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Novel one-pot synthesis of 2-thio-substituted-3-H-phenothiazin-3-ones driven by oxidation with sodium periodate

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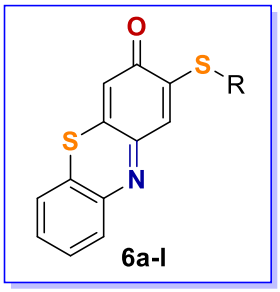
Abstract

A series of novel 2-thio-substituted-3*H*-phenothiazin-3-ones (**6h-l**) was effectively synthesized in one pot after optimization of the four-step synthesis. Treatment of a 2-alkylthio-1,4-benzoquinone (**3a-l**) made *in situ* and condensed with 1,2-aminothiophenol (**5**) followed by oxidation with $NaIO_4$ produced the desired final targets. A four-step reaction sequence in which 1,4-benzoquinone (**1**) is first reacted with an alkylthiol (**2a-l**) in the presence of sodium periodate ($NaIO_4$) and then treated with 2-aminothiophenol (**5**) followed by a second oxidation with sodium periodate was demonstrated to be effective in synthesizing 2-thio-substituted-3*H*-phenothiazin-3-

ones (**6a-g**). The one-pot synthesis is an improvement of the stepwise synthesis of these 2-thio-substituted-3*H*-phenothiazin-3-one heterocycles since four steps are run in sequence and treated as one.

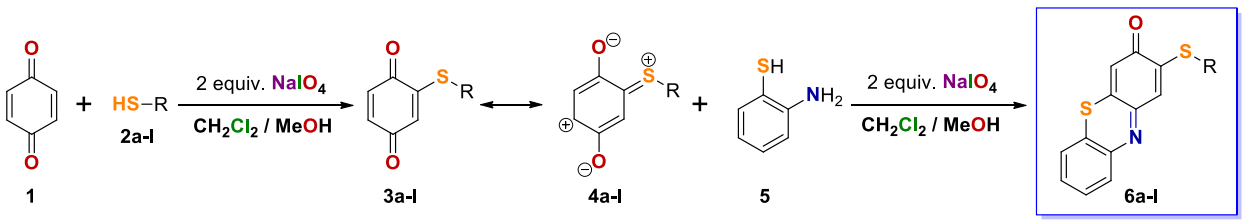


Keywords

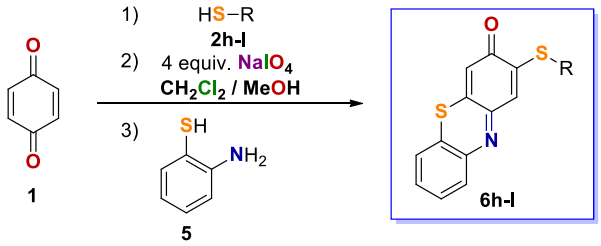
2-thio-substituted-3*H*-phenothiazin-3-ones, 2-alkylthio-1,4-benzoquinone, one-pot synthesis, addition/oxidation, heterocycles, psychopharmacological drugs, anti-infective pharmacophores.

Introduction

Derivatives of phenothiazinones have been synthesized [1-5] and studied as pharmaceutical ingredients [6,7] and as colorful dyes [8] as well. Biological testing on phenothiazinones has shown that these compounds exhibit potent antibacterial properties [9].



Scheme 1. General scheme for the synthesis of 2-(alkylthio)-3*H*-phenothiazin-3-ones.



Scheme 2. One-pot synthesis scheme for 2-(alkylthio)-3*H*-phenothiazin-3-ones.

Girard et al. work on derivatives of phenothiazine have led to the development of drugs capable of treating central nervous system (CNS) disorders [10]. Derivatives of 3*H*-phenothiazin-3-ones, which have since been demonstrated effective for the treatment of neurodegenerative disorders [11], also have the potential to treat diseases caused by leukotrienes [10]. Fortin et al. have concluded that work on inhibition of leukotriene biosynthesis and/or antagonism of leukotriene action will remarkably benefit the range of patients suffering from leukotriene-mediated diseases [12]. In the present paper, we aim to describe an innovative methodology towards the synthesis of novel 2-thio-substituted-3*H*-phenothiazin-3-ones (**6a-l**) as potential candidates for the inhibition of leukotrienes, for the treatment of neurodegenerative disorders, and as anti-infective agents.

Results and Discussion

The initially proposed dual addition/oxidation step synthetic approach for our target molecules (**Scheme 1**) was adapted from previous work implemented on the compilation of a library of 2-alkylthio-1,4-benzoquinones [13] and 6,7-bis(alkylthio- or alkylaminosubstituted)quinoline-5,8-diones [14] which require four steps. First, the 2-alkylthio-1,4-benzoquinone (**3a-l**) would be formed by reacting 1,4- benzoquinone (**1**) with an alkylthiol (**2a-l**) in the presence of sodium periodate ($NaIO_4$) and distilled water

[15]. Second, the 2-thio-substituted-3*H*-phenothiazin-3-one (**6a-l**) would be formed by reacting 2-alkylthio-1,4-benzoquinone (**3a-l**) with 2-aminothiophenol (**5**) in the presence of sodium periodate and distilled water. Once the alkylthio group is attached to the 1,4- benzoquinone (**1**) to form 2-alkylthio-1,4-benzoquinone (**3a-l**) its resonance structure (**4a-l**) would activate the benzoquinoid ring by making the C-5 position electrophilic. This occurrence will allow a second nucleophile to attack at the C-5 electron deficient position. Because the nucleophilic attack does not involve leaving groups, an oxidizing agent must be present in order for the final targets (**6a-l**) to regain their oxidized form. Therefore, sodium periodate becomes the driving force for this methodology. One important observation for these experiments is that, even though there is an abundant amount of oxidizing agent present in the media, the formation of sulfoxides or sulfones is not observed when collecting our final targets. One byproduct that is always present on the nucleophilic attack of the 2-alkylthio-1,4-benzoquinones (**2a-l**) is the presence of 2,5-bisalkylthio-1,4-benzoquinones. However, these byproducts are unreactive on the second nucleophilic attack, especially when the reaction is run as a one-pot reaction. When 2-aminothiophenol (**5**) attacks the C-5 carbon of 2-alkylthio-1,4-benzoquinone (**3a-l**), the mechanism of the reaction is believed to proceed *via* the sulfur atom attacking the C-5 carbon instead of the nitrogen atom due to greater polarizability of the sulfur atom versus the nitrogen atom. Once the sulfur atom is attached to the benzoquinone ring and the molecule is oxidized by $NaIO_4$, an intramolecular condensation reaction between the amino group and the carbonyl group at the C-4 position takes place forming the desire target compounds. One advantage that was observed when producing either intermediates **3a-l** and/or final compounds **6a-l** was that all of these molecules are good chromophores and exhibit really intense colors under the visible light region. The 2-alkylthio-1,4-benzoquinone (**3a-l**) were in most cases a bright orange to red spot as observed by

thin layer chromatography (TLC) and the 2-thio-substituted-3*H*-phenothiazin-3-one (**6a-l**) had colorations that ranged from bright red to purple colors on TLC. Therefore, we exploited these chemical properties to easily monitor our intermediates and final products by TLC. Preparative TLC was the most efficient, yet the simplest method employed to identify, isolate, and purify our desired compounds. This versatility in identifying our desired compounds by color, allowed us to improve our step-wise route into a one-pot synthesis (**Scheme 2**). Starting from 1,4-benzoquinone (**1**) and one equivalent of an alkylthiol (**2h-l**) in the presence of four equivalents of sodium periodate, 2-aminothiophenol (**5**) would be added to the reaction vessel and it will furnish 2-thio-substituted-3*H*-phenothiazin-3-ones (**6h-l**) in yields ranging from 20 to 41%. These results are overall reaction yields corresponding to a four-step total synthesis. Here, the 2-alkylthio-1,4-benzoquinone intermediates (**3h-l**) were prepared *in situ*. The isolated yield for the step-wise methodology of compounds (**6a-g**) ranged from 18 to 78% and the synthesis of 2-alkylthio-1,4-benzoquinone intermediates (**3a-g**) ranged from 14 to 92% and were synthesized using a previously published method developed by Odens and elucidated by ^{1}H NMR [13]. Thus the one-pot approach becomes cost effective when considering handling of chemicals, time of production and laboratory costs. All of these results are summarized on **Tables 1** and **2**.

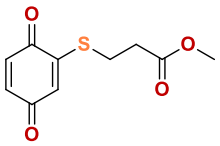
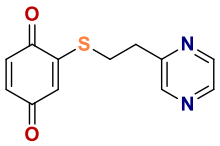
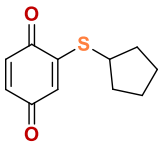
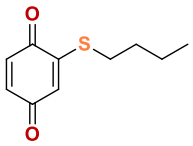
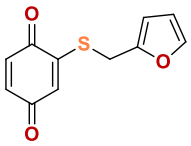
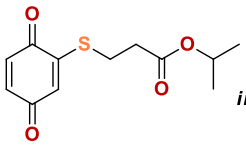
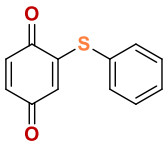
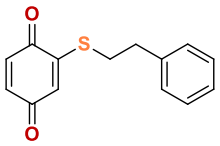
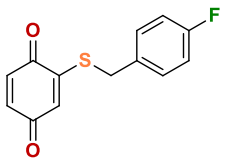
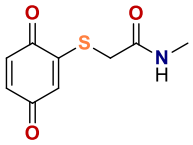
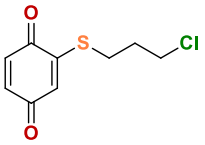
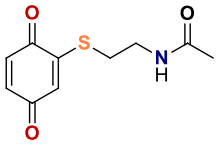
Entry	Compound	Yield	Entry	Compound	Yield	Entry	Compound	Yield
3a		53%	3e		92%	3i		*in situ*
3b		92%	3f		43%	3j		*in situ*
3c		70%	3g		14%	3k		*in situ*
3d		18%	3h		*in situ*	3l		*in situ*

Table 1. Synthetic results of 2-alkylthio-1,4-benzoquinone intermediates (**3a-l**). Isolated yields are shown. Compounds **3h-l** were not isolated but were confirmed on the one-pot synthesis by monitoring *via* thin layer chromatography.

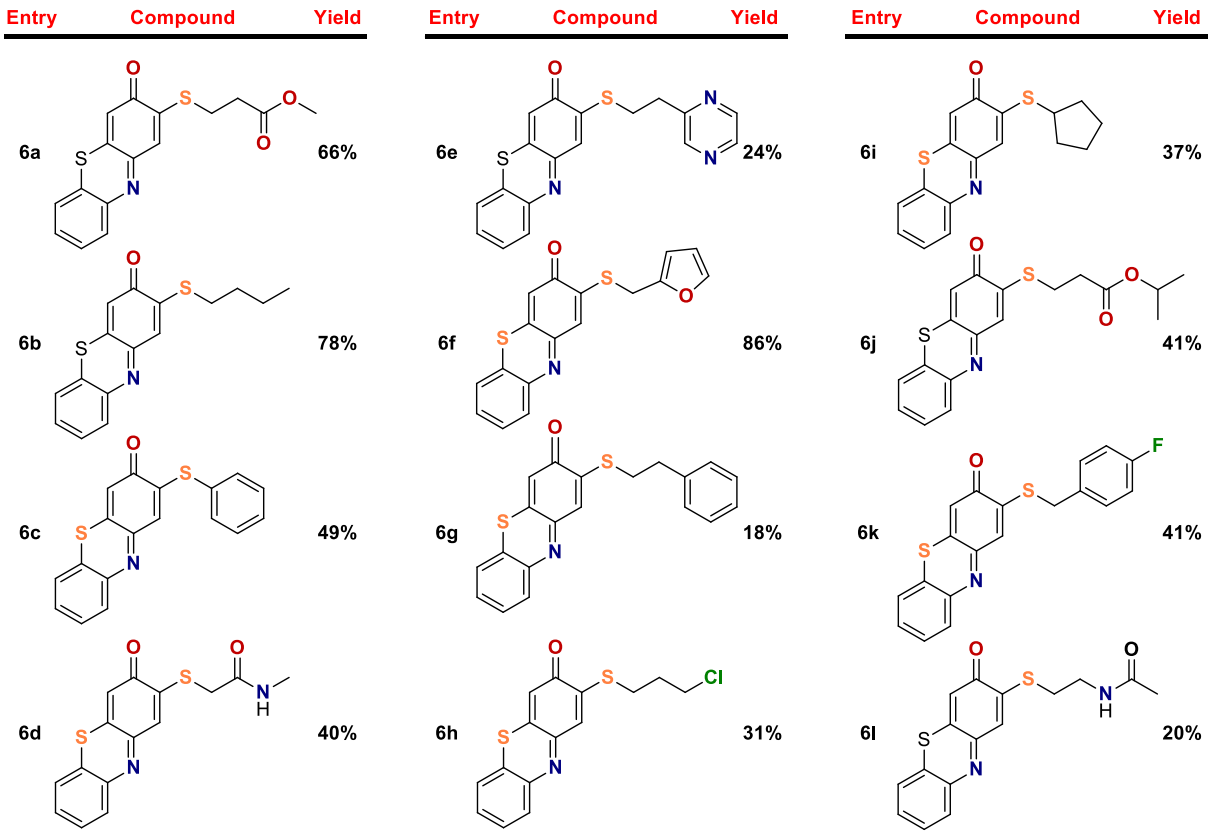


Table 2. Synthesis of novel 2-thio-substituted-3*H*-phenothiazin-3-ones (**6a-l**). Isolated yields are shown.

Conclusion

The one pot synthesis method for running the reactions is a more efficient means of using all of the required reagent equivalents to acquire the desired final product. It creates an atmosphere for the reaction in which the reaction components do not have to be tampered with separately as they are added individually to the reaction. This method for reactions is also time efficient and provides the luxury of being able to run several reactions at the same time. The one pot protocol allows for addition reactions that produce moderate to good yields without the need of good leaving groups. The choice of sodium periodate as the oxidizing agent proved to be an efficient one, since sodium iodate, its reduced product, can be easily filtered out during work up after the reaction is complete. The current investigation successfully establishes a novel

synthetic approach for 2-(alkylthio)-3*H*-phenothiazin-3-ones (**6a-l**). Twelve examples of these interesting compounds will be assessed for their activity as psychopharmacological drugs and other disorders of the central nervous system (CNS) or as anti-infective pharmacophores.

Supporting Information

Supporting Information File 1

Full experimental procedures and compound characterization.

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