

SYNTHESIS OF SOME RHODANINE DERIVATIVES

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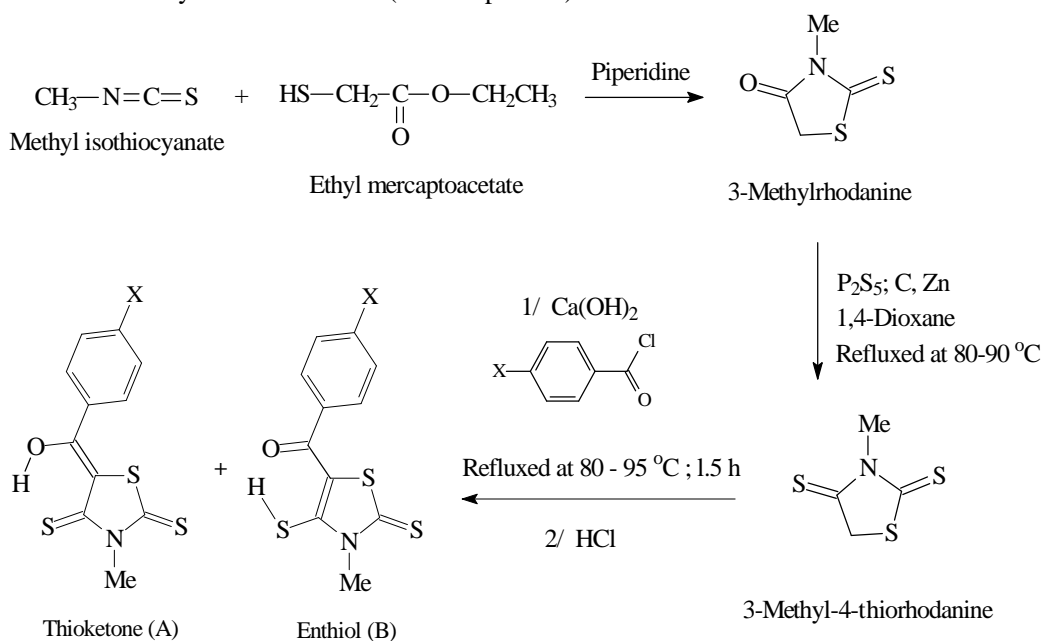
ABSTRACT: Thioketone and enthiol compounds were synthesized from methyl isothiocyanate and ethyl mercaptoacetate through thionation with P_2S_5 and acylation with aromatic carboxylic acid chlorides.

Key words: thiocompound, thionation, acylation, synthesis of derivatives of rhodanine, thioketone-enol - ketone-enthiol tautomerism.

1. INTRODUCTION

Organosulfur compounds are valued not only for their rich and varied chemistry, but also for many important biological properties. Transformation of a carbonyl group to thiocarbonyl group has been an important interest to synthetic organic chemists for many years. In this report, we studied on the transformation carbonyl group to thiocarbonyl group, and then acylated this thio-compound. We also studied on the influence of different substituents on the intramolecular hydrogen bond in these products from acylation and the thioketone-enol - ketone-enthiol tautomerism.

In the experiment, 3-methylrhodanine was first synthesized because it could not be commercially obtained. Second, it was converted to 4-thio-3-methylrhodanine by using diphosphorous pentasulfide. And then this thio-compound was acylated with different aromatic carboxylic acid chlorides (ten compounds).

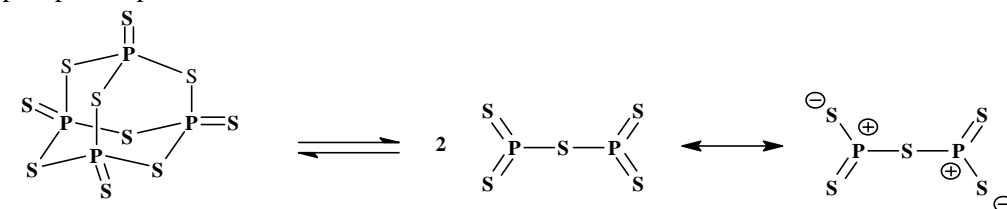


Scheme1. Series of the reactions conducting to the final products

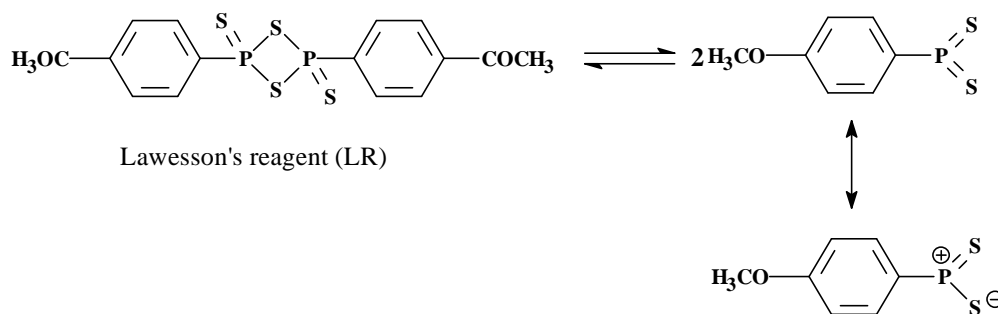
2. RESULT AND DISCUSSION

Two reagents - Diphosphorous pentasulfide (P_4S_{10}) and Lawesson's reagent (LR) - are the most widely used to transform a carbonyl group to thiocarbonyl group. Thionation of ketones to thioketones can be done by P_4S_{10} , but typically in rather low yield. In recent years Lawesson's reagent (LR) has replaced P_4S_{10} as the reagent of choice for many thionations. However, besides its high cost, LR results in the formation of by-products derived from the reagent itself, which cannot be easily removed by column chromatography, making the method more expensive.^[1,2,3,4,5,6,7,8]

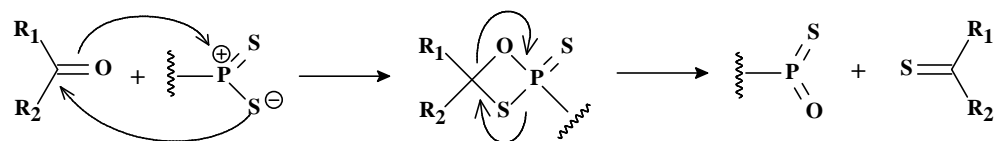
In this paper, we report a procedure for the conversion of ketone into thioketone using diphosphorus pentasulfide with charcoal and zinc dust in 1, 4-dioxane.^[9]



Diphosphorous pentasulfide (P_4S_{10})



Lawesson's reagent (LR)



Ketone

Thioketone

Scheme 2. Mechanism of the conversion of carbonyl group to thiocarbonyl group by P_4S_{10} or Lawesson's reagent.^[1]

The corresponding C-acylated derivatives were obtained by reaction of aromatic carboxylic acid chlorides with 4-thio-3-methylrhodanine. That the compound existed in the enthiol or thioketone form or the mixture of these two forms is based on the study of 1H -NMR spectra (presented in table 1). There was a remark: if the compound presented in thioketone-enol form (A), the hydroxyl group at C-6 chelated with thiocarbonyl ($C=S$) resonated at about 15.5 ppm. If the product presented in ketone-enthiol form (B), the mercapto group at C-4 chelated with carbonyl ($C=O$) resonated at about 7.00 – 7.13 ppm. Further more, the N-methyl group resonated at about 3.82 ppm relatively in lower field comparing to the one of (B), excepted for $X = -NO_2$ and $-N(CH_3)_2$.

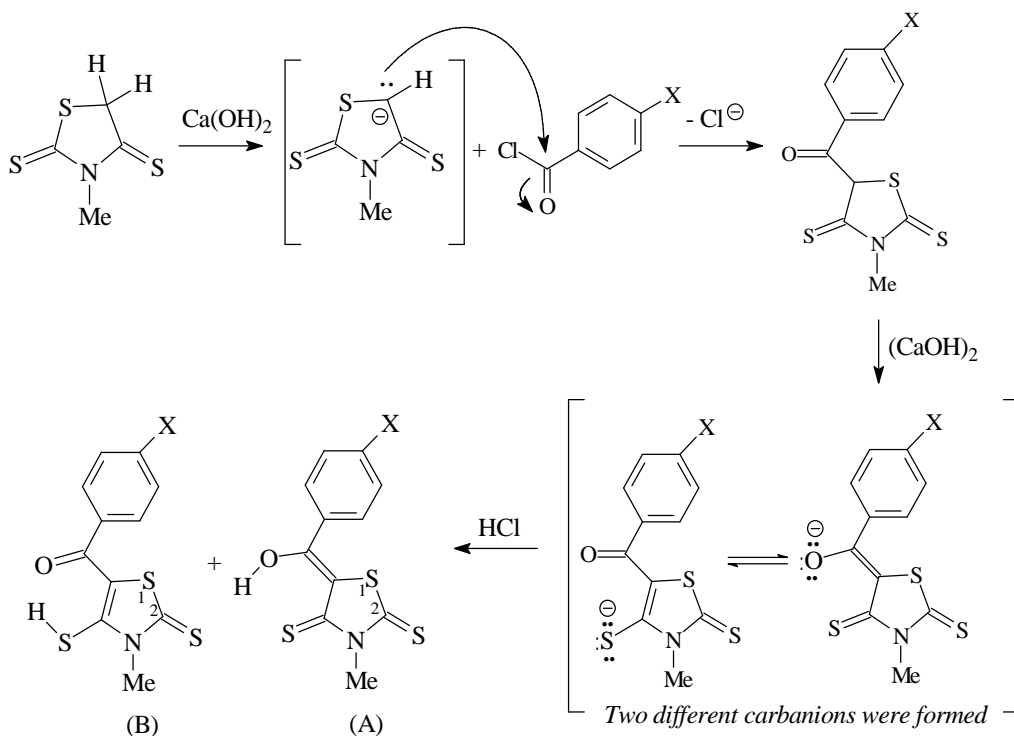
We also observed that there is an enthiol – thioketone tautomerism between product (A) and (B). The different substituents at the *para*-position of aromatic ring affect on the percentage of (A) and (B) in the mixture products. Especially, if X is -F or -CF₃, the product appeared completely in the form of thioketone (A). In contrast if X is -OCH₃ or -C(CH₃)₃, the product is totally enthiol form (B).

3. EXPERIMENTAL

3.1 Synthesis of 3-methylrhodanine

Methyl isothiocyanate (60.1 g, 0.5 mol) and ethyl mercaptoacetate (36.5 g, 0.5 mol) were mixed in a 250 ml conical flask, and then added 10 drops of piperidine. The reaction mixture was stirred for 2 hours at room temperature. After that the reaction flask was put in a refrigerator for 24 hours. No crystal was precipitated, so a solution of water: ethanol (1:1) (50ml) was added, and the mixture was refluxed for 1 hour. The color changed from yellow to orange-red. The solution was cooled to get crystalline products. After isolating by filtration, the product was recrystallized from ethanol.

3-Methylrhodanine: orange-red solid (mp 69.0 – 69.5 °C). ¹H-NMR (300 MHz, CDCl₃) δ : 4.01 (s, 2H), 3.38 (s, 3H). ¹³C-NMR (300 MHz, CDCl₃) δ : 201.3 (C2), 173.7 (C4), 35.6 (C5) and 31.2 (C6).



Scheme 3. Mechanism of synthesis of C-acylation 4-thio-3-methylrhodanine derivatives

3.2. Synthesis of 4-thio-3-methylrhodanine

P₂S₅ (22.23 g, 0.1 mol) and anhydrous 1,4-dioxane (100 ml) were mixed in a three-necked flask fitted with a reflux condenser and stirrer. The flask was heated in an oil bath and when

the temperature in the flask reached 80-90°C, 3-methylrhodanine (7.36 g, 0.05 mol) was added; the whole was stirred and refluxed at this temperature in 1 hour. The mixture changed from yellow to red. Active charcoal (1 g) and zinc dust (2 g) were put into the flask, and the whole was continued refluxing in 15 minutes. The reaction mixture was filtered through a 2-centimetre silica gel layer. After evaporating the solution under the reduce pressure, the product was recrystallized from ethanol to get yellowish-orange crystal.

4-Thio-3-methylrhodanine: yellowish-orange solid (mp 101.6 – 102.2 °C). ¹H-NMR (300 MHz, CDCl₃) *d*: 4.44 (s, 2H), 3.72 (s, 3H). ¹³C-NMR (300 MHz, CDCl₃) *d*: 203.7 (C2), 203.6 (C4), 46.2 (C5) and 35.7 (C6).

3.3. C-acylation of 4-thio-3-methylrhodanine derivatives

Calcium hydroxide (0.74 g, 10 mmol) was added to a solution of 4-thio-3-methylrhodanine (0.816 g, 5 mmol) in anhydrous 1,4-dioxane (10 ml). Then appropriate carboxylic acid chloride (5 mmol) was added with stirring to the mixture. The mixture was heated up slowly on an oil bath. When the temperature rose to 80 – 95 °C, stirring was continued for another 1.5 hours at this temperature. After reaction, the mixture was poured into 25 ml of 2 M hydrochloric acid. Within some minutes, crystals appeared. The crystals were removed by filtration, washed with water, and recrystallized from ethanol

Table 1. Percentage of (A) and (B) in the mixture products and their ¹H-NMR data

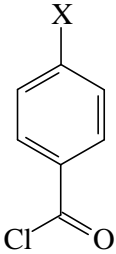
	X=	Percentage (%)		¹ H-NMR of (A) (CDCl ₃)		¹ H-NMR of (B) (CDCl ₃)	
		Ketone (A)	Enthiol (B)	-OH	-NCH ₃	-OH	-NCH ₃
	-NO ₂	30	70	15.53	3.83	7.10	3.68
	-CF ₃	100	0	15.56	3.82	-	-
	-Br	77	23	15.59	3.81	7.13	3.67
	-Cl	80	20	15.60	3.82	7.13	3.67
	-F	100	0	15.64	3.82	-	-
	-H	95	5	15.64	3.82	7.12	3.66
	-CH ₃	89	11	15.67	3.82	7.12	3.66
	-C(CH ₃) ₃	0	100	-	-	7.03	3.66
	-OCH ₃	0	100	-	-	7.02	3.67
	-N(CH ₃) ₂	57	43	-	3.66	7.11	3.68

Table 2. ¹³C-NMR data of product (A)

X=	C(X)	C-2	C-3'	C-4	C-5	C-6	C-7	C-8	C-9	C-10
-CF ₃	123.3	193.2	34.8	187.8	111.3	165.7	137.5	128.5	126.2	133.9
-Br		193.2	34.8	187.2	110.8	166.8	132.9	129.5	132.6	127.7
-Cl		193.2	34.8	187.16	110.8	166.8	129.6	129.5	129.6	132.5
-F		193.3	34.8	186.9	110.6	167.1	130.3	130.7	116.58	165.1
-H		193.6	34.7	186.8	110.9	168.6	134.2	128.1	129.2	132.8
-CH ₃	21.7	193.6	34.7	186.4	110.6	169.0	130.1	128.2	129.9	131.3
-C(CH ₃) ₃	35.2 C(CH ₃) ₃ 31.0 C(C(CH ₃) ₃) ₃	-	-	-	-	-	-	-	-	-
-OCH ₃	55.7	-	-	-	-	-	-	-	-	-

TỔNG HỢP MỘT SỐ DẪN XUẤT TỪ RHODANINES

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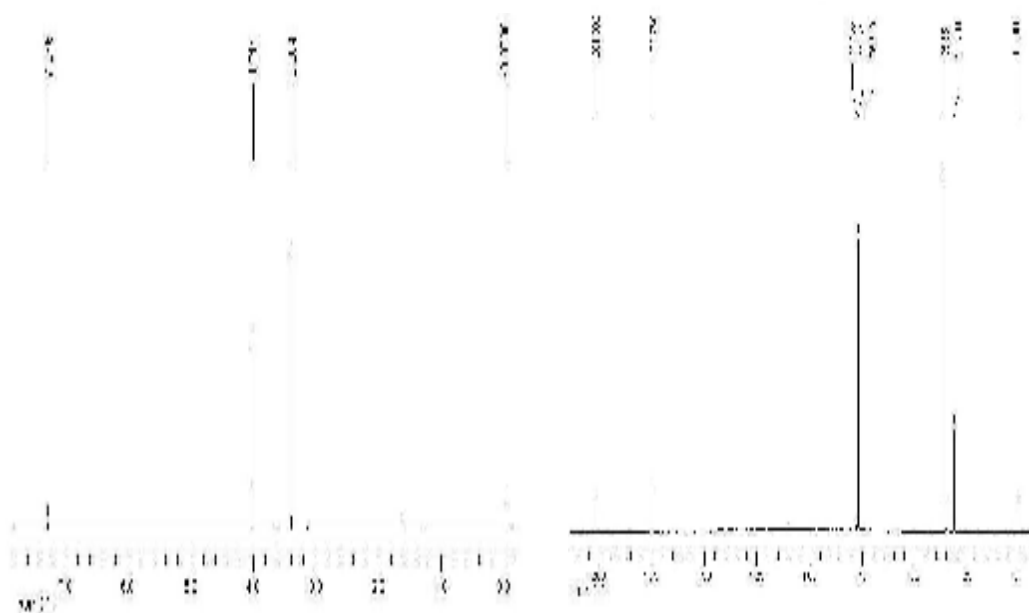
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TÓM TẮT: Hợp chất sulfur thường có hoạt tính sinh học hấp dẫn nên gần đây loại hợp chất này được các nhà hoá học rất quan tâm. Trong báo cáo này chúng tôi tổng hợp một số hợp chất entiol và tioceton từ metyl isotiocyanat và etyl mercaptoacetat thông qua phản ứng thio hóa và acyl hóa. Sản phẩm thu nhận được hiện diện ở một trong hai dạng đồng phân tioceton-enol - ceton-entiol, hoặc ở hỗn hợp của hai dạng trên tùy thuộc nhóm thế ở vị trí para của vòng thơm. Việc xác định cấu trúc hóa học của các hợp chất này được thực hiện dựa trên phổ ¹H-NMR và ¹³C-NMR.

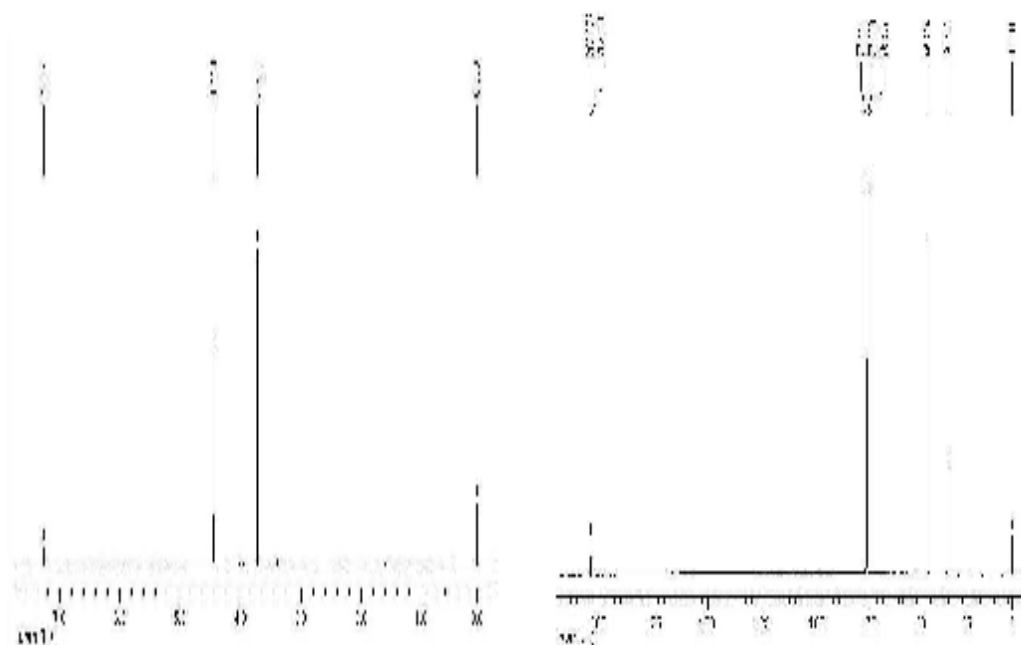
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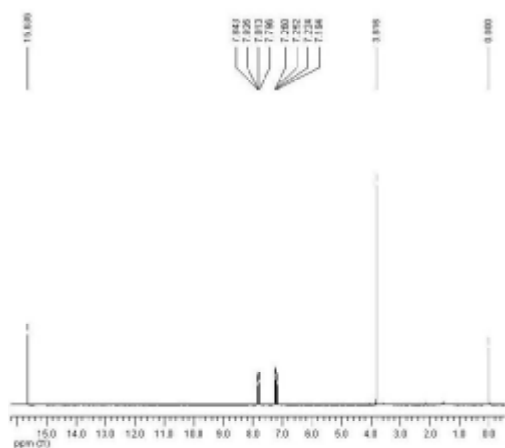
APPENDIX



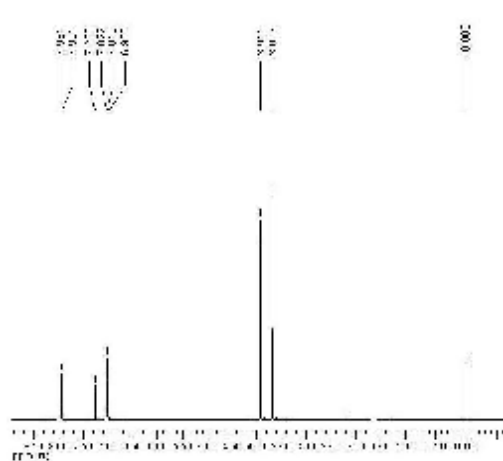
Appendix 1. ^1H and ^{13}C -NMR spectra of 3-methylrhodanine



Appendix 2. ^1H and ^{13}C -NMR spectra of 4-thio-3-methylrhodanine



Appendix 3. ^1H -NMR spectrum of thioketone form corresponding to substituent $\text{X} = -\text{F}$.



Appendix 4. ^1H -NMR spectrum of enthiol form corresponding to substituent $\text{X} = -\text{OCH}_3$.