledgment

We thank the Indo-French Center for the Promotion of Advanced Research (IFCPAR) for the financial support of this project.

References

(1) IICT communication no. 060914.
(2) (a) Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648. (b) Domon, K. M. K.; Tanino, K.; Kuwajima, I. *Synlett* **1996**, 157. (c) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621.
(3) (a) Sader, H. S.; Johnson, D. M.; Jones, R. N. *Antimicrob. Agents Chemother.* **2004**, *48*, 53. (b) Johannesson, P.; Lindeberg, G.; Johansson, A.; Nikiforovich, G. V.; Gogoll, A.; Synnergren, B.; LeGreves, M.; Nyberg, F.; Karlen, A.; Hallberg, A. *J. Med. Chem.* **2002**, *45*, 1767. (c) Ceruti, M.; Balliano, G.; Rocco, F.; Milla, P.; Arpicco, S.; Cattel, L.; Viola, F. *Lipids* **2001**, *36*, 629. (d) Marcantoni, E.; Massaccesi, M.; Petrini, M.; Bartoli, G.; Bellucci, M. C.; Bosco, M.; Sambri, L. *J. Org. Chem.* **2000**, *65*, 4553. (e) Lam, H. W.; Cooke, P. A.; Pattenden, G.; Bandaranayake, W. M.; Wickramasinghe, W. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 847. (f) Morimoto, K.; Tsuji, K.; Iio, T.; Miyata, N.; Uchida, A.; Osawa, R.; Kitsutaka, H.; Takahashi, A. *Carcinogenesis* **1991**, *12*, 703.
(4) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.
(5) Miller, R. D.; Hassig, R. *Tetrahedron Lett.* **1985**, *26*, 2395.
(6) (a) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614. (b) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (c) Ogawa, A. *J. Organomet. Chem.* **2000**, *611*, 463. (d) Kuniyasu, H. In *Catalytic Heterofunctionalization*; Togni, A.; Grützmacher, H., Eds.; Wiley-VCH: Weinheim Germany, **2001**, Chap. 7. (e) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(7) (a) Beauchemin, A.; Gareau, Y. *Phosphorus, Sulfur Silicon Relat. Elem.* **1998**, 139. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1035. (c) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103. (d) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J. L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647. (e) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273.

(8) (a) Azusa, K.; Kazuaki, T.; Hideki, Y.; Koichiro, O. *J. Org. Chem.* **2005**, *70*, 6468. (b) Sugoh, K.; Kuniyasu, H.; Sugae, T.; Ohtaka, A.; Takai, Y.; Tanaka, A.; Machino, C.; Kambe, N.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 5108. (c) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (d) Koelle, U.; Rietmann, C.; Tjoe, J.; Wagner, T.; Englert, U. *Organometallics* **1995**, *14*, 703. (e) Bäckvall, J. E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850. (f) Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902. (g) Mcdonald, J. W.; Corbin, J. L.; Newton, W. E. *Inorg. Chem.* **1976**, *15*, 2056.

(9) (a) Truce, W. E.; Simms, J. A.; Boudakian, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 695. (b) Truce, W. E.; Simms, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 2756. (c) Truce, W. E.; Tichenor, G. J. W. *J. Org. Chem.* **1972**, *37*, 2391.

(10) (a) Aucagne, V.; Tatibouet, A.; Rollin, P. *Tetrahedron* **2004**, *60*, 1817. (b) Stephan, E.; Olaru, A.; Jaouen, G. *Tetrahedron Lett.* **1999**, *40*, 8571. (c) Ishida, M.; Iwata, T.; Yokoi, M.; Kaga, K.; Kato, S. *Synthesis* **1985**, 632. (d) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *Synthesis* **1975**, 278. (e) Kumamoto, T.; Hosoi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2742.

(11) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry, Theory and Practice*; Oxford University Press: Oxford, **1998**. (b) Eissen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 414.

(12) (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackli Academic and Professional: London, **1998**. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, **1997**.

(13) (a) Szejtli, J.; Osa, T. In *Comprehensive Supramolecular Chemistry*, Vol. 3; Pergamon Press: Oxford, **1996**. (b) Martin Del Valle, E. M. *Proc. Biochem.* **2004**, *39*, 1033.

(14) (a) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Chem. Commun.* **2005**, 669. (b) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Adv. Synth. Catal.* **2004**, *346*, 346. (c) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 9119.

(15) **General Procedure**: β-Cyclodextrin (1 mmol) was dissolved in H_2O (1 mL) by warming to 60 °C until a clear solution was formed. Then alkyne (1 mmol) dissolved in acetone (1 mL) was added dropwise and the mixture was allowed to cool to r.t. Thiol (1 mmol) was then added and the mixture was stirred at r.t. until the reaction was complete (Table 1). The organic material was extracted with EtOAc, the extract was dried and concentrated under reduced pressure and the resulting product, although seen as single compound by TLC, was further purified by passing through a column of silica gel. The cyclodextrin was recovered by filtration and reused.

(16) (a) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (b) Huang, X.; Zhong, P.; Guo, W. R. *Org. Prep. Proced. Int.* **1999**, *31*, 201.

(17) (a) Demarco, P. V.; Thakkar, A. L. *Chem. Commun.* **1970**, 2. (b) Schneir, H.-J.; Hacket, F.; Rudiger, V. *Chem. Rev.* **1998**, *98*, 1755.