Synthesis of benzyl sulfides via substitution reaction at the sulfur of phosphinic acid thioesters†

Yoshitake Nishiyama, † Takamitsu Hosoya ‡ and Suguru Yoshida ‡ *

An ambident electrophilicity of phosphinic acid thioesters is disclosed. Unexpected carbon–sulfur bond formation took place in the reaction between phosphinic acid thioesters and benzyl Grignard reagents. The developed method for benzyl sulfides has a wide substrate scope and was applicable for the synthesis of a drug analog.

Sulfides play significant roles in various fields such as medicinal chemistry, agrochemistry, and materials science, and thus many synthetic methods for sulfides have been developed.1,2 Especially, a group of benzyl sulfides have attracted synthetic chemists because of their utility. Benzyl sulfides are used not only as protected thiols3 or precursors of sulfonyl chlorides,4 but also as important structures of bioactive compounds such as sulconazole5 or dosulepin.6 However, the synthesis of benzyl sulfides depends almost only on the nucleophilic attack of thiols to alkyl halides, often suffering from the limited scope as well as the unpleasant odor of thiols, especially of benzyl mercaptans. Herein, we disclose a new synthetic method for benzyl sulfides via the reaction between benzyl Grignard reagents and phosphinic acid thioesters, which have a phosphorus–sulfur bond.

Previously, we found that Grignard reagents attacked the phosphorus atoms7,8 of phosphonic acid dithioesters to give phosphinic acid thioesters, which also reacted with Grignard reagents at higher temperature by further substitution reactions on the phosphorus atoms to provide a wide range of phosphine oxides.9 In the course of further investigation for the reactivity of phosphinic acid thioesters, we unexpectedly found that these compounds behaved as two-faced “ambident” electrophiles.10,11 Thus, while S-(4-tolyl) diphenylphosphiniothioate (1a) reacted with phenylmagnesium bromide at the phosphorus atom to smoothly give triphenylphosphine oxide (2a), treatment of 1a with a benzyl Grignard reagent furnished the target phosphine oxide 2b only in low yield, along with benzyl sulfide 3a as the major product (Fig. 1A). This result suggested a possibility that benzyl sulfide 3a was obtained directly by the reaction of the benzyl Grignard reagent at the sulfur atom of phosphinic acid thioester 1a,12 contrary to our previous report that C–P bond formation took place using allyl and aryl Grignard reagents.

To date, several reports switching the bond-forming site have been reported in the substitution reaction using electrophiles bearing a heteroatom–heteroatom bond depending on the nucleophiles examined (Fig. 1B). For instance, reactions of sulfonyl chlorides with aryl Grignard reagents result in C–Cl bond formation to afford aryl chlorides10e or C–S bond formation to afford sulfones10d according to the type of Grignard reagents (Fig. 1C). Two types of substitution reactions of sulfonylamides have been also developed; P–N bond formation occurred by the reaction with phosphide anion,10c while various nucleophiles such as water attacked selectively on the sulfur atom (Fig. 1D). However, limited numbers of the ambident electrophiles were reported so far and controlling the ambident electrophilicity is not easy.11 These limited but significant site-selective reactions motivated us to examine the C–S bond-forming reaction of phosphinic acid thioesters with benzyl Grignard reagents in terms of the site-selectivity for efficient synthesis of benzyl sulfides (Fig. 1E).

To improve the site-selectivity and to clarify the generality of the reaction, a variety of phosphinic acid thiocesters 1, which have different substituents on the phosphorus atoms, were subjected to the reaction with a benzyl Grignard reagent (Table 1). Changing the substituents on the phosphorus atom from a phenyl group to alkyl groups such as butyl or cyclohexyl group decreased the selectivities, affording the desired sulfide 3a in low yields (entries 2 and 3). On the other hand, S-benzyla-

Department of Chemistry, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: s-yoshida.cb@tmd.ac.jp

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electrophilicity of phosphinic acid thioesters by changing the substrates, enabling efficient S-benzylation in terms of the yield and selectivity. With a bulkier mesityl group, the selectivity rather degraded (entry 5). In addition, when using thiophosphoric acid ester 1f, benzyl sulfide 3a was obtained with perfect selectivity (entry 6).

Benzylation of phosphinic acid thioester 1e using other benzyl Grignard reagents allowed for efficient preparation of various benzyl sulfides (Fig. 2). Indeed, 4-chlorobenzylation and 1-naphthylmethylation of 1e proceeded smoothly to give 3b and 3c, respectively. A benzyl Grignard reagent bearing a methyl group at the benzylic position was also applicable to the C–S bond formation, affording benzyl sulfide 3d in high yield. Furthermore, bulky (2-phenylpropan-2-yl)magnesium chloride successfully reacted with 1e to furnish sulfide 3e, which is not easy to synthesize by the conventional method using thiols and alkyl halides. In addition, a 1-phenylvinyl Grignard reagent did not participate in the C–S bond forming reaction.

The use of readily available thiophosphinic acid 4 enabled easy access to various alkyl di(2-tolyl)phosphinothioates 1, which were also benzylated by treating with a benzyl Grignard reagent (Table 2). Alkylation of 4 with a variety of alkyl halides afforded phosphinothioates 1g–k without damaging functional

**Table 1**

| Entry | R     | Yield (%) | Product | Yield (%) |
|-------|-------|-----------|---------|-----------|
| 1     | Ph    | 62        | 2b      | 7         |
| 2     | n-Bu  | 12        | 3a      | 30        |
| 3     | c-Hex | 33        | 2d      | 7         |
| 4     | o-Tol | 86 (88)b  | 5 (6)b  |
| 5     | Me    | 69        | ND      |
| 6     | OEt   | 79        | ND      |

NMR yields unless otherwise noted. a Isolated yields in parentheses. b Not detected.

**Table 2**

| Entry | R-X   | Yield (%) | Product | Yield (%) |
|-------|-------|-----------|---------|-----------|
| 1     | MeI   | 97        | 3g      | 82        |
| 2     | TsO   | 11        | 3h      | 78        |
| 3     | BrH   | 96        | 3i      | 80        |
| 4     | i   | Quant   | 3j      | 40        |
| 5     | Me    | 83        | ND      |

Isolated yields. a Not detected.
groups such as amino, bromo, and tosylxy groups (entries 1–4). When the synthesized phosphinic acid thioesters 1g–j were treated with benzylmagnesium chloride, S-benzylation proceeded smoothly to give benzyl sulfides 3g–j. Notably, a bromo group and a tosylxy group were tolerated under the benzylation conditions. On the other hand, S-benzylation of bulky α-methylbenzyl ester prepared from 1k did not occur (entry 5).

Not only alkyl phosphinothioates, an array of aryl phosphinothioates were also prepared via the Chan–Lam–Evans-type deborylthiolation (Table 3). Treatment of the corresponding boronic acid with thiophosphinic acid 4 in the presence of triethylamine and a catalytic amount of copper(II) triflate and bipyridyl afforded a variety of phosphinic acid thioesters, such as substituted phenyl thioesters 1l–p (entries 1–5), 2-naphthyl thioester 1q (entry 6), 3-thienyl thioester 1r (entry 7), and styryl thioester 1s (entry 8). Benzylation of these phosphinic acid thioesters proceeded smoothly to give corresponding benzyl sulfides 3l–s (entries 1–8). It is noteworthy that benzyl 3-thienyl sulfide (3r) and benzyl styryl sulfide (3s) were generally difficult to synthesize because of the lack of the availability of the corresponding thiols. Thus, these results clearly demonstrated the utility of this method via the Chan–Lam–Evans-type deborylthiolation.

We next turned our attention to the mechanism of this unusual S-benzylation (Fig. 3). Plausible reaction mechanism is shown in Fig. 3A including direct substitution reaction of phosphinic acid thioesters 1 with a benzyl Grignard reagent on the sulfur atom (path a). Other reaction mechanisms involving the ligand coupling of pentavalent organophosphorus intermediates I (path b) or the single-electron transfer (SET) (path c) could not be excluded at this stage. Considering that C–P bond formation took place using various alkyl or aryl Grignard reagents probably through pentavalent phosphorus intermediates, the S-benzylation via P-benzylation and subsequent ligand coupling of the resulting pentavalent phosphorus intermediate I to give the benzyl sulfide is also possible (path b). Another possibility is shown as path c through the SET mechanism, followed by S-benzylation between thiyl radical III and benzyl radical to give the benzyl sulfide.

To gain insight into the mechanism, we at first examined the products of the reaction between di(2-tolyl)phosphinic acid thioester 1e and a benzyl Grignard reagent on the sulfur atom (path a). Other reaction mechanisms involving the ligand coupling of pentavalent organophosphorus intermediates I (path b) or the single-electron transfer (SET) (path c) could not be excluded at this stage. Considering that C–P bond formation took place using various alkyl or aryl Grignard reagents probably through pentavalent phosphorus intermediates, the S-benzylation via P-benzylation and subsequent ligand coupling of the resulting pentavalent phosphorus intermediate I to give the benzyl sulfide is also possible (path b). Another possibility is shown as path c through the SET mechanism, followed by S-benzylation between thiyl radical III and benzyl radical to give the benzyl sulfide.

Table 3 Chan–Lam–Evans-type synthesis and benzylation of phosphinic acid thioesters

| Entry | R     | 1 Yield (%) | 3 Yield (%) |
|-------|-------|-------------|-------------|
| 1     | MeO   | 1l 86       | 3l 97       |
| 2     | MeN   | 1m 83       | 3m 88       |
| 3     | F   | 1n 59       | 3n 61       |
| 4     | Me   | 1o 82       | 3o 77       |
| 5     | Br    | 1p 74       | 3p 57       |
| 6     | Iq    | 1q 83       | 3q 67       |
| 7     | S    | 1r 41       | 3r 87       |
| 8     | Ph    | 1s 53       | 3s 61       |

* Isolated yields. bpy = 2,2'-bipyridyl.
diarylphosphine oxide, suggesting that path b involving reductive elimination of the phosphorus is not plausible. In order to verify the possibility of the SET mechanism, S-(4-penten-1-yl)di(2-tolyl)phosphinic acid thioester (1u) was subjected to the S- benzylation reaction (Fig. 3D). While benzyl 4-penten-1-yl sulfide (3t) was obtained in high yield, any radical cyclization products were not detected in the reaction. From these results, benzyl sulfides would be generated via direct attack of benzyl Grignard reagents on the sulfur atoms of phosphinic acid thioesters.

By using the developed benzyl sulfide synthesis, we synthesized an analog of tiopinac, which is a highly potent anti-inflammatory, analgesic, and anti-pyretic agent. Treatment of phosphinic acid thioesters with 2-bromo-5-methoxybenzylmagnesium bromide results in C–P bond formations, while the reactions using various alkyl and aryl Grignard reagents on the sulfur atoms of phosphinic acid thioesters subjected to the reductive elimination of the phosphorus is not plausible.

Synthesis of tiopinac analog. DPPP = 1,3-bis(diphenylphosphino)propane. PPA = polyphosphoric acid.

### Conflicts of interest
There are no conflicts to declare.

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