Proceeding

The International Conference on Drug Development from Natural Resources

ICDDNR

Jambuluwuk Malioboro Boutique Hotel
June 30th, 2012

www.icddnr.com

ISBN : 978-979-18458-5-4

PROCEEDING

INTERNATIONAL CONFERENCE ON DRUG DEVELOPMENT OF NATURAL RESOURCES

Jambuluwuk Malioboro Boutique Hotel
June 30th, 2012

THE INTERNATIONAL CONFERENCE ON DRUG DEVELOPMENT FROM NATURAL RESOURCES YOGYAKARTA, INDONESIA, 2012

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Published by :
Faculty of Pharmacy, Ahmad Dahlan University
Jln. Prof. Dr. Soepomo, Warungboto, Yogyakarta
Indonesia

ISBN : 978-979-18458-5-4

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PREFACE FROM THE EDITORS

The proceeding was produced based on paper and posters presented at the International Conference on Drug Development from Resourses (ICDDNR) that was held in Jambuluwuk Malioboro Boutique Hotel, Yogyakarta, in June 30th, 2012.

This proceeding contains of research from various field in pharmacy including natural product chemistry, analytical chemistry, drug synthesis, drug formulation, pharmacology, clinical pharmacy and social pharmacy.

Hopefully, this proceeding will be useful for natural drug development and drug development in general. I would like to give appreciation for all member of editors that have been working hard to collect and review the manuscrip.

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WELCOME SPEECH FROM COMITTE

The trend back to nature made large impact on development of drug from natural resources. The development of drug from natural resources were addressed to prevention, diagnosis, therapy, as well as rehabilitation.

On the other hand, collaboration involving researchers, pharmacist, physician and other health professionals have many benefit in increasing the drug development and also application in health improvement.

Faculty of Pharmacy in celebrating 16th anniversary, successfully held an International Joint Conference " International Conference on Drug Development from Natural Resources (ICDDNR)". ICDDNR will be organized every 2 years in rotation by three universities (University of Ahmad Dahlan, University of Muhammadiyyah Malang and Guangxi Medical University.

We would like to express our gratitude and appreciation to all the writers in this proceeding, keynotes speakers, presenters, participants, member of steering committees and technical committees, as well as all of our colleagues for the invaluable contributions in this conference. We wish all participants will find this conference intellectually beneficial as well as fascinating.

Sincerelly,

Dr. Nurkhasanah, M.Si, Apt

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REMARK OF THE DEAN OF PHARMACY FACULTY AHMAD DAHLAN UNIVERSITY

Assalamu'alaikum wr wb

Alhamdulillahirrabilamin,

This kind day, on behalf of Faculty of Pharmacy Ahmad Dahlan University, I would like to come all of you in Yogyakarta. I am very pleased and grateful of your attention and participation in International Conference of Drug Discovery From Natural Resources.

This conference is organized by collaboration among Ahmad Dahlan University, Muhammadiyah Malang University and Guangxi University. This conference is also held to celebrate the 16th Anniversary of Pharmacy Faculty Ahmad Dahlan University. As part as of university collaboration, this conference will be held continually every year in Muhammadiyah Malang University and Guangxi University.

Drug discovery of the natural resources is announced as the major theme of this conference. As the second biodiversity in the world, Indonesia is favorable for natural product development especially in drug discovery. The Asian natural drug discoveries have been developed long years ago by empirical usage. This time, the development of the natural drug discovery showed a high acceleration, in line with the progress of science and technology. This is indicated by a lot of researches in discovery of bioactive compounds and natural product formulations that were produced by universities and research institutions. Even today natural medicine became a mainstay commodity for some countries in Asia. Communication and discussion of all the researchers from various fields related to the development of natural resources is a must in order to accelerate the discovery of natural medicines. Our expectation, this conference to be involved of that part.

Special thanks to the plenary speakers from Indonesia, Malaysia and China. Thanks you very much for your attendance and experiences that will be shared. I also appreciate the participation of both oral and poster speakers or other participants who wish to know the development of the discovery of natural medicines.

By attending this conference, I hope there will be many collaboration in the future, especially among the universities to develop the evidence based drug from the natural resources. Please, make networking during the whole day of conference.

Finally, my high appreciation to the committee which has organized this event and to all the participants, have a nice conference. Thanks you very much

Wassalamu'alaikum wr wb

ISBN : 978-979-18458-5-4

SPEECH OF THE DEAN OF HEALTH SCIENCE FACULTY OF UNIVERSITY OF MUHAMMADIYAH MALANG

Bismillahinahmanirrahim

The Honorable,

Rector and Academic staffs of Ahmad Dahlan University, Indonesia

Rector and Academic staffs of Guangxi Medical University Nanning China.

Rector and Academic staffs of University of Muhammadiyah Malang, Indonesia

Ladies and gentlemen, all the conference participants

Assalamu'alaikum Warahmatullahi Wabarakatuh

We must say thankful to Allah SWT, that we have been given a chance to attend this International Conference of Drug Development from Natural Resources (ICDDNR) in Ahmad Dahlan Universi6,, and on behalf of the steering committe, I welcome you to the beautiful ci5, of Yogyakarta, Indonesia.

This year's meeting is a very good moment to infoduce the biodiversif of Indonesia and its potential as natural dnrg resources. This is also a great time for both, researchers and practitioners; especially in the field of natural drug resources, to share and stengthen their knowledge in purpose to give a meaningful contribution for health and humanity. We really hope that at the end of this conference, there will be new ideas and latest technologr of pharmacy and natural medicine that could be introduced to the world. Furthermore, those ideas are not only written on the paper but can also be put into practice of health and medical.

Ladies and gentlemen,

The Universities of Muhammadiyah are built in Indonesia as a commitrnent of the Organisation of Muhammadiyah to play a part in the development of science and technology. As the member of this conference's committe, along with Ahmad Dahlan University and GuangXi Medical University China, University of Muhammadiyah Malang is committed to firlfil this purpose.

We sincerely thank the university representatives and all the participants for their valuable contributions to. this conference. In addition to the outstanding scientific prograrn, we also hope that you can enjoy the pulture and beautiful sights of Yoryakarta, Indonesia. May all of you have a great and memorable time in Indonesia.

Billahi fi sabilil haq, fastabiqul khairat

Wassalamu'alaikum warahmatullahi wabarakatuh

Yogyakarta, 30 June 2012

Dean of Faculty of Health Science

University of Muhammadiyah Malang

Tri Lestari Hadayani, M.Kep, Sp. Mat

CONTENS

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SYNTHESIS OF 4-CHLOROBENZOYLTHIOUREA FROM 4-CHLOROBENZOIL CHLORIDE AND THIOUREA WITH DIFFERENT HEATING TIME AND TEMPERATURE

Dini Kesuma
Faculty of Pharmacy University of Surabaya

Abstract

To find new compounds acting on central nervous system (CNS), the research of structure modification of benzoylthiourea (4-chlorobenzoylthiourea) uses the Topliss approach model by acylating the thiourea with derivated benzoyl chloride. These compounds have higher lipophilic and electronic properties compared to the lead compound benzoylthiourea, with the expectation of the increase of the central nervous system depressant. 4-chlorobenzoylthiourea had been made by reacting 4-chlorobenzoyl chloride with thiourea in tetrahydrofuran. The heating temperatures were 90° C, 100° C, 110° C and 120° C with the percentage yields of 28,99%, 41,07%, 48,79% and 45,14%. The highest percentage yield of 4-chlorobenzoilthoiurea was given at 110° C. The heating time was 0.5 hours; 1 hours; 1.5 hours and 2 hours with the percentage of the product of 4-chlorobenzoylthiourea compound were 41,65%; 50,84%; 46,39% ; 43,18%. The highest percentage yield of 4-chorobenzoylthiourea was obtained 1 hour of heating time. The purity test of the synthesis product was shown by the single spot on the Thin Layer Chromatogram (TLC) and small difference of melting point. Characterization of the products of the synthesis was based on the analysis with Ultraviolet (UV) and Infra Red (IR) spectrophotometer, ^{1}H-NMR spectrometer and gas chromatography mass spectrometer (GC-MS), it was concluded that the structure of the synthesis product were in accordance to the prediction.

Keyword : *4-chlorobenzoylthiourea, synthesis, heating time, heating temperature.*

ISBN : 978-979-18458-5-4

INTRODUCTION

People with stress and mental disorders are usually treated with the central nervous system depressant drugs, which inhibits the activity of the central nervous system, such as the drugs from sedative-hypnotic class. The use of these medications occasionally causes moderate to severe side effects with not necessarily optimal activity. Overdose can lead to coma and death due to depression of vital centers in the medulla of the brain and long-term use causes tolerance and physical dependence (Siswandono dan Soekardjo, 2000).

Barbiturate derivatives are the first sedative hypnotics that often used. It is a cyclic ureida derivative and its activity has been known as a depresant of the central nervous system. With the passage of time demands of a new drug discovery is increasing, because there are no good medications for specific diseases and the discovery of various side effects resulting from the use of drugs that are already known, so further studies is done to develop the structure of the existing drugs or search and find a new cure. The drug discovery is intended for the treatment of certain diseases, improving the drug activity , lowering adverse side effects or toxicity, and improving the drug selectivity (Block, 1991).

Siswandono (1998) have modified the structure of molecules of a compound used as a sedative hypnotic drugs by synthesizing benzoilurea which is an acyclic ureida from the acylation reaction of a primary amine groups of urea with benzoyl chloride.

Kesuma (2004), have synthesized benzoylthiourea by doing an acylation reaction between one of the NH2 group of thiourea with benzoyl group of benzoyl chloride.

From the results of the activity assay, it turns out that the compounds synthesized have a depressant effect of central nervous system. The benzoylthiourea derivative structure modification was done by replacing the O atom in the urea with a S atom into thiourea; and because the electro negativity of the O atom is greater than the S atom, the modification is expected to increase the lipophilicity of benzoylthiourea derivative compounds.

In conducting the drug development, the structure modification of the compound can be done in several ways, one of which is to use the Topliss approach model. The structure modification of the compound with Topliss approach model is done by modifying several functional groups with specific lipophilic, electronic, dan steric properties. The lipophilic properties can be increased by inserting a non-polar groups, such as alkyl groups on the aromatic ring. In addition, electronegative substituent such as halogen groups can be inserted into the aromatic ring to increase the electronic properties (Siswandono and Soekardjo, 2000).

Theoretically benzoylthiourea compounds have lipophilicity values ??(logP) of 1.12. With the presence Cl atom on the aromatic ring the lipophilicity properties (log P) would be increased to 1.68, while the optimal log P value of the central nervous system depressant is 2 (Siswandono and Soekardjo, 2000).

In a synthesis of organic compound, it is expected to produce the final product synthesis as much as possible, so the factors that influence the percentage of the synthesis, such as the temperature and duration of heating, should be noted. Temperature and duration of heating is required in almost every organic chemical reaction to increase the kinetic energy which is to increase inter-particle collisions/impacts that affects the reaction.

Katherine (2005) has conducted the synthesis of benzoylthiourea at a temperature of 90°C, 100°C, 110°C, and 120°C for 1.5 hours. Most of the products of the synthesis was obtained at a temperature of 110°C. In this

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study, the same heating temperatures, which were 90°C, 100°C, 110°C, and 120°C, were used with the duration of heating of 1.5 hours. Heating temperature which indicates the largest percentage of products was used as a reference for the optimization of the heating, which were 0.5, 1.0, 1.5, 2.0 hours.

The purity of compounds synthesized were tested with melting point determination and thin layer chromatography. Structural characterization was performed using UV Spectrophotometer, Infrared Spectrophotometer (IR), Nuclear Magnetic Resonance Spectrometer (1 H-NMR), Gas Chromatography - Mass Spectroscopy (GC-MS).

2. THE OBJECTIVES OF THE STUDY

The objectives of this study are :

a. To find out the percentage of the synthesis products on different temperatures and heating time.

b. To find out the temperature and duration of heating that can result in the largest percentage of the synthesis products of 4-chlorobenzoylthiourea.

THE BENEFIT OF THE STUDY

With this study, it is expected to provide useful information on the effects of temperature and heating time on the percentage of the products synthesis of compounds 4-chlorobenzoylthiourea to be further developed in order to obtain compounds with more activity of the central nervous system deppresant (CNS Depressant).

METHODS

Materials for the synthesis of 4-chlorobenzoylthiourea

a. 4-chlorobenzoyl chloride (Merck)
b. Thiourea (Merck)
c. Tetrahidrofuran (THF) (Merck)
d. Natrium bicarbonate (Merck)
e. Ethanol 96 % p.a (Merck)

Materials for the TLC test

a. Silica Gel F254 (Merck)
b. Methanol p.a (Merck)
c. Ethanol 96 % p.a (Merck)
d. Ethyl acetate p.a (Merck)
e. Acetonitrile p.a (Merck)

Materials for the identification of 4-chlorobenzoylthiourea

Ethanol 96 % p.a pro UV spectrometer (Merck)

KBr pro infrared spectroscopy

DMSO-d6 pro MRI Spectroscopy

Ethanol pro GC-MS

Instruments

a. Analytical balance *'Ohaus'* (Model AS120, Serial No 2325)
b. Laboratory glasswares
c. Magnetic stirrer and magnetic stirring bars (type Pyro-Mag, Labinco)
d. Thermometer
e. Buchner Funnel
f. Vacuum pump (VP 11-16)
g. Oven (Memmert type)
h. Fisher Johns Melting Point Apparatus
i. Chromatography chamber (Camag)
j. Capillary tubes
k. Hitachi U-2001 UV-Spectrophotometer
l. Spectrophotometer "Jasco FT/IR-5300"

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m. Spectrometer "Hitachi FT-NMR-R 1900"

n. Gas Chromatography - Mass Spectrometry "Hewlett Packard 5972 Series Mass Selective Detector and 5890 Series III Plus Gas Chromatograph"

Procedures

The Synthesis and Recrystallization of 4-chlorobenzoythiourea

Thiourea, with the weight of 3.805 grams (equivalent to 0.05 mol) was suspended in 25 ml of Tetrahydrofuran in 250 ml beaker. Meanwhile, a solution of 4-chlorobenzoyl chloride 0.025 ml (4.375 g) in 15 ml of THF solvent was made. After that, the solution of 4-chlorobenzoyl chloride in THF was added dropwise using the dropping funnel into the thiourea suspension in the beaker at room temperature. Then, the mixture of the solutions was stirred using a heating magnetic stirrer (magnetic stirrer with a hot plate) at a temperature of 90° C for 1.5 hours (based on previous study) starting from the time when the temperature desired was reached, so that the reaction worked perfectly. The process was repeated with the heating temperatures of 100° C, 110° C, and 120° C.

For the optimization of heating, the mixture was stirred and heated using the heating magnetic stirrer at a temperature of 110° C (based on the optimal temperature of the previous study) for 0.5 hours, 1 hour, 1.5 hours, and 2 hours each.

The product of the reaction (which was yellow thick substance (ointment mass)) was added a saturated sodium bicarbonate solution with stirring until the mixture didn't produce foam or bubble of gas, and then it was washed with 2 x 25 ml of water, and filtered with Buchner funnel and flask connected with vacuum pump.

The mixture then was transfered into Erlenmeyer flask 250 ml and added hot Ethanol 96% p.a with continuous heating at temperature of 70° C - 80° C on a heating magnetic stirrer until it was exactly dissolved. After that, the solution was cooled down quickly with ice bath until the crystals of 4-chlorobenzoylthiourea was formed. The crystals were then filtered with buchner funnel and flask connected with vacuum pump. The separated crystals were washed with 10 ml of ethanol 96% twice, then they were transfered to a weighed petry disk and dried in

Temperature (°C)	Replication	The weight of practical products (g)*	Percentage of the synthesis products (%)	Mean weight (%)
90° C	1	1,5476	28,8596	28,99
	2	1,5523	28,9641	
	3	1,5625	29,1375	
100° C	1	2,1635	40,3449	41,07
	2	2,2226	41,4470	
	3	2,2208	41,4135	
110° C	1	2,6540	49,4918	48,79
	2	2,5821	48,1510	
	3	2,6134	48,7347	
120° C	1	2,4210	45,1469	45,14
	2	2,4130	44,9977	
	3	2,4280	45,2773	

* The weight of theoretical products : 5,3625 grams

(The synthesis was conducted for 1.5 hours based on the previous study)

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Duration of heating (hours)	Replication	The weight of practical products (g)*	Percentage of the synthesis products (%)	Mean weight (%)
0.5	1	2.2940	42.7786	41.65
	2	**2.1629**	**40.3338**	
	3	2.2433	41.8331	
1.0	1	2.7696	51.6475	50.84
	2	**2.6831**	**50.0345**	
	3	2.7254	50.8233	
1.5	1	2.4622	45.9152	46.39
	2	**2.5012**	**46.6424**	
	3	2.5001	46.6219	
2.0	1	2.3313	43.4741	43.18
	2	**2.3240**	**43.3380**	
	3	2.2910	42.7226	

* The weight of theoretical products : 5,3625 grams

(The synthesis was conducted at a temperature of 110° C based on the optimization results of the experiment above)

the oven at the temperature of 50° C. The dried crystals was then weighed to calculate the percentage of 4-chlorobenzoylthiourea crystals produced.

Analysis and Identification of The Purity of The Synthesis Product

The analysis and purity identification of the synthesis product was done using TLC, Melting Point determination, UV-Spectrophotometry, Infrared Spectrophotometry, Nuclear Magnetic Resonance (^{1}H-NMR), and Mass Spectrometry.

The Synthesis Product Of 4-Chlorobenzoylthiourea

4-robenzoylthiourea was synthetized through the acylation of 4-chlorobenzoyl chloride (0,025 mol; 4,375g) with thiourea (0,05 mol; 3,805 g). The characteristics of the product synthetized were light yellow powder with specific smell and bitter taste.

The Percentage of The Products of 4-Chlorobenzoylthiourea

The Purity Analysis Results Of The Synthesis Product

The result of Thin Layer Chromatography analysis with the mobile phase (of) Ethanol:Chloroform (3:1)

Temperature	Replication	R_f
90° C	1	0,86
	2	0,86
	3	0,86
100° C	1	0,86
	2	0,86
	3	0,85
110° C	1	0,86
	2	0,85
	3	0,86
120° C	1	0,86
	2	0,86
	3	0,86

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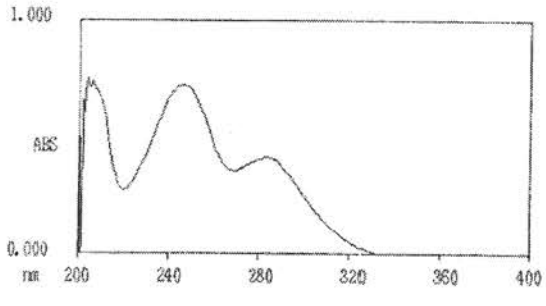
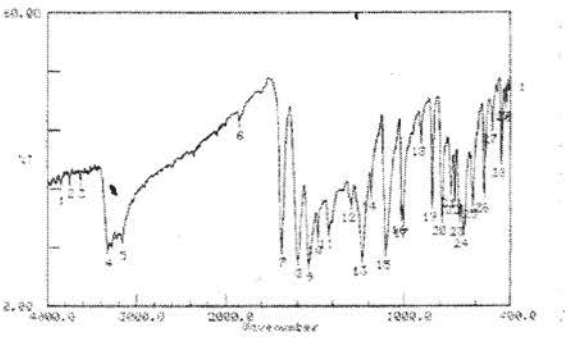
Duration of Heating (hours)	Replication	Rf
0,5	1 2 3	0,87 0,87 0,86
1.0	1 2 3	0,87 0,87 0,87
1,5	1 2 3	0,86 0,87 0,87
2,0	1 2 3	0,87 0,87 0,87

The Melting Point of 4-chlorobenzoylthiourea (Synthesis Product)

Temperature	Replication	Melting point (°C)
90° C	1 2 3	211-213 211-213 211-213
100° C	1 2 3	211-213 211-213 211-213
110° C	1 2 3	211-213 211-213 211-213
120° C	1 2 3	211-213 211-213 211-213



The UV Spectrum of 4-chlorobenzoylthiourea Synthetized in Ethanol Solvent (λmax = 246 nm and 282.5 nm)



The Infrared Spectrum of 4-chlorobenzoylthiourea Synthesis Product

Duration of Heating (hours)	Replication	Melting Point (°C)
0,5	1 2 3	211-213 211-213 211-213
1,0	1 2 3	211-213 211-213 211-213
1,5	1 2 3	211-213 211-213 211-213
2,0	1 2 3	211-213 211-213 211-213

The average melting point of the compound synthesized is 211-213°C, with the range of 2° C.

The Identification Result Of The Synthesis Product

The Result of Ultraviolet (UV) Spectrophotometry e Result of Infrared Spectrophotometry

The Infrared Wavenumbers/wavelengths of 4-Chlorobenzoylthiourea

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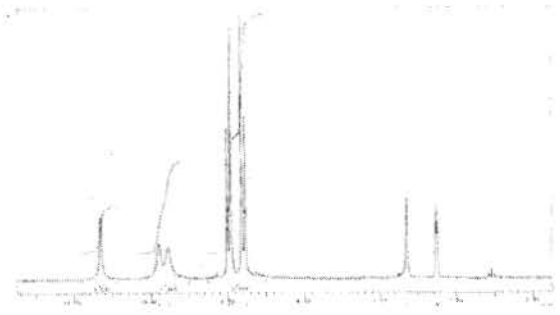
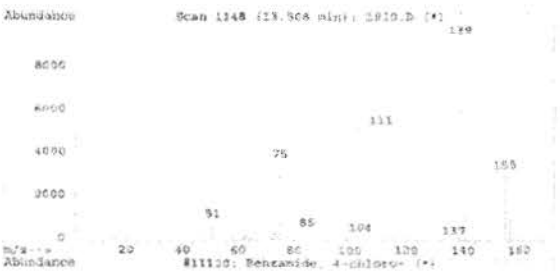


^{1}H-NMR Spectra of 4-chlrobenzoiltiourea Synthesis Product

Functional Groups	Wavenumbers (cm^{-1})	Wavenumbers (cm^{-1}) of Synthesis Product	No. of Spectra
-NH2 (stretch)	3500-3100	3325,58	4
-NH- (stretch)	3500-3350	3159,68	5
-C=O (stretch)	1680-1700	1685,94	7
aromatic -C=C- (stretch)	1600-1475	1597,20 dan 1535,48	8
-C=S	1250-1020	1232,62 ; 1101,45	13 ; 15
aromatic -C-Cl (stretch)	1170-1103	1103,07	17

The Result of ^{1}H-RMI of 4-chlorobenzoylthiourea Synthesis Product

Chemical Shift	Integration values	Multiplicity	H atom from the group of
7,516	2	Doublet	2 H atoms from the substituted aromatic ring (c)
7,872	2	Doublet	2 H atoms from the substituted aromatic ring (c)
9,522	1	Wide singlet	1 H atom from NH2 (b)
9,774	1	Wide singlet	1 H atom from NH2 (b)
11,289	1	Wide singlet	1 H atom from NH (a)



The Result of Nuclear Magnetic Resonance Spectrometry (^{1}H-NMR)

GC-MS Spectra of 4-chlorobenzoylthiourea Synthesis Product

The m/e Data of 4-chlorobenzoylthiourea Synthesis Product

No	m/e	Fragment Compounds
1	155	[(C6H4-Cl-CONH2)+]
2	139	[(C6H4-Cl-CO)+]
3	111	[(C6H5-Cl)+]
4	75	[(NH-CS-NH2)]
5	51	(C4H3)+

CONCLUSION

Based on the study results, 4-chlorobenzoylthiourea can be synthetized through the acylation of 4-chlorobenzoyl chloride with the thiourea. At heating temperatures of 90° C, 100° C, 110° C and 120° C, the percentage of the products obtained respectively were : 28,99%, 41,07%, **48,79%** and 45,14%. The synthesis products of 4-chlorobenzoylthiourea with the largest percentage was obtained at the heating temperature of 110° C.

As for the duration of heating of 0.5 hours, 1 hour, 1.5 hour and 2 hours; the percentage of the products obtained respectively were 41.65%, **50.84%**, 46.39% and 43.18%. The synthesis products of 4-chlorobenzoylthiourea with the largest percentage was obtained 1 hour heating.

ACKNOWLEDMENT

Siswandono, Harry Santosa, Okky Nugraha, Lini Hapsari

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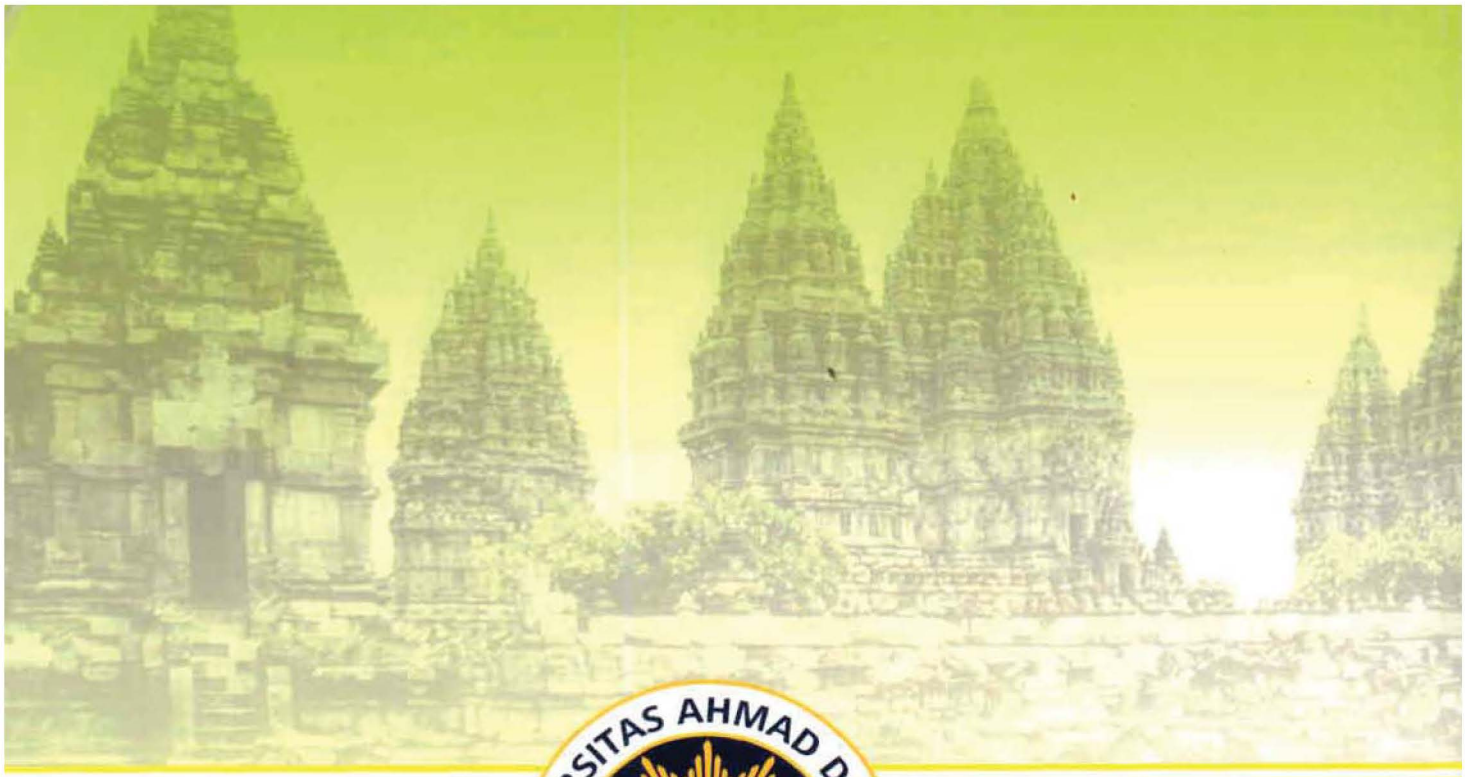

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