



## Review

# Synthesis and biological properties of selenium- and tellurium-containing dyes



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## ARTICLE INFO

Article history:  
Available online 20 May 2014

Keywords:  
Selenides  
Tellurides  
Fluorescence  
ROS  
Biological activity  
Bioanalyte detection

## ABSTRACT

This account covers the synthesis and biological applications of organoseleno- and organotelluro-based molecular dyes. The most relevant applications for photodynamic therapy (PDT), fluorescent probes for the detection of endogenous reactive oxygen species (ROS), natural bioreductors like glutathione (GSH) and metals present in physiological systems will be discussed. This manuscript covers only dyes bearing small selenium- and tellurium-containing heterocycles.

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## 1. Introduction

### 1.1. Historical background

The organic compounds of selenium and tellurium are known since the late nineteenth century. In 1852, Wöhler reported the synthesis of diethyltelluride, the first synthetic organotellurium compound described. This compound is low weight, volatile, very susceptible to oxidation and presents a very unpleasant odor. This characteristic was very well emphasized in his publication with the following comment "... and because its highly persistent and obnoxious smell is connected to unpleasantness, which one would not like to endure a second time ..." [1]. Nine years latter, in 1861, Heeren also took contact with the same compound and wrote the following sentence about its odor "*The smell is so persistent, that one has to avoid social life for several months in order not to molest other people*" [2]. These two comments probably were the main reason for the long-term latency of the organic chemistry of tellurium since these characteristics were imputed to the element and not to the specific studied compound. Indeed, by 1950 just a little more than 50 works involving organotellurides had been published, most of them from 1910. Nowadays many stable, odorless and even pleasant smelling organotellurides are known.

Selenium had almost the same development in its earlier years but the higher stability of its derivatives probably stimulated and

allowed the preparation of a larger number of organoselenium compounds. As a consequence, the selenium chemistry developed faster than those of tellurium. In 1955 Heinrich Rheinboldt published a comprehensive compendium in Houben-Weill devoted to the selenium and tellurium chemistry [3]. In 1957 Schwarz and Foltz discovered that selenium is an essential trace element, which prevents liver necrosis in rats [4] and in 1973 it was discovered that it is present in biological systems as selenocysteine, the 21st natural amino acid, as part of glutathione peroxidase, baptized as a selenoenzyme [5]. These finds changed deeply the reputation of selenium within the scientific community and many groups around the world turned their attention to it and began to devote their studies to the development of new methodologies on the preparation of selenium-containing compounds.

Albeit no natural occurrence in biological systems is known for tellurium, the similarity of these elements drove the development of this branch of chemistry. Actually there are no reports concerning the poisoning, diseases or disorders involving any tellurium-based compound. On the other hand, in 1987, Sredni reported a large spectra of bioactivities displayed by an organotellurium salt, AS101 [6]. Nowadays we can find several bioactive selenium- and tellurium-based compounds presenting a very large spectra of activities [7,8]. The preparation of organoselenium and -tellurium compounds is quite simple and general independent of its oxidation states. Their elemental forms are reactive towards many reagents allowing their incorporation into organic compounds [2,9–12]. Strategic symmetric or non-symmetric diselenides and ditellurides are also often used as starting materials for the preparation of more complex chalcogen-containing

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derivatives. The incorporation of the selenium and the tellurium moiety into an organic compound can also be achieved by employing nucleophilic or electrophilic selenium or tellurium reagents [2,9–12]. A myriad of other manners to introduce these elements into organic compounds are known and the involved chemical concepts are very well documented [2,9–12].

## 2. Molecular dyes containing selenium and/or tellurium

The development and applications of chalcogen-containing dyes has expanded significantly in the last years. Due to the particular reactivity of these elements, chalcogen-based dyes present several key properties that allow it to assume a variety of functions, especially in biological systems. Amongst the most worth noting properties of selenium and tellurium containing compounds is the ease of oxidation, leading to the corresponding chalcogenoxides/chalcogenones [13,14].

The insertion of heavier chalcogens [Se(II) and Te(II)] into the dye-chromophoric nuclei leads to fluorescence quenching; this is called “Photochemical Heavy Atom Effect” imputed by “Photoinduced Electron Transfer” (PET) [15]. The oxidation of the selenium or tellurium atom to the corresponding chalcogenoxides or chalcogenones, inhibits the PET process accompanied by the original fluorescence emission of the core. Preparation of devices containing functionalities able to reversibly quench fluorescence is of special interest, particularly in the development of photochemotherapeutic agents and fluorescent probes.

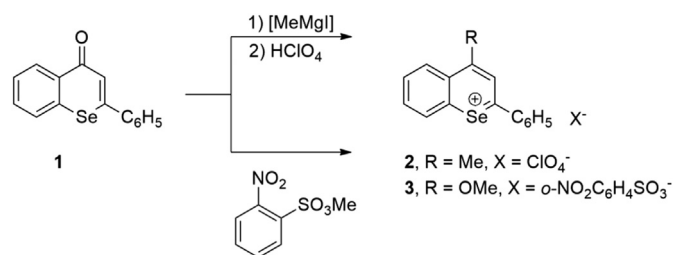
In this context, most of the studies involving heavy-chalcogen-based dyes are based on the preparation of analogues of the existing oxygen-containing dyes. For this purpose different synthetic approaches were described for the most important dye classes.

Contrary to the sulfur-containing dyes, historically, those containing selenium and tellurium have received much less attention and only more recently it has been demonstrated some of their peculiar properties opening a whole new spectra of opportunities in many different fields of applications. Thus, in this account we will cover the most relevant advances in the field of dyes based on selenium and tellurium. The synthesis, properties and applications of seleno- and telluro-dyes will be discussed, since the chemical properties of these elements are quite similar. In some cases comparative studies were presented. In addition, this account will not cover selenium- and tellurium-containing porphyrins and/or related macrocycles, since this topic have been extensively reported [16–24].

### 2.1. Selenonium and telluronium salt-based dyes

In 1971, Tolmachev and coworkers reported the synthesis of polymethine dyes containing only selenium as heteroatom in their structure. The authors pointed out that these compounds proved to be so far, the most colored known polymethine in comparison with other structurally similar oxygen or sulfur chromophores and this was the first known report describing such selenonium salt-based dyes [25,26]. Firstly it was prepared the 4-methyl- and 4-methoxyselenoflavylum salt (**2** and **3**) by reacting the selenoflavone **1** with methylmagnesium iodide and methyl *o*-nitrobenzenesulphonate, respectively, according Scheme 1.

The reaction between **2** and **3** resulted on the corresponding symmetrical selenoflavylomonomethinylcyanine **4a**, since the methyl group of **2** is nucleophilic and the methoxy group of compound **3** is susceptible to nucleophilic replacement. In the same way, reaction between **2** and **1** successfully resulted on the symmetrical compound **4a**. Compounds **4b–4d** ( $n = 1, 2$  and  $3$  respectively) and **4e** were also prepared by reacting the salt **2** with appropriated reagents and experimental conditions. Tolmachev carried out the synthesis of a large number of compounds of this



**Scheme 1.** The first reported synthesis of organoseleno salt-based dyes.

class along with comparative studies related to their photochemical properties. These studies described the influence of the chalcogen atom as well as the presence of methine groups on the bathochromic shifts. The maximum absorption wavelength ( $\lambda_{\text{max}}$  in nm) of each compound is given in parentheses. In general, the selenopyrylium salts studied by Tolmachev presented long-wavelength absorption maximum longer than the related pyrylium or thiapyrylium salts. Representative examples were selected and are presented in Fig. 1 [26–29].

In 1982 Detty reported the first examples of telluropyrylium dyes [29]. A robust and modular synthetic approach [29,30] for the preparation of such compounds is based on the double 1,4-addition reaction of an inorganic chalcogenolate ( $\text{Li}_2\text{Y}$  or  $\text{Na}_2\text{Y}$ ,  $\text{Y} = \text{Se}$  or  $\text{Te}$ ) to the diynone, resulting on the corresponding substituted chalcogenopyrone **24**. The sequential 1,2-addition reaction of an organometallic ( $\text{R}^1\text{M}$ ) followed by acid-induced dehydration/rearomatization, results on the chalcogenopyrylium core **25**. Compound **26** is obtained by the simple treatment of telluride **24** with ethyl fluorosulfate. The reaction of the electrophilic ethoxy telluropyrylium fluorosulfate (**26**) with the Meldrum's acid in pyridine resulted in compound **27**. The salt **25** can also be obtained by reaction of telluride **27** with formic acid followed by treatment with  $\text{HBF}_4$ . All of these transformations were carried out in reasonable to good yields as presented in Scheme 2.

Reaction of the telluropyrylium salt **25** with *N,N*-dimethylthioformamide in presence of acetic anhydride, gave salt **28** in 95% isolated yield. Next, the hydrolysis of the ammonium salt **28** allows the isolation of the telluro-aldehyde **29** in 90% isolated yield. A series of telluropyrylo mono- and trimethine dyes (**31–39**) were prepared by the combination of nucleophilic salts **25** and **30–30b** with electrophilic compounds **24** and **29**, according to Scheme 3.

Compound **38** was isolated in 17% overall yield from the reaction of telluropyrylium salt **25** with 1,3,3-trimethoxypropene and albeit unstable to light and oxygen when in solution, its absorption spectra could be measured and exhibited a long-wavelength absorption maximum at 885 nm. The authors presented the long-wavelength absorption for compound **39** ( $n = 2$ ,  $\lambda_{\text{max}}$  1010 nm) as listed in Scheme 3 but they emphasize that this compound was impossible to be isolated or even detected in all attempts to prepare it [29]. On the other hand, they successfully prepared and isolated compound **40** (Scheme 4), a derivative containing a six-membered ring between the two heterocycles. This compound was prepared by reaction of pyrylium tetrafluoroborate salt **25** with the aldehyde **41** and exhibited a long-wavelength absorption maximum at 1190 nm, a much higher value than the selenium analog **42**, which presented long-wavelength absorption maxima at 1050 nm (Scheme 4) [31].

Reaction of diethylamine with **26**, aiming the substitution reaction of the methoxy group by the diethylamine residue, looking for the isolation of **43**, results on the alkylation of the nitrogen atom leading to triethylammonium fluorosulfate and tellurodione **24**. Other alkylamino-substituted telluropyrylium dyes **44–44b** were prepared by the reaction of **25** with the corresponding alkylamino-

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