Facile oxidation of electron-poor benzo[*b*]thiophenes to the corresponding sulfones with an aqueous solution of H_2O_2 and $P_2O_5^{\dagger}$

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A facile oxidation for the clean conversion of benzo[b]thiophenes to their corresponding sulfones is described employing an aqueous solution of H₂O₂ and P₂O₅; the solution can be prepared and stored on a multi-gram scale with a shelf-life of up to two weeks.

Benzo[b]thiophene 1,1-dioxides are an emerging class of heterocyclic compounds with synthetic and medicinal chemistry applications. These unsaturated sulfones are dipolarophiles that have been shown to undergo a number of synthetically useful cycloaddition reactions^{1,2} and to be useful synthons for various chemical transformations.^{3–5} Also, this class of cyclic sulfones possesses a variety of biological activities.^{6–11} Nevertheless, their potential is under-exploited due to a lack of synthetic methods to prepare derivatives with a wide range of substituents. Benzo[b]thiophene 1,1-dioxides are commonly obtained from benzo[b]thiophenes using synthetic methods based on a small number of reagents capable of oxidizing thiophenes bearing electron-donating groups (EDGs). Fewer reagents are available for the more challenging derivatives bearing electron-withdrawing groups (EWG).^{12–15} The sulfur atom of the benzo[b]thiophene ring system is even more difficult to oxidize to 1,1-dioxides and few methods have been explored.¹⁶⁻¹⁸ In particular, no general methods have been reported for the direct synthesis of benzo[b]thiophene 1,1-dioxides possessing EWGs by oxidation of the corresponding benzo[b]thiophenes. Based on studies in the literature for thiophenes and benzo[b]thiophenes, oxidizing systems that could be successfully exploited include the use of hydrogen peroxide (30% aqueous solution) at room temperature with metal-based salts such as MoO₂Cl₂,¹⁹ ZrCl4¹⁸ or binuclear manganese,¹⁶ the use of 98% hydrogen peroxide with trifluoroacetic anhydride,12 or the use of dimethyl dioxirane (DMD).¹⁵ Metal-free catalysis is desirable from an environmental viewpoint, and 98% hydrogen peroxide is highly explosive, has to be produced "in loco" and then the oxidizing species (i.e., trifluoroperacetic acid) formed in situ by mixing the H₂O₂ with TFAA.¹² Its instability

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is also an issue for storage purposes; reactions cannot be carried out at temperatures higher than 35 °C as the trifluoroperacetic acid degrades.¹² Finally, the use of DMD is problematic in reactions of more than 100 mg scale, as the complex preparation²⁰ of this reagent limits its scalability.

Thus, we focused on developing an oxidation method that would allow the conversion of benzo[b]thiophenes to benzo[b]-thiophene 1,1-dioxides in a facile manner, and on a multigram scale for potential industrial applications. We report here the use of an aqueous solution of H_2O_2 (60%) and P_2O_5 that involves inexpensive and environmentally friendly reagents. A further advantage of this oxidizing system is that it does not need to be freshly prepared *in situ*, but can be prepared on a multi-gram scale as a single reagent containing the reactive species peroxymonophosphoric acid²¹ (0.88 M aq.). The solution has a shelf-life of up to two weeks when stored at 4 °C.²²

To evaluate the versatility of this reagent we investigated the oxidation of benzo[*b*]thiophenes bearing EWGs, where the sulfur atom is more difficult to oxidize. In particular, we selected the more challenging benzo[*b*]thiophene carboxamides (Table 1) whose oxidation to 1,1-dioxides has not been reported. For each of these derivatives, the carboxamide group is at the 2-, 3- or 5-positions of the benzo[*b*]thiophene system, and the phenyl ring of the amide possesses an EDG or EWG. For comparison purposes two other oxidative methods were investigated alongside involving a novel H₂O₂/TFAA procedure employing non-explosive 60% aq. H₂O₂, and DMD.²⁰ For these preliminary investigations we used the benzo[*b*]thiophene **1** (Scheme 1).

The reactions were carried out in parallel at room temperature in acetonitrile using 2 equivalents of the oxidizing agent. Clean sulfone formation (*i.e.*, no by-products) allowed efficient isolation of the products in excellent yields. Longer reaction times were required for substrates possessing a nitro group. Only in the case of entry 3 was the desired product not formed and starting material fully recovered. 60% aq. H_2O_2 and TFAA afforded the desired compounds in lower yields when compared to H_2O_2 – P_2O_5 , which was particularly noticeable for the nitro-substituted substrates. The use of DMD afforded the oxidized products in comparable yields to the H_2O_2 – P_2O_5



Scheme 1 Oxidation of 1 with aqueous $H_2O_2-P_2O_5$.

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 $[\]dagger$ Electronic supplementary information (ESI) available: Experimental details for preparation of the aqueous $H_2O_2-P_2O_5$ reagent and for all the reactions described here. Full characterisation of all starting materials and products is also included. See DOI: 10.1039/b924333j

Table 1 Conversion of benzo[*b*]thiophene carboxamides to benzo[*b*]thiophene carboxamide 1,1-dioxides with the $H_2O_2-P_2O_5$ reagent





^{*a*} Monitored by LC-MS. ^{*b*} Characterized by ¹H- and ¹³C-NMR, IR, MS, HRMS, CHN. ^{*c*} $H_2O_2-P_2O_5$ reagent (2.0 eq), CH₃CN (see ESI[†] for details). ^{*d*} Isolated yield. ^{*e*} TFAA (10 eq), 60% aq. H_2O_2 (10 eq), CH₃CN (see ESI[†] for details). ^{*f*} 0.07–0.09 M DMD in acetone (2.4 eq), DCM (see ESI[†] for details). ^{*g*} As indicated by LC-MS. ^{*h*} An additional equivalent of $H_2O_2-P_2O_5$ reagent (3.0 eq overall) was added after 24 h (see ESI[†] for details).

reagent and with a higher reaction rate. However, the reactions could not be performed in parallel due to the limitations of manufacturing the DMD.²⁰

To address the reaction time of the $H_2O_2-P_2O_5$ reagent, we varied the temperature for the formation of compounds **4g**, **k** and **4i** (Table 2) that required the longest reaction times at

Table 2 The effect of temperature variation on the oxidation of benzo[*b*]thiophene-3-carboxamides with the H_2O_2 - P_2O_5 reagent^{*a*}

| Entry | Temperature ^b | Time ^c | Product ^d | Yield ^e (%) |
|--------|--------------------------|-------------------|----------------------|------------------------|
| 1 2 | 60 °C 60 °C 120 °C | 10 min 10 min | 4g 4k | 98 98 |
| 3 | 130 °C 60 °C | 1 min 4 h | 4 i | 98 40 |

^{*a*} H₂O₂–P₂O₅ reagent (2.0 eq), CH₃CN (see ESI[†] for details). ^{*b*} Oil bath. ^{*c*} Monitored by LC–MS. ^{*d*} Characterized by ¹H- and ¹³C-NMR, IR, MS, HRMS. ^{*e*} Isolated yield. ^{*f*} Additional 2.0 eq of H₂O₂–P₂O₅ were added after 3 h.

room temperature. We found that reactions were significantly faster upon heating to 60 °C while affording the same yields for **4g** and **4h**. For the nitro-derivative **4i** a lower yield was observed due to degradation of the product during the reaction.

The highly efficient and facile sulfone formation observed prompted us to extend the reaction to other types of bennzo[*b*]thiophenes, and to representatives of classes of sulfur-containing compounds such as thiophenes, and acyclic and aromatic sulfides (Table 3).

The $H_2O_2-P_2O_5$ oxidizing reagent again allowed formation of the desired sulfones in excellent yields, and, as anticipated, shorter reaction times were required than for the benzo[*b*]thiophenes carboxamides.

In summary, a novel oxidizing method using a $H_2O_2-P_2O_5$ reagent has been developed for the preparation of sulfones from their corresponding sulfides. This reagent allows facile and efficient oxidation in a parallel manner, and also allows large scale oxidations. The $H_2O_2-P_2O_5$ aqueous solution can be prepared as a single reagent that can be stored on a multigram scale with a shelf-life of up to two weeks. Furthermore, it is able to oxidize challenging substrates such as benzo[*b*]-thiophene derivatives bearing EWGs to afford the corresponding sulfones in excellent yields. This allows access to a wide range

Table 3 Examples of oxidation of other sulfur-containing substrates with the H_2O_2 - P_2O_5 reagent^a

| Entry | Time ^b | Product ^c | Yield (%) |
|-------|----------------------------|----------------------|-----------------|
| 1 | 1.5 h | Br C 5 | 96 ^e |
| 2 | 1.5 h | | 98 ^e |
| 3 | 18 h | | 91 ^e |
| 4 | 15 min ^{<i>f</i>} | | 80^d |
| 5 | 10 min | | 98 ^e |
| 6 | 10 min | | 75 ^e |

^{*a*} H₂O₂–P₂O₅ reagent (2.0 eq), (see ESI[†] for details). ^{*b*} Monitored by LC-MS. ^{*c*} Characterized by ¹H- ¹³C-NMR, IR, MS, HRMS, CHN. ^{*d*} As indicated by LC-MS. ^{*e*} Isolated yield. ^{*f*} H₂O₂–P₂O₅ reagent (3.0 eq).

of benzo[b]thiophene 1,1-dioxides. A final advantage is that the reagent does not employ environmentally-damaging materials such as metal ions, and is thus attractive for industrial applications. To further exploit the potential of aq. H_2O_2 - P_2O_5 , the oxidation of alcohols and unsaturated carbon bonds is under investigation, in parallel with its application to a wider range of sulfur-containing derivatives.

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