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## DDQ-mediated synthesis of functionalized unsymmetrical disulfanes†

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We developed a simple and efficient method for the synthesis of functionalized unsymmetrical disulfanes under mild conditions in good yields. The designed method is based on the reaction of bis(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-yl)disulfane with thiols in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The developed method allows the preparation of unsymmetrical disulfanes bearing additional hydroxy, carboxy, or amino functionalities.

Compounds with the structure R–S–S–R, where the R group can be alkyl, vinyl or aryl are termed symmetrical disulfides when the R groups are the same. The wide range of unsymmetrical disulfides in which the R groups are different is also well known. These compounds are often termed organic disulfides in the literature; however, the IUPAC recommended nomenclature is disulfanes.<sup>1</sup> The name disulfide should only be applied to ionic compounds, such as sodium disulfide (Na<sub>2</sub>S<sub>2</sub>). Moreover, the term disulfane is more widely applicable than disulfide because it facilitates naming, even when the R groups are acyl and/or phosphoryl.

The synthesis of unsymmetrical disulfanes is an important transformation in organic synthesis and medicinal chemistry.<sup>2–5</sup> Recent developments in disulfide bond formation have been reviewed.<sup>6–9</sup> Although many different methods exist for the preparation of unsymmetrical disulfanes, the most prevalent approach involves substitution of a sulfenyl derivative with a thiol or its derivative. To date, the most commonly utilized sulfenyl derivatives are the following: sulfenyl chlorides,<sup>10–12</sup> *S*-alkyl thiosulfates and *S*-aryl thiosulfates (Bunte salts),<sup>13,14</sup> *S*-alkylsulfanyl-isothioureas,<sup>15</sup> benzothiazol-2-yl disulfanes,<sup>16,17</sup> benzotriazolyl-sulfanes,<sup>18</sup> dithioperoxyesters,<sup>19</sup> (alkylsulfanyl)dialkylsulfonium salts,<sup>20</sup> 2-pyridyl disulfanes and derivatives,<sup>21,22</sup> *N*-alkyltetrazolyl disulfanes,<sup>23</sup> sulfenamides,<sup>24</sup> sulfenyldimesylamines,<sup>25</sup> sulfenylthiocyanates,<sup>26</sup> 4-nitroarenesulfenylamides,<sup>27</sup> thiolsulfonates,<sup>28–31</sup> sulfanyl-sulfonamides,<sup>32</sup> thionitrites,<sup>33</sup> sulfenylthiocarbonates,<sup>34</sup> thioimides,<sup>35–37</sup> and thiophosphonium salts.<sup>38</sup> Other practical procedures involve the reaction of a thiol with a sulfenylbenzimidazole,<sup>39</sup> the rhodium-catalyzed disulfide exchange,<sup>40,41</sup> an electrochemical method,<sup>42</sup> ring opening of aziridines using tetrathiomolybdate in the presence of symmetrical disulfanes,<sup>43,44</sup> and the use of diethyl azodicarboxylate (DEAD)<sup>45</sup> or a solid support<sup>46</sup> in a sequential coupling of two different thiol groups. Recently, the oxidation of a mixture of two different thiols by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to produce an unsymmetrical disulfane has also been reported.<sup>47,48</sup>

Disulfanes have been used for the preparation of self-assembled monolayers (SAMs)<sup>49,50</sup> and monolayer-protected clusters (MPCs) with a number of versatile properties.<sup>51,52</sup> Compounds containing the disulfide linkage have also been used for the preparation of dynamic combinatorial libraries,<sup>53</sup> catenanes,<sup>54,55</sup> macrocycles,<sup>5,56</sup> carceplexes,<sup>57</sup> dendrimers,<sup>58</sup> rotaxanes, micelles,<sup>59,60</sup> and a wide range of chemosensors and pro-drugs.<sup>61</sup> These species illustrate the wide applications of disulfanes and show that the synthesis of the disulfide bond is a critical transformation in organic chemistry.<sup>6–9</sup>

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfanes,<sup>62</sup> alkyl-aryl disulfanes,<sup>63</sup> 'bioresistant' disulfanes,<sup>64</sup> the unsymmetrical disulfanes of *L*-cysteine and *L*-cystine,<sup>65</sup> and diaryl disulfanes,<sup>66</sup> based on the readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1**. These disulfanyl derivatives **1** of phosphorodithioic acid were also convenient for the preparation of  $\alpha$ -sulfenylated carbonyl compounds,<sup>67</sup> functionalized phosphorothioates,<sup>68</sup> as well as symmetrical<sup>69,70</sup> and unsymmetrical<sup>71,72</sup> trisulfanes (Fig. 1).

As part of our continued interest in the preparation of functionalized unsymmetrical disulfanes, in this study, we report an efficient and convenient synthesis of unsymmetrical disulfanes **1** directly from phosphorodithioic acid disulfane **2a** and functionalized thiols **3**.

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† Electronic supplementary information (ESI) available: Experimental details and spectroscopic data for all new compounds **1**. See DOI: 10.1039/c5ra04173b