A Versatile and Convenient Preparation of Unsymmetrical Diaryl Disulfides

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Abstract: We have developed a convenient method for the synthesis of unsymmetrical diaryl disulfides under mild conditions in excellent yields. The described method is based on the straightforward preparation of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-sulfenyl bromide from readily available 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane or bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide. The unsymmetrical diaryl disulfides can be obtained from aromatic thiol derivatives bearing electron-withdrawing or electron-donating groups.

Key words: unsymmetrical diaryl disulfides, sulfenyl bromide, aromatic thiols, arenes, heterocycles

The synthesis of unsymmetrical disulfides is an important transformation in modern organic synthesis and medicinal chemistry.[1] Although there are many different approaches for the preparation of disulfides, the majority of them are not applicable to the synthesis of unsymmetrical diaryl disulfides, due to the fast thiol–disulfide exchange reaction. Furthermore, preparative methods that are efficient for the preparation of symmetrical diaryl disulfides are very often ineffective for the preparation of unsymmetrical diaryl disulfides. The most common methods for obtaining unsymmetrical diaryl disulfides include the thioalkylation of a thiol or its derivative by sulfenyl derivatives: sulfenyl chlorides,[2] *N*-(trifluoroacetyl)arenesulfenamides,[3] benzotriazolyl sulfides,[4] *S*-arylarenothiosulfonates,[5] 4-nitroarenesulfenanilides,[6] and toluene-4-sulfinic acid.[7] Other practical procedures involve disulfide exchange catalyzed by rhodium,[8] triphenylphosphine,[9] or tetrathiomolybdate.[10]

Several unsymmetrical substituted aromatic donor–acceptor disulfides have been analyzed for their second-order nonlinear optical properties. These compounds exhibit moderately high first hyperpolarizability with excellent transparency in the visible region.[11] Although this class of molecules has potential application in optical data processing and communication, these disulfides are provided in only moderate or poor yield by the available synthetic methods.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfides, alkyl aryl disulfides,[12] 'bioresistant' disulfides,[13] and unsymmetrical disulfides based on L-cysteine and L-cystine derivatives.[14] The excellent results encouraged us to extend the strategy to the preparation of unsymmetrical diaryl disulfides based on organophosphorus sulfenyl bromides as activating agents for unsymmetrical disulfide bond formation.

Treatment of the stable and readily available bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl) disulfide (**1**)[15] with bromine at –30 °C quantitatively affords 5,5-dimethyl-2-thioxo-1,3,2-dioxophosphorinane-2-sulfenyl bromide (**3**) (Table 1). Subsequent treatment, without prior isolation, of sulfenyl bromide **3** with arenethiols provides the corresponding aryl 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl disulfides **4a–f**, which can be isolated in very good yields (Table 1, method A, entries 1–6). These compounds are stable at room temperature for several months; formation of symmetrical disulfides or decomposition by moisture was not observed. Moreover, compounds **4a–f** can be prepared from 5,5-dimethyl-2-sulfanyl-2-thioxo-1,3,2-dioxaphosphorinane (**2**)[15] in similar, very high yields (Table 1, method B, entries 1–6). Although the use of dithiophosphoric acid derivative **2** is simpler with regard to the availability of reagents required for the preparation of sulfenyl bromide **3**, the formation of hydrogen bromide as side product was observed. In some cases strong acidic conditions are responsible for the removal of protective group and poor reaction yield.[14] From this point of view, method B can only be applied to the preparation of disulfide derivatives **4** from thiols without acid-sensitive groups. The results for both methods are summarized in Table 1.

The reaction of disulfide **4a** with one equivalent of 4-methylbenzenethiol in the presence of triethylamine afforded unsymmetrical disulfide **5a** in moderate yield (67%), together with the other symmetrical disulfides. However, in the presence of a 5% excess of **4a** relative to 4-methylbenzenethiol, the same reaction gave product **5a** in excellent yield (97%) (Table 2). These observations show that unsymmetrical disulfide **5a** forms very fast from 4-methylbenzenethiol and compound **4a**, and that further disulfide exchange takes place in the presence of thiolate anion. Therefore, unsymmetrical disulfides **5** need to be prepared in the presence of only a small excess of reagent **4**. The influence of the thiolate anion on the disulfide exchange reaction was confirmed by treatment of isolated unsymmetrical disulfide **5a** with 4-methylbenzenethiol (5 mol%) in the presence of triethylamine. After 15 minutes an equal amount of both symmetrical disulfides was observed and after 30 minutes only 65% of starting **5a** was present in the reaction mixture (confirmed by TLC and ^{1}H NMR).

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