Pergamon

Tetrahedron 58 (2002) 215–219

TETRAHEDRON

The reaction of oximes with tributylphosphine–phenyldisulfide: mechanistic insight and new synthetic possibilities

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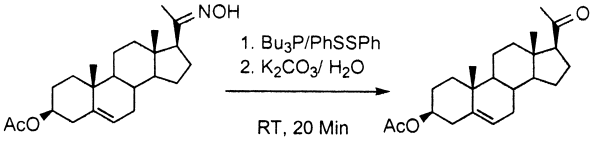
Received 11 September 2001; accepted 15 November 2001

Abstract—Reduction of oximes to imines with tributylphosphine–phenyldisulfide reagent proceeds via formation of phenylthioimino intermediates which are subsequently reduced to imines with tributylphosphine in the presence of a proton source. The latter reaction provides the first practical method for conversion of phenylthioimines into ketones.

1. Introduction

Conversion of ketones into oximes represents a useful protection strategy for the functionalization of this type of carbonyl compounds.[1] However, this methodology remains underutilized, because the reverse reaction—deoximation—is not always straightforward and often requires harsh conditions hardly compatible with highly functionalized organic molecules.[2]

In our search for a mild method for deoximation of erythromycin derived compounds, we were particularly attracted by the procedure described by Barton et al.[3] It was reported that treatment of oxime **1** with tributylphosphine–phenyldisulfide reagent (further referred as TBP–PDS), followed by aqueous work up gave corresponding ketone **2** in 90% yield (Eq. (1)).



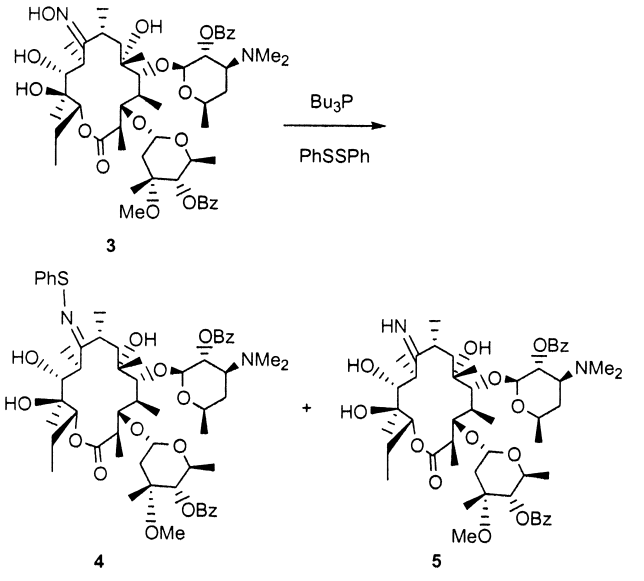
1 **2**, 90% (1)

Our application of this method to derivatives of erythromycin oxime revealed that the above reaction proceeded via the formation and subsequent reduction of phenylthioimino intermediates and resulted in the discovery of the first mild and efficient method for conversion of phenylthioimines into corresponding ketones. Some important details of this work are described as follows.

2. Results and discussion

2.1. Reaction of erythromycin oxime with tributylphosphine–phenyldisulfide

Treatment of erythromycin oxime dibenzoate **3** (benzoate functionality was introduced for convenient reaction monitoring by HPLC method) with TBP–PDS under standard conditions[3] produced no ketone. Instead, a clean reaction gave 2:1 mixture of two macrolide compounds which were isolated and identified as *N*-(phenylthio)imine **4** and imine **5** (Eq. (2)).



(2)

More interestingly, when *the same reaction mixture* was worked up in a different way—basic aqueous quench solution was replaced with moderately acidic one—imine

Keywords: oximes; thioimines; imines; reduction.

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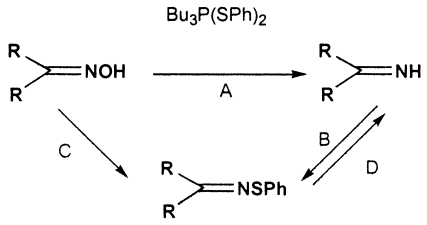
PII: S0040-4020(01)01154-1



Scheme 1.

5 was isolated as a *single* macrolide product in about 80% yield. Apparently, thioimine **4** was somehow reduced to imine **5** during *the work up*, indicating that thioimine **4** could serve as a precursor to imine **5** in this reaction. This observation prompted us to investigate the mechanism of this deoximation in more detail.

The authors of Ref. 3 demonstrated earlier that TBP–PDS actually reduced oximes to imines which were further hydrolyzed to corresponding ketones during the aqueous work up. Knowing that erythromycin imines were resistant to hydrolysis[4] the absence of the ketone product in the reaction mixture was not surprising. The formation of phenylthioimines was also previously observed in some of these reactions, especially if an excess of phenyldisulfide was employed.[3,5] The authors of Ref. 3 considered several mechanistic pathways for the reduction which are outlined in Scheme 1. At that time direct reduction of oxime (Path A) seemed more appealing. The formation of thioimines was attributed to sulfenylation of imines with an excess of the reagent (Path B).[3]However, it is important to note that all previously described reductions of oximes with TBP–PDS involved only unstable imines, which in fact, *were never isolated or directly observed in the reaction mixtures*.[3,5] Under these circumstances, it was very difficult to predict the correct sequence of the events in this reaction. We felt that stable imine **5** (whose formation or consumption could be easily monitored) would be very instrumental for better understanding of the mechanism of this reduction.

Indeed, when tributylphosphine (3 equiv.) was added in 0.5 equiv. portions to a solution of oxime **3** and phenyldisulfide (2 equiv.) in THF, monitoring the reaction by HPLC demonstrated that phenylthioimine **4** was produced as a major product. The concentration of imine **5** in the reaction mixture remained low (8–12% relative to **4**) from the beginning of phosphine addition and until complete conversion of starting oxime **3**. When the unquenched reaction was left overnight slow conversion of thioimine **4** into imine **5** was observed and the concentration of the latter increased to ~30%. After addition of water about 80% of thioimine **4** was converted into imine within 4 h. No thioimine was left in this mixture after additional 15 h.

A separate experiment with isolated imine **5** demonstrated that it was inert to TBP–PDS and no thioimine formation was observed. This control experiment indicated that the thioimine formation from the imine via Path B (Scheme 1) was not plausible.

The above results let us to conclude that the conversion of oxime **3** into imine **5** with TBP–PDS proceeded via formation and subsequent reduction of phenylthioimine **4** (Eq. (3), or Paths C and D in Scheme 1). The mechanism of the first step—the formation of thioimine **4** from oxime **3**—could be analogous to a Mitsunobu type sulfenylation of alcohols with TBP–PDS.[6]

$$\mathbf{3} \xrightarrow[-\ Bu_3PO\ -\ PhSH]{Bu_3P(SPh)_2} \mathbf{4} \xrightarrow[[H^+]]{Bu_3P} \mathbf{5} \qquad (3)$$

As the thioimine reduction step seemed to be substantially slower than sulfenylation, we thought that the former reaction could be suppressed by controlling the concentration of tributylphosphine in the mixture. Indeed, slow addition of tributylphosphine (1.1 equiv.) to oxime **3** and phenyldisulfide (2 equiv.) gave thioimine **4** which was isolated in 79% yield after work up. Thus, using appropriate reaction conditions it was possible to prepare either previously unknown thioiminoerythromycin **4**, or imine **5** (See Section 4).[7]

2.2. Reductive cleavage of phenylthioimines

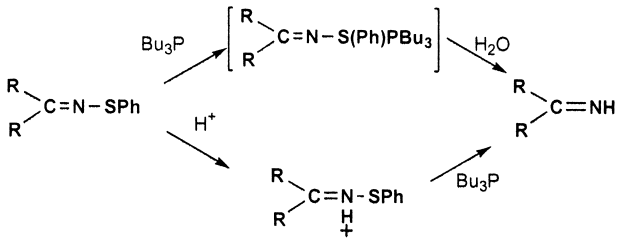
Over the years phenylthioimines were regarded as synthetic equivalents of unstable unsubstituted imines and numerous synthetic applications of these compounds were developed.[8] However, one of the most important transformation of thioimines—conversion to ketones—remained hardly achievable. Thus, attempted hydrolyses of thioimines typically gave complex mixtures of products originating from competitive attack of nucleophiles either on sulfur or on carbon of C=N–S fragment.[8,9] In the related chemistry of tritylthioimines only oxidative hydrolysis in the presence of mercury(II) salts was found successful.[10] Alternatively reduction of phenylthioimines to imines with tributyltin hydride was reported.[5]

We felt that the earlier described reduction of thioimines to imines with tributylphosphine could be developed into the first practical method for conversion of thiomines into carbonyl compounds. In this part of the paper we provide the results of a more detailed investigation of this reaction.

Tributylphosphine was found critical for the reduction. In its absence phenylthioimine **4** remained unchanged in THF solution after addition of water, 50% aqueous acetic acid, or glacial acetic acid for at least 2 h. Addition of tributylphosphine to these mixtures initiated the reduction. At least 1 equiv. of the reagent was required to complete the reaction. The reduction was sharply accelerated under acidic conditions. For example, with 1.25 equiv. of tributylphosphine at rt the reaction was complete within 48 h in water, 15 h in 50% acetic acid, and 1 h in glacial acetic acid. All reactions were clean and imine **5** was isolated in 80–85% yield from the preparative scale runs (see Section 4). Thus, we were able to explain how thioimine **4** was reduced to imine **5** during the aqueous quench of the reaction mixture (Eq. (4)).

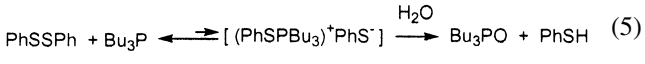
$$\mathbf{4} + Bu_3P + H_2O \longrightarrow \mathbf{5} + Bu_3PO + PhSH \qquad (4)$$

However, the source of proton required for the formation of imine **5** in this reaction *before* aqueous quench remained to be identified. The absence of water in this mixture was

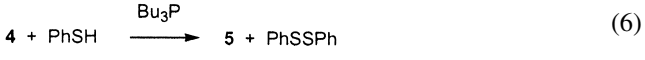


Scheme 2.

assured by its fast consumption with TBP–PDS reagent as outlined in Eq. (5).[11]



We assumed that thiophenol (which was formed as a side product of the sulfenylation step Eq. (3)) provided a proton required for the reduction. Indeed, the addition of tributylphosphine (1.4 equiv.) to a solution of thioimine **4** and thiophenol (2 equiv.) in dry THF resulted in slow but complete formation of imine **5** (Eq. (6)). Control experiment demonstrated that in the absence of tributylphosphine thiophenol was not capable reducing thioimine **4**.



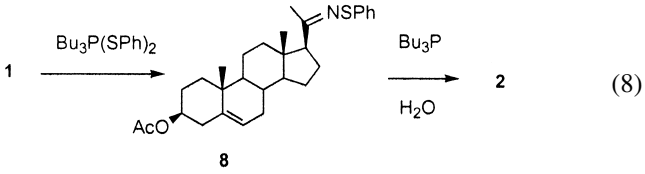
Based on the earlier described observations we propose that the reduction of thioimines to imines proceeded via phosphine attack on the sulfur atom of C=N–S fragment as outlined in Scheme 2. Under acidic conditions the sulfur atom is further activated toward nucleophilic attack due to protonation at the neighboring nitrogen atom (Scheme 2).[8]

We have also found that under even more acidic conditions than the previously described, the reaction could take a different course. Thus, dropwise addition of conc. hydrochloric acid to THF solution of thioimine **4**, *even in the absence of tributylphosphine*, resulted in precipitation of imine **5** as corresponding hydrochloride salt which was isolated in 90% yield. Benzenesulfenyl chloride was identified as a second product in this reaction (Eq. (7)). Apparently, under highly acidic conditions (pH <3) hydrochloric acid protonated the nitrogen and the resulting chloride anion attacked the sulfur of the thioimino group.

Clean formation of imine **5** in this type of acidic degradation of thioimines is quite unusual and could be attributed to the fact that the second potential reactive site—the carbon atom in the C=N fragment of Compound **4**—is sterically hindered. The same type of steric hindrance is responsible for the unusual resistance of erythromycin imines like **5** toward hydrolysis.

Clearly, erythromycin derivatives often display unusual chemical behavior. Thus, it was interesting to see if the reduction of phenylthioimines with tributylphosphine could be extended beyond this type of compounds. If successful, non-hindered imines produced in the reaction would be instantly hydrolyzed to the corresponding ketones providing a desired method for the preparation of ketones from thioimines.

To check this idea, we prepared a number of structurally different phenylthioimines (**8**–**11**). Moderately hindered oxime **1**,[3] non-hindered cyclopentanone oxime (**12**), and strained camphor oxime (**13**) were successfully sulfenylated using TBP–PDS reagent under the described aforementioned optimized conditions (see Section 4). However, less nucleophilic conjugated benzophenone oxime (**14**) was inert to TBP–PDS reagent. Thioimine **11** was prepared from benzophenone imine as described in the literature.[12] We were pleased to find that all phenylthioimines **8**–**11** were cleanly converted into corresponding ketones (Eqs. (8)–(11)) in tributylphosphine—water, or tributylphosphine—acetic acid systems.



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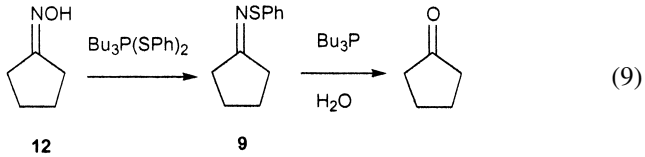

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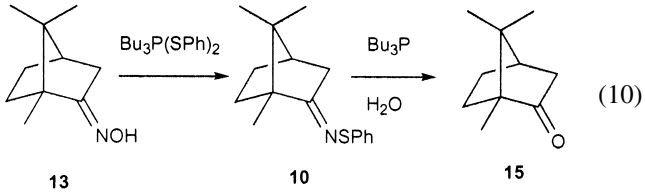

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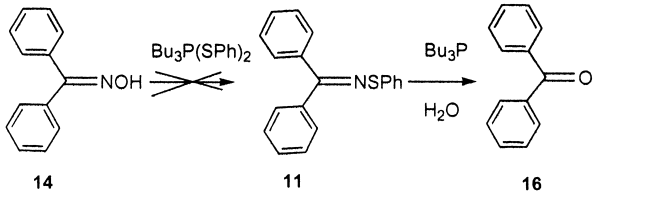

(11)

Thus ketones **2**, **15**, **16** were isolated in 82, 76, and 80% yields, and 98% yield of cyclopentanone was determined by GC analysis. On the other hand, control experiments with thioimines **8** and **9**, where their conversion into ketones was attempted with hydrochloric acid in the *absence of phosphine* produced only complex reaction mixtures.

Clearly, tributylphosphine assisted hydrolytic cleavage of phenylthioimines provides the first practical and general method for their conversion into ketones.

Finally, it is noteworthy, that the knowledge of the two step mechanism of the reduction of oximes to imines could be very helpful for establishing a new, mild, and non-acidic deoximation technique. Thus, according to the original

protocol reported by Barton et al.[3], (e.g. Eq. (1)) imines were hydrolyzed to the ketones *after* the reduction of oximes was complete due to incompatibility of PDS–TBP reagent and water. This method was only applicable to the imines which were sufficiently stable and did not undergo di- or polymerization. Our study suggests that this limitation could be overcome by charging water and an additional equivalent of tributylphosphine to the reaction mixture *after the formation of thioimine intermediate*. Under these conditions formation of the imine and its hydrolysis would occur simultaneously.

3. Conclusions

1. We have established that the reduction of oximes to imines with TBP–PDS reagent developed by Barton et al.[3] proceeds in two steps (i) conversion of the oxime into thioimine and (ii) subsequent reduction of this thioimine to imine with tributylphosphine in the presence of a proton donor.
2. Thus uncovered, tributylphosphine assisted hydrolytic cleavage of phenylthioimines provides the first practical and general method for the conversion of these compounds into ketones.

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere. Tributylphosphine, phenyldisulfide, cyclopentanone oxime, and benzophenone imine were purchased from Aldrich. Tetrahydrofuran was peroxide free and contained not more than 0.04% water. Zorbax R_x C8 column was used for HPLC monitoring of reactions at 205 nm. *N*-Phenylthioiminobenzophenone **11** was prepared according to Ref. 12.

4.2. General method for the preparation of phenylthioimines 4, 9, 10

Tributylphosphine (5.4 mL, 22 mmol) was added over 1 h to a solution of oxime (20 mmol) and phenyldisulfide (8.8 g, 40 mmol) in tetrahydrofuran (50 mL) at 0–5°C. After additional 1 h the mixture was quenched by pouring into 5% aqueous solution of sodium carbonate (150 mL). If a precipitate was formed, it was filtered off and recrystallized (Compound **4**). Oils were extracted with isopropyl acetate, concentrated and purified by column chromatography (Compounds **8**–**10**).

4.2.1. 9-(Phenylthioimino)erythromycin-2′,4″-dibenzoate (4). Isolated in 79% yield: ^{1}H NMR ($CDCl_3$, δ): 0.72–0.81 (6H), 0.95 (3H, CH_3), 1.03 (3H, CH_3), 1.10–1.22 (12H), 1.34–1.94 (7H), 1.62 (3H, CH_3), 2.33 (6H, CH_3), 2.46 (1H), 2.80 (2H), 2.94 (2H), 3.20 (1H), 3.52 (3H, CH_3), 3.61 (2H), 3.89 (2H), 4.48 (2H), 4. 76 (1H), 4.90–5.17 (7H), 7.18 (1H), 7.3–7.50 (8H), 7.59 (2H), 8.01–8.09 (4H); ^{13}C NMR ($CDCl_3$, δ): 9.3, 10.5, 14.5, 15.9, 16.0, 16.1, 18.3, 18.4, 21.0 (CH_2), 21.2, 21.8, 26.0, 27.4, 31.5 (CH_2), 35.3 (CH_2), 36.4, 37.5 (CH_2), 37.9, 38.6, 40.9 (2C, CH_3N), 44.3, 49.5, 63.4, 67.6, 70.1, 72.4, 72.9 (C), 74.9 (C), 76.6, 78.9, 79.2, 83.6, 95.7 (–OCHO–), 100.2 (–OCHO–), 125.3 (2C), 126.2, 128.2 (2C), 128.3 (2C), 128.9 (2C), 129.56 (2C), 129.60 (2C), 129.9 (C), 130.8 (C), 132.6, 133.3, 138.1 (C), 165.5 (C═O), 166.1 (C═O), 174.9 (C═O), 182.4 (C═N). Anal. Calcd. for $C_{57}H_{80}N_2O_{14}S$: C, 65.24; H, 7.68; N, 2.67. Found: C, 64.98; H, 7.68; N, 2.67.

4.2.2. 20-(Phenylthioimino)pregn-5-en-3β-ol acetate (8). Isolated in 65% yield: ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[3]

4.2.3. (Phenylthioimino)cyclopentane (9). Isolated in 60% yield: ^{1}H NMR ($CDCl_3$, δ): 1.75–2.0 (4H, m), 2.3–2.5 (4H, m), 7.17 (1H, m), 7.33 (2H, m), 7.52 (2H, m); ^{13}C NMR ($CDCl_3$, δ): 25.3, 25.5, 33.8, 37.4, 125.6 (2C), 139.0 (C), 178.6 (C═N). Anal. Calcd. for $C_{11}H_{13}NS$: C, 69.06; H, 6.80; N, 7.32. Found: C, 69.04; H, 6.94; N, 7.26.

4.2.4. *N*-Phenylthio-1,7,7-trimethylbicyclo[2.2.1]heptane-2-imine (10). Isolated in 71% yield: ^{1}H and ^{13}C NMR spectra were identical to those reported in the literature.[5]

4.3. General method for the reduction of phenylthioimines 4, 8–11 with tributylphosphine and water

A solution of thioimine (2 mmol) and tributylphosphine (0.5 g, 2.5 mmol) in THF (10 mL) and water (0.4 mL) was stirred at rt for 48 h. The mixture was poured into 5% aqueous sodium bicarbonate. If a precipitate was formed (compounds **2**, **5**), it was collected by filtration and dried under vacuum and purified by reslurrying in cold hexane. Oils were extracted with isopropyl acetate, concentrated and purified by column chromatography (compounds **9**, **15**, **16**).

These reductions were complete in less then 15 h when water was replaced with 50% aqueous acetic acid.

4.3.1. 5-Pregnen-3β-ol-20-one acetate (2). Isolated in 82% yield. It was identical to the material obtained from Fluka.

4.3.2. 9-Iminoerythromycin-2′,4″-dibenzoate (5). Isolated in 80% yield. Anal. Calcd. for $C_{51}H_{76}N_2O_{14}$: C, 65.08; H, 8.13; N, 2.97. Found: C, 64.68; H, 7.63; N, 2.66. ^{1}H and ^{13}C NMR spectra of this material were complicated due to the presence of 6,9- and 9,12-cyclic hemiaminal tautomeres in solution. Such behavior of erythromycin imines is well documented.[4] Identical material was obtained by free basing hydrochloride salt of imine **5** which structure was confirmed by NMR methods (see next).

Cyclopentanone was obtained in 98% yield as determined by GC using toluene as an internal standard.

4.3.3. 1,7,7-Trimetylbicyclo[2.2.1]heptan-2-one (15). Isolated in 76% yield. It was identical to the material obtained from Aldrich.

Benzophenone (**16**) was isolated in 80% yield. It was identical to the material obtained from Aldrich.

4.3.4. Preparation of 9-iminoerythromycin-2′,4″-dibenzoate (5) hydrochloride from oxime 3. Tributylphosphine (6.25 mL, 25 mmol) was added to a solution of erythromycin oxime dibenzoate **3** (9.6 g, 10 mmol) and phenyldisulfide (4.4 g, 20 mmol) in tetrahydrofuran (30 mL) at rt. After 2 h, the mixture was quenched by addition of hydrochloric acid (~6N) to pH 3.5–4. The mixture was diluted with *tert*-butylmethylether (MTBE, 30 mL) and the precipitate was filtered off and washed with MTBE. Drying under vacuum gave iminoerythromycin **5** hydrochloride (7.8 g, 80%): ^{1}H NMR ($CDCl_3$, δ): 0.58 (3H, CH_3), 0.74 (3H, CH_3), 0.87 (3H, CH_3), 0.91 (3H, CH_3), 1.10 (3H, CH_3), 1.16 (3H, CH_3), 1.22 (6H), 1.34 (1H), 1.35 (3H, CH_3), 1.46 (1H), 1.54 (3H, CH_3), 1.58 (2H), 1.69 (1H), 1.72 (1H), 1.94 (1H), 2.44 (1H), 2.75–2.87 (9H), 3.45 (1H), 3.49 (3H, CH_3), 3.63–3.77 (4H), 3.98–4.00 (2H), 4.30 (1H), 4. 38 (1H), 4.90 (1H), 4.98–5.02 (3H), 5.34 (1H), 7.50 (2H), 7.61–7.67 (4H), 7.97–8.00 (4H), 11.07 (1H), 12.92 (1H); ^{13}C NMR ($CDCl_3$, δ): 9.4, 10.3, 13.9, 15.9, 16.7, 16.1, 18.1, 19.1, 20.5, 20.7, 20.8 (CH_2), 21.0, 26.0, 26.1, 34.1 (CH_2), 35.0, 35.2 (CH_2), 37.9, 38.0 (CH_2), 38.3, 44.3, 49.7, 63.7, 64.1, 66.6, 67.9, 69.7, 73.2 (C), 73.6 (C), 75.0 (C), 77.0, 78.3, 78.9, 83.6, 95.7, 99.1, 128.6, 128.8 (2C), 128.9 (2C), 129.2 (C), 129.4 (2C), 129.8 (2C), 133.8 (C), 134.1 (C), 164.9 (C═O), 166.2 (C═O), 175.7 (C═O), 204.7 (C═N). Complete assignment of the signals in ^{1}H and ^{13}C NMR spectra was accomplished using 2D-NMR experiments.

Treatment of hydrochloride **5** with 5% aqueous sodium carbonate in tetrahydrofuran gave imine **5** free base.

4.3.5. Preparation of imine 5 by cleavage of phenylthioimine 4 with hydrochloric acid. Conc. hydrochloric acid was added dropwise to a solution of thioimine **4** (1.1 g, 1 mmol) in tetrahydrofuran (10 mL) at 0°C until pH 2.5–3 was achieved. The mixture was diluted with acetonitrile (5 mL) and the product was isolated by filtration and drying in 84% yield. Benzenesulfenyl chloride was identified as a second product of this reaction by comparison with the authentic sample by HPLC method.

4.4. Monitoring the reaction of oxime 3 with tributylphosphine–phenyldisulfide

Tributylphosphine (0.6 g, 3 mmol) was added in portions (~0.1 g/h) to a solution of oxime **3** (0.96 g, 1 mmol) and phenyldisulfide (0.44 g, 2 mmol) in THF (5 mL) at 0–5°C. The reaction was monitored by HPLC. The concentration of imine **5** in the reaction mixture remained 8–12% relative to **4** from the beginning of phosphine addition and until complete conversion of starting oxime **3**. The mixture was left overnight at rt and the concentration of imine **5** increased to ~30%. Water (0.25 m) was added. The concentration of imine **5** relative to thioimine **4** increased to 80% (4 h) and 100% (15 h).

4.5. Attempted conversion of imine 5 into thioimine 4

Tributylphosphine (0.25 g, 1.25 mmol) was added to a solution of imine **5** (1 mmol) and phenyldisulfide (0.27 g, 1.25 mmol) in THF (5 mL). No reaction was observed after 2 h at rt.

4.6. Control experiments

Solutions of phenylthioimine **4** (0.55 g, 0.5 mmol) in THF (2.5 mL) were treated respectively with: (a) water (0.2 mL), (b) 50% aqueous acetic acid (0.2 mL), (c) glacial acetic acid (0.1 mL), (d) thiophenol (0.11 g, 1 mmol). After 2 h at rt, no reactions were observed by HPLC analysis. Tributylphosphine (0.7 mmol) was added to these solutions (a)–(d). The reductions were monitored by HPLC and completed after 48, 15, 1, and 60 h, respectively.

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