Contents lists available at SciVerse ScienceDirect

Chinese Chemical Letters

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





A simple and convenient method for the synthesis of *S*-aryl phosphorothioates catalyzed by cesium hydroxide



CrossMark

CCI

Yue-Jun Ouyang ^{a,b}, Yuan-Yuan Li^b, Ning-Bo Li^b, Xin-Hua Xu^{b,*}

^a Department of Chemistry and Chemical Engineering, Huaihua University, Huaihua 418000, China
^b College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

ARTICLE INFO

Article history: Received 3 May 2013 Received in revised form 8 June 2013 Accepted 13 June 2013 Available online 16 July 2013

Keywords: Cesium hydroxide Diaryldisulfides 0,0-Dialkyl-S-arylphosphorothioates

ABSTRACT

In the presence of a catalytic amount of cesium hydroxide, the corresponding *S*-aryl phosphorothioates can be obtained by the reactions of dialkyl phosphites with diaryldisulfides in excellent yields at room temperature, using DMSO as a solvent. The reaction mechanism was discussed. The method provides a new and expedient path for the preparation of *S*-aryl phosphorothioates.

© 2013 Xin-Hua Xu. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

1. Introduction

Thiophosphoric acid esters containing C–S–P bonds are of special interest as pesticides and as thioanalogues of naturally occurring phospholipids with phospholipase-inhibitory, cytostatic, or hypotensive activity [1–11]. They can be prepared by the reaction of sulfenyl halogenides with trialkyl phosphites [11–13], the redox reaction of a phosphorous triester with a thiol in the presence of TeCl₄ and tertary amines [14], the reaction of thiosuccinimides with trialkyphosphines [15,16], the reaction of disulfides with dialkyl phosphites [(RO)₂P(O)H] catalyzed by CuI in the presence of organic base [17]. But the first two methods involved extremely labile reagents sulfenyl halogenides (ArSX) and TeCl₄. Moreover, TeCl₄ is expensive. The third method had limited application because of its poor yield. The forth method is an atomeconomical reaction and has excellent yields, but it needs a stoichiometric amount of organic base.

Cesium hydroxide, which acts as a super inorganic base, can react with weak acids to give a strongly nucleophilic anion. The diaryldisulfides are not only nucleophiles but also electrophiles [18–20]. The P–H bond in dialkyl phosphites [(RO)₂P(O)H] is a polar bond, making it a weak acid, which should react with cesium hydroxide to form the highly nucleophilic (RO)₂P⁻(O)Cs⁺. Therefore, we hypothesized that cesium hydroxide could catalyze

* Corresponding author. *E-mail address:* xhx1581@hnu.edu.cn (X.-H. Xu). the reaction of diaryldisulfides with dialkyl phosphites. In this paper, we report the results.

2. Experimental

Cesium hydroxide (0.2 mmol) was added to a solution of dialkyl phosphites (1.0 mmol) and diaryldisulfides (0.5 mmol) in DMSO (5.0 mL) in a round bottomed flask. The reaction mixture was stirred at room temperature under an air atmosphere for 20 h. The reaction was monitored by TLC analysis. Then water (15 mL) was added and the mixture was extracted with ethyl acetate (15 mL \times 3). The combined organic phase was washed with water (20 mL \times 2) and dried over anhydrous Na₂SO₄, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 3:1). Compound **3b**: ³¹P NMR (162 MHz, CDCl₃): δ 22.79. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (dd, 2H, *J* = 8.8 Hz, *J* = 1.6 Hz), 7.35–7.33 (m, 3H), 4.24–4.14 (m, 4H), 1.32–1.28 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 134.3, 129.2, 129.0, 126.4, 63.9, 15.9. MS (*m/z*): 246 (M⁺).

3. Results and discussion

The experimental results showed that diaryldisulfides reacted with dialkyl phosphites $(RO)_2P(O)H$ efficiently in the presence of 20% cesium hydroxide at room temperature under air atmosphere in DMSO in 20 h, producing the corresponding *S*-aryl phosphorothioates in excellent yields (Scheme 1). The results were summarized in Table 1.

1001-8417/\$ – see front matter © 2013 Xin-Hua Xu. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved. http://dx.doi.org/10.1016/j.cclet.2013.06.020



Table 1	
The synthesis	of O,O-dialkyl-S-arylphosphorothioates.

Entry	R	Ar	Product	Мр	Yield (%)
1	Me	Ph	$(MeO)_2 P(O)SPh (3a) [9]$	Oil	91
2	Et	Ph	$(EtO)_2 P(O)SPh (3b) [9]$	Oil	92
3	<i>n</i> -Bu	Ph	$(n-BuO)_2 P(O) SPh (3c) [9]$	Oil	92
4	Me	p-ClC ₆ H ₄	$(MeO)_2P(O)SC_6H_4Cl-p$ (3d) [13]	Oil	85
5	Et	p-ClC ₆ H ₄	$(EtO)_2 P(O)SC_6 H_4 Cl-p$ (3e) [13]	Oil	86
6	<i>n</i> -Bu	p-ClC ₆ H ₄	$(n-BuO)_2 P(O)SC_6 H_4 Cl-p$ (3f) [13]	Oil	83
7	Me	p-CH ₃ C ₆ H ₄	$(MeO)_2P(O)SC_6H_4 CH_3-p (3g) [17]$	Oil	95
8	Et	p-CH ₃ C ₆ H ₄	$(EtO)_2 P(O)SC_6H_4 CH_3 - p (3h) [17]$	Oil	93
9	<i>n</i> -Bu	p-CH ₃ C ₆ H ₄	$(n-BuO)_2 P(O)SC_6 H_4 CH_3 - p$ (3i) [17]	Oil	94

		CsOH (10 mmol%), DMSO	$(\mathbf{D}\mathbf{O}) \mathbf{D}(\mathbf{O}) \mathbf{S} \mathbf{A} \mathbf{\pi}$
$(RO)_2 P(O)H$	+ 0.5ArSSAr		$(\mathrm{KO})_2\mathrm{P}(\mathrm{O})\mathrm{SAF}$
1	2	r.t., air, 20 h	3a~3i

Scheme 1. The synthesis of O,O-dialkyl-S-arylphosphorothioates.

Inspection of Table 1 revealed that the reactions worked extremely well for a variety of diaryldisulfides and dialkyl phosphites. The results also showed that the functional groups present in the phenyl group of diaryldisulfides did not affect the reaction yields significantly. Substrates containing both electron donating and electron withdrawing groups led to the corresponding thiophosphoric acid esters in high yields. Thus, this method could be widely used in the synthesis of a variety of thiophosphoric acid esters.

We studied the solvent effects on the reaction by using compound **3a** as a model substrate. We found that the reactions can hardly occur in dichloromethane or toluene even with a prolonged reaction time. When THF or DMF was used as the solvent, the reactions afforded compound **3a** in 69% and 75% yield, respectively in 20 h (Table 1, entry 8 and 10). The highest yield was obtained in DMSO, which is considered the best solvent for the reaction (Table 2, entry 12). This surprising result together with the lack of reactivity in other solvents suggests that DMSO acts not only as the solvent, but also as an oxidant in the reaction [21,22].

To investigate the influence of the catalyst loading on the reaction, different amount of catalyst was used for the reaction (Table 3). We found that increasing the catalyst from 5% to 20% had noticeable impact on the yield. Interestingly, when 25% of catalyst was added, there was no further increase of the yield of compound **3a**. It appears that 20% amount of catalyst is sufficient to produce a high yield of compound **3b**.

Table 2										
Influence	of	solvents	on	the	reaction	for	dimethyl	phosphites	with	diphenyl
disulfidas										

Entry	Solvent	<i>T</i> (h)	Yield (%)	
1	CH_2Cl_2	10	Trace	
2	CH ₂ Cl ₂	20	9	
3	Toluene	10	Trace	
4	Toluene	20	16	
5	EtOH	10	18	
6	EtOH	20	46	
7	THF	10	35	
8	THF	20	69	
9	DMF	10	40	
10	DMF	20	75	
11	DMSO	10	52	
12	DMSO	20	91	

In order to assess the catalytic ability of cesium hydroxide in catalyzing S–P bond formation, we evaluated several common bases including lithium hydroxide, sodium hydroxide, potassium hydroxide and rubidium (Table 4). The results showed that cesium hydroxide was most efficient in catalyzing the S–P bond formation under the same conditions.

A possible reaction mechanism for the reaction of diaryldisulfides and dialkyl phosphites to *O*,*O*-dialkyl-*S*-arylphosphorothioates in the present of cesium hydroxide is depicted in Scheme 2.

Dialkyl phosphites reacted with cesium hydroxide to give $(RO)_2P^-(O)Cs^+$, which underwent nucleophilic attack on ArSSAr to give *S*-aryl phosphoroselenoates and ArS⁻Cs⁺. The latter was oxidized in the presence of water to form diaryldisulfides and the cesium hydroxide catalyst [23].

Table 3

Influence of catalyst amount on the reaction for dimethyl phosphites with diphenyl disulfides.

CsOH (mol%)	Yields (%)
5	60
10	71
15	85
20	93
25	93

Table 4

Influence of various bases on the reaction for dimethyl phosphites with diphenyl disulfides.

	Entry					
	1	2	3	4	5	
Base Yield (%)	LiOH 0	NaOH 21	КОН 29	RbOH 70	CsOH 91	



Scheme 2. Proposed mechanism for the synthesis of *O*,*O*-dialkyl-*S*-arylphosphorothioates catalyzed by CsOH.

4. Conclusion

In summary, we have developed a highly efficient and simple method for the preparation of *S*-aryl phosphoroselenoates. It has many merits such as mild reaction conditions, convenient operation, non-anhydrous solvents, using catalytic amount of cesium hydroxide and high yields.

Acknowledgment

The project was supported by the National Nature Science Foundation of China (Nos. 21273068, 21172061, J1210040).

References

- [1] Z.J. He, W.B. Chen, F.P. Ma, et al., The chlorination reaction of O-alkyl S-alkyl (aryl) thiophosphoric (nic) aicd derivatives with phosphorus, Phosphorus Sulfur Silicon Relat. Elem. 142 (1998) 49–55.
- [2] K.K. Adhikary, H.R. Barai, H.W. Lee, Kinetics and mechanism of the benzylaminolysis of O,O-dimethyl S-aryl phosphorothioates in dimethyl sulfoxide, Bull. Korean Chem. Soc. 32 (2011) 3587–3591.
- [3] S.B. Hong, F.M. Raushel, Metal-substrate interactions facilitate the catalytic activity of the bacterial phosphotriesterase, Biochemistry 35 (1996) 10904–10912.
- [4] A. Blaskó, C.A. Bunton, A. Kumar, Oxidative hydrolysis of phosphorus (V) esters of thiols by peroxymonosulfate ion. Reactions of peroxymonosulfate ion with phosphorus (V) esters of thiols, J. Phys. Org. Chem. 10 (1997) 427–434.
- [5] C.E. Müller, H.J. Roth, A new synthesis of thiophosphoric acid esters with a C-S-P bond, Tetrahedron Lett. 31 (1990) 501-502.
- [6] A. Gautier, G. Garipova, O. Dubert, H. Oulyadi, S.R. Piettre, Efficient and practical aerobic radical addition of thiophosphites to alkenes, Tetrahedron Lett. 42 (2001) 5673–5676.
- [7] T.F. Herpin, W.B. Motherwell, B.P. Roberts, S. Roland, J.M. Weibel, Free radical chain reactions for the preparation of novel anomeric carbohydrate difluoromethylenephosphonates and -phosphonothioates, Tetrahedron 53 (1997) 15085–15100.
- [8] C. Lopin, G. Gouhier, A. Gautier, S.R. Piettre, Phosphonyl, phosphonothioyl, phosphonodithioyl, and phosphonotrithioyl radicals: generation and study of their addition onto alkenes, J. Org. Chem. 68 (2003) 9916–9923.

- [9] Q. Xu, C.G. Liang, X. Huang, Free radical reaction of dialkyl phosphites and organic dichalcogenides: a new facile and convenient preparation of arylselenophosphates, Synth. Commun. 33 (2003) 2777–2785.
- [10] G. Maryam, S. Soheil, A novel and efficient synthesis of alkyl thiocyanates from alkyl halides in water using phase transfer catalysts, Chin. Chem. Lett. 22 (2011) 659–662.
- [11] W. Hong, J. Dowden, Facile synthesis of N-6 adenosine modified analogue toward S-adenosyl methionine derived probe for protein arginine methyltransferases, Chin. Chem. Lett. 22 (2011) 1439–1442.
- [12] N.M. Yousif, K.Z. Gadalla, S.M. Yassin, Synthesis of O,O-dialkyl S-phenyl phosphorothiolates- and dithiolates, Phosphorus Sulfur Silicon Relat. Elem. 60 (1991) 261–263.
- [13] D.D. Liu, D.W. Chen, Z.C. Chen, Hypervalent iodine in synthesis. XII. A new and convenient method for preparation of O,O-dialkyl S-aryl phosphoro thiolates, Synth. Commun. 22 (1992) 2903–2908.
- [14] Y. Watanabe, S. Inoue, T. Yamamoto, S. Ozaki, Phosphorothioate synthesis based on the redox reaction of phosphite with tellurium(IV) chloride, Synthesis (1995) 1243–1244.
- [15] S. Masson, J.F. Saint-Clair, M. Saquet, Two methods for the synthesis of (2mercaptophenyl) phosphonic acid, Synthesis (1993) 485–486.
- [16] R.G. Harvey, H.I. Jacobson, E.V. Jensen, Phosphonic acids. VI. The reaction of trivalent phosphorus esters with organic disulfides, J. Am. Chem. Soc. 85 (1963) 1618–1623.
- [17] Y.X. Gao, G. Tang, Y.F. Zhao, A novel and general method for the formation of Saryl, Se-aryl, and Te-aryl phosphorochalcogenoates, Synthesis (2009) 1081.
- [18] Y.H. Li, J.P. Li, X. Xia, et al., A new synthesis of alkynyl tellurides promoted by CsOH and 4 Å MS, Chin. Chem. Lett. 19 (2008) 1401–1402.
- [19] K.P. Nandre, V.S. Patil, S.V. Bhosale, CsF mediated rapid condensation of 1,3cyclohexadione with aromatic aldehydes: comparative study of conventional heating vs. ambient temperature, Chin. Chem. Lett. 22 (2011) 777–780.
- [20] A.H. Yu, R.H. Qiu, N.Y. Tan, et al., Cesium hydroxide-catalyzed hydrothiolation of alkynyl selenides to highly stereo- and regioselectively synthesize (Z)-1-organoseleno-2-arylthio-1-alkenes, Chin. Chem. Lett. 22 (2011) 687–690.
- [21] B. Karimi, H. Hazarkhani, D. Zareyee, Trimethylchlorosilane (TMSCI) and cyanuric chloride (CC) catalyzed efficient oxidative coupling of thiols with dimethylsulfoxide, Synthesis (2002) 2513–2516.
- [22] C.N. Yiannios, J.V. Karabinos, Oxidation of thiols by dimethyl sulfoxide, J. Org. Chem. 28 (1963) 3246–3248.
- [23] T.J. Wallace, A. Schriesheim, W. Bartok, The base-catalyzed oxidation of mercaptans. III. Role of the solvent and effect of mercaptan structure on the rate determining step, J. Org. Chem. 28 (1963) 1311–1314.