Stereospecific Synthesis of Alkyl Aryl Sulfides from Alcohols and 2-Sulfanylbenzothiazole Using Aryl Diphenylphosphinite and Azide Compounds by a New Type of Oxidation–Reduction Condensation

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The preparation of alkyl aryl sulfides from alcohols and 2-sulfanylbenzothiazole using phenyl diphenylphosphinite and azide compounds by a new type of oxidation–reduction condensation is described. The chiral secondary and tertiary alcohols are converted into the corresponding chiral sulfides with almost complete inversion of configurations under mild and neutral conditions.

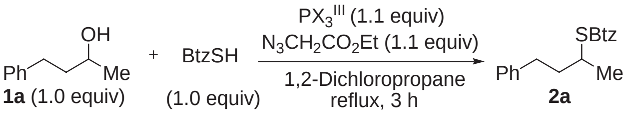
A reaction of organic azides[1] with trivalent phosphorous compounds that affords the corresponding iminophosphoranes (aza-ylides) is known as "the Staudinger reaction."[2] This reaction has become one of the most widely used synthetic tools in organic chemistry[3] and biology[4] as well because of versatile properties of iminophosphoranes: namely, 1) primary amines are given by hydrolysis with water, 2) the corresponding imines are afforded by the reaction with carbonyl compounds (the aza-Wittig reaction). However, there are only few reports on the intermolecular dehydration condensation reactions between alcohols and acidic components via this key intermediate, iminophosphorane, except for condensation reaction of carboxylic acids or imides with primary alcohols by the combined use of triphenylphosphine and benzyl azide.[5] Although it provides O- and N-alkylated products under neutral conditions, secondary or tertiary alcohols were not used as substrates in this reaction system and also a condensation reaction of thiols with alcohols was not examined.

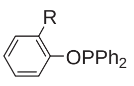
Recently, a new type of oxidation–reduction condensation[6] was reported from our laboratory by using the combination of aryl diphenylphosphinite ($ArOPPh_2$) and benzoquinone derivatives, which was employed in the syntheses of sulfides from alcohols and a sulfur nucleophile such as 2-sulfanylbenzothiazole.[7] It is noteworthy that this dehydration condensation proceeded under mild and neutral conditions to produce chiral sulfides from chiral alcohols with almost complete inversion of their stereochemistries. This is the first example of aryl diphenylphosphinite to be employed in oxidation–reduction condensation as a reductant. In order to extend the utility of this aryl diphenylphosphinite, our attention was next focused on oxidation–reduction condensation using organic azide[8] as oxidant in stead of benzoquinone derivatives.

In this communication, we would like to describe a new method for stereospecific synthesis of *sec*- and *tert*-alkyl aryl sulfide from alcohols and 2-sulfanylbenzothiazole by a new type of oxidation–reduction condensation using a phosphorus compound and an azide.

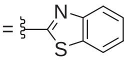
In order to find the most suitable reductant, effects of phosphorus(III) compounds were first examined by taking the condensation reaction of 4-phenylbutan-2-ol and 2-sulfanylbenzothiazole in the presence of ethyl azidoacetate as a model (Table 1). Then, it was shown that the desired sulfide **2a** was not obtained when PPh_3 or PBu_3 was used (Entries 1 and 2) while it was afforded by the use of $P(OPh)_3$, $PhP(OPh)_2$, and Ph_2PCl (Entries 3–5). In the case of using aryl diphenylphosphinites, the yield of **2a** markedly increased (Entries 6–8) and phenyl diphenylphosphinite ($PhOPPh_2$) was among the best (Entry 6).

Table 1. Screening of phosphorus(III) compounds



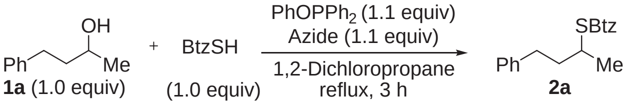
Entry	PX_3	Yield/%[a]	Entry	PX_3		Yield/%[a]
1	PPh_3	trace	5	Ph_2PCl		11
2	PBu_3	N.D.	6		R = H	69
3	$P(OPh)_3$	34	7		R = Cl	65
4	$PhP(OPh)_2$	58	8		R = OMe	61

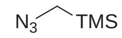
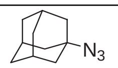
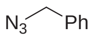
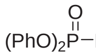
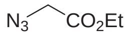
[a]Isolated yield.

Btz = 

Next, various azide compounds were examined in order to find a suitable oxidant (Table 2), and a condensation reaction using trimethylsilylmethyl azide afforded the desired product **2a** in moderate yield (Entry 1). The alkly azide such as benzyl azide or ethyl azidoacetate gave **2a** in good yields while 1-azidoadamantane, diphenylphosphoryl azide, or trimethylsilyl azide did not work well (Entries 2–6). In the cases of benzyl azide and ethyl azidoacetate, the yields increased up to 81 and 84% by changing the solvent from 1,2-dichloropropane to toluene (Entries 2 and 3).

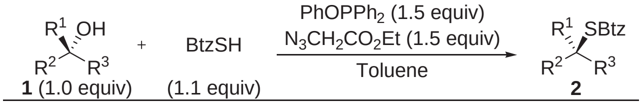
Table 2. Screening of azide compounds

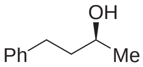
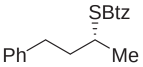
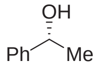
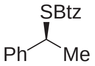
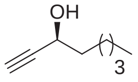
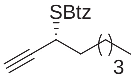
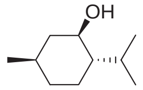
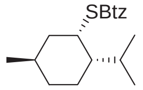
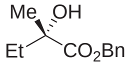
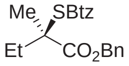
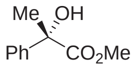
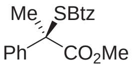
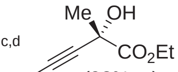
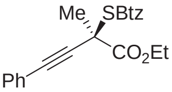


Entry	Azide	Yield/%[a]	Entry	Azide	Yield/%[a]
1		53	4		34
2		67 (81)[b]	5	 $(PhO)_2P(=O)-N_3$	N.D.
3		69 (84)[b]	6	$TMSN_3$	7

[a]Isolated yield. [b]Toluene was used instead of 1,2-dichloropropane.

Table 3. Thioetherification of various chiral alcohols



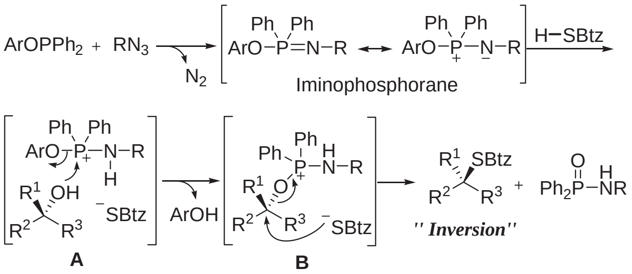
Entry	ROH	1	Temp., Time	Product **2**	Yield/%[a] (%ee)[b]
1		**1b**	40 °C, 24 h		99 (>99)
2[c]		**1c**	rt, 12 h		83 (97)
3[c]		**1d**	rt, 24 h		89 (98)
4		**1e**	80 °C, 6 h		85
5[d]		**1f**	40 °C, 48 h		76 (>99)
6[d,e]		**1g**	40 °C, 48 h		90 (99)
7[c,d]	 (92%ee)	**1h**	27 °C, 48 h		87 (92)

[a]Isolated yield. [b]Determined by HPLC analysis. [c]The solution of $PhOPPh_2$ and ethyl azidoacetate was stirred at 80 °C for 20 min, followed by addition of alcohol and BtzSH at rt. [d]The reaction was carried out by using BtzSH (4.0 equiv), $PhOPPh_2$ (4.0 equiv), and ethyl azidoacetate (4.0 equiv). [e]Ref 9.

After a suitable reductant and an oxidant were selected, condensations of various chiral alcohols were tried in order to examine the scope of this reaction under the optimized conditions (Table 3). A reaction of chiral secondary alcohol **1b** proceeded smoothly to afford the corresponding sulfide in quantitative yield with complete inversion of stereochemistry (Entry 1). Chiral benzylic alcohol **1c** was also successfully used in this reaction (Entry 2) and the reaction of 2-propynylic alcohol **1d** gave the desired product in high yield with high enantiomeric excess (Entry 3). The thioetherification of sterically hindered (−)-menthol (**1e**) gave the inverted product in high yield without any other products (Entry 4). Further, more-hindered tertiary alcohols were employed as substrates in order to investigate potential application of this reaction to the asymmetric construction of quaternary carbon (Entries 5–7). Then, the reaction of chiral tertiary alcohol **1f** proceeded smoothly to afford the corresponding sulfide in good yield with complete inversion of stereochemistry (Entry 5). Similarly, chiral benzylic alcohol **1g** bearing the α-ester group gave the desired product in high yield with excellent enantiomeric excess (Entry 6). Also, thioetherification of chiral 2-propynylic alcohol **1h** gave the inverted product in high yield (Entry 7).

Since the chiral *tert*-alkyl Btz sulfide was converted to the corresponding chiral tertiary thiol in high yield by treating with $LiAlH_4$,[10] a concise method for the preparation of chiral tertiary thiol from the corresponding alcohols was established.

A plausible reaction mechanism is shown in Scheme 1: the reaction of aryl diphenylphosphinite ($ArOPPh_2$) and azide compound initially gave an iminophosphorane and the following deprotonation of BtzSH by iminophosphorane resulted in the formation of intermediate **A**. Subsequent nucleophilic attack of alcohol to the positively charged phosphorus atom led to an intermediate **B**. Finally, a nucleophilic attack of the thiolate anion ($BtzS^-$) to its phosphonium part via S_N2 manner gave the inverted sulfide.



Scheme 1.

Thus, a new type of oxidation–reduction condensation by the combined use of aryl diphenylphosphinite and azide compounds was established. Chiral *sec*- or *tert*-alkyl sulfides were formed from the corresponding chiral alcohols with almost complete inversion of configuration under mild and neutral conditions. This is the first example of the stereospecific synthesis of an inverted chiral tertiary thiol from a chiral tertiary alcohol by an S_N2 displacement except in the case of the previously reported oxidation–reduction condensation using alkyl diphenylphosphinite.[10]

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References and Notes

1 For a review of organic azides, see: S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
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5 S. Torii, H. Okumoto, M. Fujikawa, M. A. Rashid, *Chem. Express.* **1992**, *7*, 933.
6 For reviews on oxidation–reduction condensation, see: a) T. Mukaiyama, H. Yamabe, *Chem. Lett.* **2007**, *36*, 2. b) T. Mukaiyama, K. Ikegai, H. Aoki, W. Pluempanupat, K. Masutani, *Proc. Jpn. Acad., Ser. B* **2005**, *81*, 103. c) T. Mukaiyama, *Angew. Chem., Int. Ed.* **2004**, *43*, 5590.
7 K. Kuroda, Y. Hayashi, T. Mukaiyama, *Chem. Lett.* **2008**, *37*, 592.
8 For oxidation–reduction condensation using azides, see: a) H. Aoki, K. Kuroda, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1266. b) T. Mukaiyama, K. Kuroda, H. Aoki, *Chem. Lett.* **2005**, *34*, 1644.
9 Typical experimental procedure is as follows (Table 3, Entry 6): to a solution of $PhOPPh_2$ (222.6 mg, 0.80 mmol) and chiral alcohol **1g** (35.8 mg, 0.199 mmol) in dry toluene (0.60 mL) were added BtzSH (133.8 mg, 0.80 mmol) followed by ethyl azidoacetate (103.3 mg, 0.80 mmol) at rt under an argon atmosphere. The reaction mixture was stirred at 40 °C for 48 h and the crude product was purified by preparative TLC to the corresponding sulfide (58.9 mg, 90%).
10 For condensation of 2-sulfanylbenzothiazole with alkyl diphenylphosphinite ($ROPPh_2$) prepared from alcohols, see: K. Ikegai, W. Pluempanupat, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 780.

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