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Synthesis of New Compounds by Selective Oxidation of Sulfide Group Present in Tetrahydropyridines †

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Abstract

This study explores the oxidation reaction of sulfide groups present in methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-(methylthio)phenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate towards the corresponding sulfoxide and sulfone, under green reaction conditions: ethanol as solvent, aqueous hydrogen peroxide as oxidant agent, phosphomolybdic acid as redox catalyst at atmospheric pressure. The optimum conditions for obtaining the sulfoxide were 0.2 mmol substrate, 0.34 mL H_2O_2 30% w/V, 1% mol phosphomolybdic acid, ethanol at 50 °C for 15 h; meanwhile, the sulfone was obtained at the reflux temperature. To our knowledge, neither the oxidation reaction of the sulfur atom in tetrahydropyridines nor the corresponding sulfoxides and sulfones are reported in the literature.

Keywords: catalytic oxidation; tetrahydropyridine; mild reaction conditions; sulfoxide; sulfone

1. Introduction

Tetrahydropyridines (THP), especially highly substituted ones, present diverse biological activities as anti-inflammatory [1,2], antimalarial [3], antimicrobial [4,5], anticancer [6,7], antioxidant [8,9], among others. Different synthetic methodologies for preparing substituted THP have been reported [10]. However, the multicomponent reaction involving two equivalents of an aniline, two equivalents of aromatic aldehyde, and one equivalent of β-ketoester, assisted by an acid catalyst, stands out since its high Atom Economy and operational simplicity [11,12].

As an acid catalyst for the multicomponent reaction, we employed commercial phosphomolybdic acid (PMo). This solid Keggin heteropolyacid possesses strong Brönsted acidity and can be used in catalytic amounts, unlike traditional inorganic acids, which are used stoichiometrically and require large amounts of alkali for neutralization, generating high volumes of waste [13,14]. Moreover, PMo presents redox properties, making it suitable for use as a catalyst in oxidation reactions for activating eco-friendly oxidizing agents, such as aqueous hydrogen peroxide. Our research group has successfully employed PMo under

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mild conditions for the synthesis of high-value-added compounds and the oxidation of alcohols, phenols, anilines, and sulfides [15–18].

This work focuses on THP obtained using 4-(methylthio)benzaldehyde. These THPs, with sulfur atoms, will then be oxidized to sulfoxide or sulfone, using hydrogen peroxide as the oxidant agent and PMo as a catalyst (Figure 1). In order to analyze the selectivity towards the corresponding sulfoxide and sulfone, different temperatures and amounts of oxidizing agent and catalyst were tested.

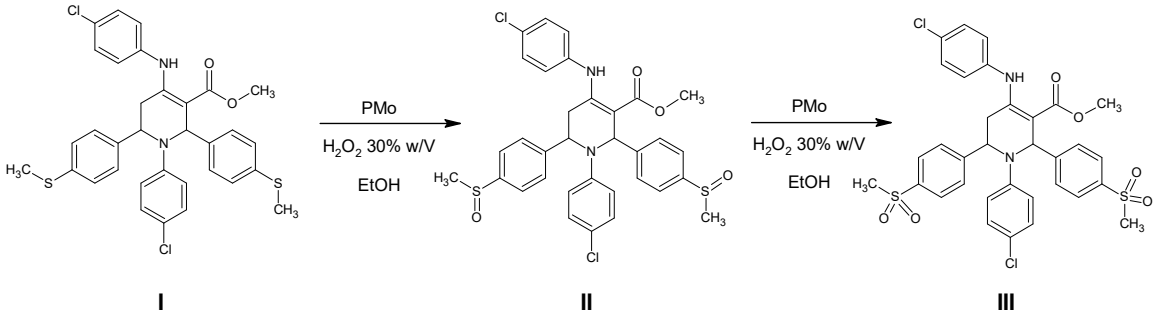


Figure 1. Oxidation reaction of THP.

The oxidation compounds, which are unreported in the literature, are expected to present biological properties, as pyridine analogues with proven biological activity. On the other hand, sulfoxides and sulfones are of interest in both industry and research, particularly due to their therapeutic properties [19,20].

2. Materials and Methods

The starting THP **I** (methyl 1-(4-chlorophenyl)-4-((4-chlorophenyl)amino)-2,6-bis(4-(methylthio)phenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate) was prepared via a one-pot multicomponent reaction between methyl acetoacetate, 4-chloroaniline, and 4-(methylthio)-benzaldehyde, in a 1:2:2 molar ratio, in methanol under reflux for 5 h. assisted by phosphomolybdic acid, which acts in this case as an acid catalyst.

The oxidation reaction was carried out in a glass reaction tube, in which **I** (0.1 mmol) was put in contact with PMo (as catalyst) and H_2O_2 30% w/V (as oxidant agent) in ethanol (2 mL). The reaction mixture was maintained under magnetic stirring in an oil bath. Various temperatures and amounts of the oxidizing agent were tested. The reaction was monitored by thin-layer chromatography, using petroleum ether/ethyl acetate (2:1) as eluent. The product was purified by column chromatography and characterized by melting point determination (Bioamerican apparatus) and Nuclear Magnetic Resonance (NMR) spectroscopy (Bruker Avance Neo 500 and Bruker 300 Ultrashield, Germany).

All reagents were commercial products used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF 254 plates (Merck KGaA, Darmstadt, Germany). Flash column chromatography was performed on silica gel (200–300 mesh).

3. Results and Discussion

Compound **I** was isolated from the reaction mixture as an insoluble solid after cooling, washed with fresh ethanol, dried, and recrystallized from *i*-propanol. A pale-yellow solid (52% yield) was obtained, mp: 157–159 °C, ^{1}H-NMR (500 MHz, Chloroform-*d*) δ 10.22 (s, 1H, NH), 7.29 (s, 1H Ar), 7.21 (s, 2H Ar), 7.19 (s, 1H Ar), 7.12 (d, 2H Ar), 7.06 (d, 4H Ar), 7.02 (d, 2H Ar), 6.43 (d, 2H Ar), 6.31 (d, 2H Ar), 6.29 (s, 1H H2), 5.07 (d, 1H H6), 3.95 (s, 3H Me), 2.85 (dd, 1H H5), 2.70 (dd, 1H H5), 2.50 (d, 6H MeS).

The oxidation of **I** was first carried out at 50 °C by adding 0.09 mL of H_2O_2 at the beginning of the reaction and an additional portion after 4 h (Table 1, Entry 1). Scaling up the reaction required a longer reaction time (Table 1, Entry 2). Next, a larger amount of oxidant agent was used (Table 1, Entry 3), which enhanced the reaction yield. Finally, performing the reaction under reflux led to a decrease in yield (Entry 4).

Table 1. Optimization of the oxidation reaction of THP **I**.

Entry	PMo (mg)	Temp. (°C)	H_2O_2 (mL)	Time (h)	Yield (%)	mp (°C)	Product
1 [a]	2	50	0.09 × 2	8	83	212–216	**IIa**
2 [b]	4	50	0.17 × 2	15	39	227.5–228.5	**IIb**
3 [b]	4	50	0.17 × 7	15	71	226–230	**IIc**
4 [b]	4	reflux	0.17 × 3	15	41	219–221	**III**

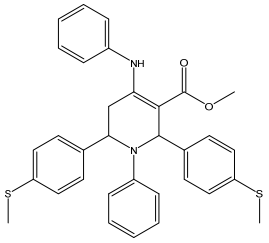
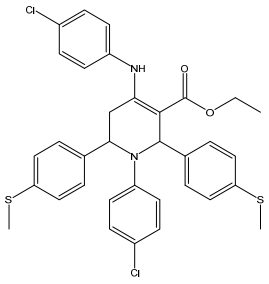
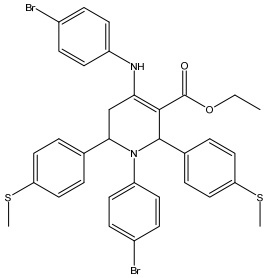
[a] THP **I** = 0.1 mmol, ethanol = 2 mL; [b] THP **I** = 0.2 mmol, ethanol = 4 mL.

Compound **IIb:** ^{1}H-NMR (300 MHz, Acetone-d_6) δ 10.33 (s, 1H NH), 7.90 (d, 4H Ar), 7.70 (d, 2H Ar), 7.51 (d,2H Ar), 7.26 (d, 2H Ar), 7.08 (d, 2H Ar), 6.59–6.50 (m, 5H H2,Ar), 5.64 (d, 1H H6), 3.96 (s, H Me), 3.15 (d, 2HH5), 2.11 (s, 6H MeSO).

Compound **III:** ^{1}H-NMR (500 MHz, Chloroform-*d*) δ 10.20 (s, 1H NH), 7.89 (m, 6H Ar), 7.51 (d, 2H Ar), 7.41 (dd, 1H, Ar), 7.33 (d, 2H Ar), 7.28 (s, 1H Ar), 7.16 (d, 2H Ar), 7.05 (d, 2H Ar), 6.43 (s, 1H H2), 5.27–5.22 (m, 1H H6), 3.99 (s, 3H Me), 3.09 (s, 6H $MeSO_2$), 2.87 (d, 1H H5), 2.79 (d, 1H H5).

The optimized reaction conditions to obtain the sulfoxide (0.2 mmol **I**, 0.34 mL H_2O_2 30% w/V, 1% mmol phosphomolybdic acid, 4 mL ethanol, 50 °C, 15 h) were extended to other THP prepared from different alkyl acetoacetates and substituted anilines (Table 2).

Table 2. Oxidation of different THP.

Started THP	t (h)	T (°C)	Yield (%)	mp (°C)
	9	50	52	210–213
	13	50	23	238–243
	12	50	35	174–177

4. Conclusions

In the present work, various THPs were efficiently synthesized through an atom-economical multicomponent reaction catalyzed by PMo acting as a solid acid. Furthermore, the sulfide groups of these THPs were selectively oxidized (to the sulfoxide at 50 °C and the sulfone at reflux) under green conditions using ethanol, hydrogen peroxide, and PMo, now operating as a redox catalyst. Following reaction optimization, three oxidation products were obtained and comprehensively characterized by melting point and NMR spectroscopy. To our knowledge, neither the oxidation reaction of the sulfur atom in THP nor the corresponding sulfoxides and sulfones are reported in the literature.

Author Contributions: E.M.C.: Methodology, data curation, formal analysis. M.B.C.M.: Conceptualization, methodology, investigation, supervision, data curation, formal analysis, writing—review and editing. M.C.M.: Methodology, data curation, formal analysis. V.P.: Conceptualization, methodology, investigation, supervision, data curation, formal analysis, writing—review and editing. G.P.R.: Conceptualization, methodology, writing—review and editing, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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