


 Cite this: *RSC Adv.*, 2018, 8, 9718

Received 22nd January 2018

Accepted 1st March 2018

DOI: 10.1039/c8ra00659h

[rsc.li/rsc-advances](http://rsc.li/rsc-advances)

# Convenient and efficient synthesis of functionalized unsymmetrical Z-alkenyl disulfanes†

 M. Musiejuk, J. Doroszuk and D. Witt \*

We developed a simple and efficient method for the synthesis of functionalized unsymmetrical Z-alkenyl disulfanes under mild conditions in moderate to good yields. The designed method is based on the reaction of Z-alkenyl thiosulfates with thiols in the presence of base. The developed method allows the preparation of unsymmetrical Z-alkenyl disulfanes bearing additional hydroxy, carboxy, or amino functionalities.

## Introduction

Compounds with R-S-S-R structures, where the R groups are alkyl, vinyl or aryl, are known as symmetrical disulfides if the R groups are the same. A large number of unsymmetrical disulfides, in which the R groups are different, are also well known. In the literature, these compounds are often called organic disulfides; 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 groups.

The formation of unsymmetrical disulfanes is an important transformation in organic synthesis and medicinal chemistry.<sup>2</sup> Recent developments in disulfide bond formation reactions have been reviewed.<sup>3</sup> Although many different methods exist for the preparation of unsymmetrical disulfanes, the most common approach involves substitution of a sulfenyl derivative with a thiol or thiol derivative. To date, the most commonly utilized sulfenyl derivatives are sulfenyl chlorides,<sup>4</sup> S-alkyl thiosulfates and S-aryl thiosulfates (Bunte salts),<sup>5</sup> S-alkylsulfanylisothioureas,<sup>6</sup> benzothiazol-2-yl disulfanes,<sup>7</sup> benzotriazolyl sulfanes,<sup>8</sup> dithioperoxyesters,<sup>9</sup> (alkylsulfanyl)dialkylsulfonium salts,<sup>10</sup> 2-pyridyl disulfanes and derivatives,<sup>11</sup> N-alkyltetrazolyl disulfanes,<sup>12</sup> sulfenamides,<sup>13</sup> sulfenyldimesylamines,<sup>14</sup> sulfenyl thiocyanates,<sup>15</sup> 4-nitroarenesulfenylidides,<sup>16</sup> thiosulfonates and thiosulfonates,<sup>17</sup> sulfanylsulfonamides,<sup>18</sup> thionitrites,<sup>19</sup> sulfenyl thiocarbonates,<sup>20</sup> thioimides,<sup>21</sup> and thiophosphonium salts.<sup>22</sup> Other practical procedures involve the reaction of a thiol with a sulfinylbenzimidazole,<sup>23</sup> a rhodium-catalyzed disulfide exchange,<sup>24</sup> an electrochemical method,<sup>25</sup> the ring opening of

an aziridine using tetrathiomolybdate in the presence of a symmetrical disulfane,<sup>26</sup> or the use of diethyl azodicarboxylate (DEAD)<sup>27</sup> or a solid support<sup>28</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>29</sup>

Earlier studies demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyl disulfanes,<sup>30</sup> alkyl-aryl disulfanes,<sup>31</sup> 'bioresistant' disulfanes,<sup>32</sup> the unsymmetrical disulfanes of L-cysteine and L-cystine,<sup>33</sup> and diaryl disulfanes<sup>34</sup> based on the readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives. These disulfanyl derivatives of phosphorodithioic acid were convenient for the preparation of  $\alpha$ -sulfenylated carbonyl compounds,<sup>35</sup> functionalized phosphorothioates,<sup>36</sup> and unsymmetrical alkynyl sulfides<sup>37</sup> as well as symmetrical<sup>38</sup> and unsymmetrical<sup>39</sup> trisulfanes.

Ajoene was first isolated by Block<sup>40</sup> in 1984 as an E/Z-mixture of a rearrangement product of allicin produced from freshly crushed garlic. It was established to be an allyl sulfoxide containing an unusual vinyl disulfane functionality, which is rarely seen in the structures of natural products. Z-Ajoene is more active than its E-isomer as an anti-thrombotic agent,<sup>41</sup> and some studies on anticancer treatments have focused primarily on the Z-isomer.<sup>42</sup>

Although many different synthetic methods exist for the preparation of unsymmetrical disulfanes, the preparation of unsymmetrical alkenyl disulfanes can be achieved by only two methods. The first method is based on the reaction of sulfenyl bromide with trityl-alkenyl sulfide.<sup>43</sup> The second method involves the low temperature hydroxide-promoted cleavage of an alkenyl thioester followed by sulfenylation with an appropriate S-alkylated p-toluenethiosulfonate to afford vinyl disulfide in high yield after chromatography.<sup>44</sup> Unfortunately, the methods provide exclusively E or a mixture of Z/E alkenyl disulfanes, respectively. In this context, we set out to investigate

Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland. E-mail: chemwitt@pg.gda.pl; Fax: +48 58 3472694

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra00659h