Charles University in Prague
Faculty of Pharmacy in Hradec Králové
Department of Inorganic and Organic Chemistry

Diploma Thesis

Synthesis of substituted arylguanidines as potential drugs VII

Supervisor: PharmDr. Karel Palát CSc.

Hradec Králové, 2012

Nasir Bromand

Acknowledgments

I would like to thank Dr. Karel Palat and the department of Inorganic and Organic Chemistry for giving me the opportunity to take part in their research. Dr. Palat granted me a volunteer position in his laboratory to extend his research since my first year of studies at the Faculty of Pharmacy, Charles University. For the past three years, Dr. Palat has been an excellent supervisor and has taught me new techniques and excellent laboratory practice.

Abstract

Pathological fungi carry the ability to cause serious medical problems and moreover cause various diseases. Drug therapy and new active compounds against these medical problems are still being researched. The long-term objective is to uncover the active compounds at the Faculty of Pharmacy, Charles University. In our study, we synthesized 3-(4-bromophenyl)-1,1-diethylguanidine, and 2 novel compounds: 3-(4-dodecylsulfanylphenyl)-1,1-diethylguanidine and 3-(3-bromophenyl)-1,1-diethylguanidine. We also studied the oxidation of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate, thus, making it the third novel compound 1-(4-tetradecylsulfonylphenyl)guanidinium nitrate we synthesized.

Abstrakt

Patologické plísně jsou vážným medicínským problémem, protože způsobují řadu onemocnění. Léková terapie a nové aktivní sloučeniny proti těmto chorobám jsou stále studovány. Našim dlouhodobým cílem na Farmaceutické fakultě Univerzity Karlovy je najít nové aktivní sloučeniny.

Během předkládané studie byl syntetizován 3-(4-bromfenyl)-1,1-diethylguanidin a dvě nové sloučeniny: 3-(4-dodecylsulfanylfenyl)-1,1-diethylguanidin a 3-(3-bromfenyl)-1,1-diethylguanidin. Taktéž byla studována oxidace 1-(4-tetradecylsulfanylfenyl)guanidinium nitratu a připravena třetí nová sloučenina 1-(4-tetradecylsulfonylfenyl)guanidinium nitrat.

Table of Contents

1. INTRODUCTION

In humans, fungal infections or mycoses are able to cause various range of diseases. Mycoses infect humans superficial, which involves the skin, cutaneous, which involves hair, nail or disseminated infection involving major organs such as the brain, heart, lungs, liver, spleen, and kidneys. There are many possible ways fungal infections can be classified, which include site of infection, route of acquisition, and type of virulence. Classification by site of infection can be superficial, cutaneous, subcutaneous, and deep[1]. Superficial mycoses essentially elicit no inflammation. However, subcutaneous mycoses develop an inflammatory response. Deep mycoses involve the lungs, abdominal viscera, bones and or central nervous system. The most common portals of entry are the respiratory tract, gastrointestinal tract, and blood vessels. The route of acquisition can be designated as exogenous or endogenous in origin. Airborne, cutaneous, or percutaneous routes can transmit exogenous acquired fungal infection. Endogenous fungal infection may be acquired from colonization or reactivation of a fungus from an underlying infection. Lastly, classification according to virulence can be categorized as primary pathogens, which may establish in a normal host, or as opportunistic pathogens, which requires some compromise of host defenses in order for infection to become established.

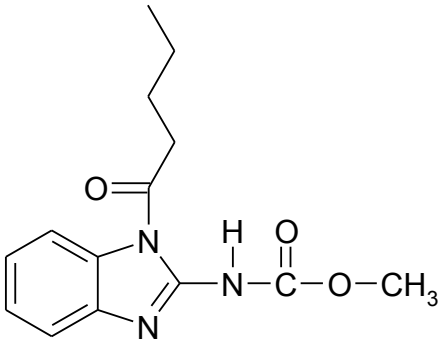
1.1 Problems of mycoses

The population at risk for invasive fungal infections continues to expand beyond patients with the acquired immunodeficiency syndrome. Risks extend to those immunosuppressed due to therapy for cancer, organ transplantation, and those undergoing major surgical procedures. These immunosuppressed patients are at a high risk of developing invasive fungal infections[2]. As the population at risk continues to expand so also does the spectrum of opportunistic fungal pathogens infecting these patients also continue to increase. Early detection and effective treatment are often difficult with deep invasive mycosis involving the lungs, bones, and or central nervous system. Thus, the development of new approaches to diagnosis and treatment of invasive fungal infections is the subject of our research.

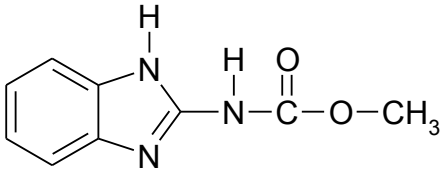
1.2 Current state of knowledge

Presently, antimycotics[3] are used to treat superficial, cutaneous, or disseminated mycosis. Antimycotics, however, lack in variety and are extremely limited. Azole and its derivatives, today, are used for standard therapy. Examples of azole antifungals include: imidazoles such as miconazole or ketoconazole, triazole such as fluconazole or itraconazole, or thiazole such as abafungin. However, if the patient is allergic, pregnant, or resistant to azole antifungals there are no other options of antimycotics to offer to the patient. Thus, leading to hospitalization and intravenous therapy of Amphotericin B.

Moreover, fungi are not only harmful to the human body but they are also harmful to agricultural products and plants. Fungi attack produce as it is being delivered, resulting in a large loss for the agricultural industry. In this case, antimycotics can also be used for the preventive protection of products and for the treatment and prevention of grown plants. However, in spite of antimycotics, guanidine derivatives have taken up the important role among active compounds. These guanidine groups can be heterocyclic derivatives of 2-aminobenzimidazole, or free alkyl or arylguanidines. For many years, heterocyclic guanidine derivatives have been used in two forms; benomyl[4] [methyl 1-[butylcarbamoyl]-2-benzimidazolecarbamate] (I) and carbendazim[5] [methyl 2-benzimidazolecarbamate] (II).

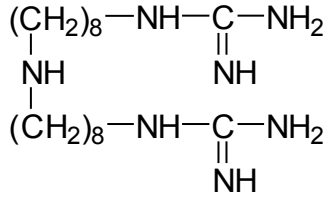


I



II

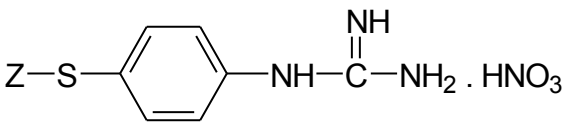
Generally, fungicides of this type inhibit the affects of ascomycetes, deuteromycetes, and some basidiomycetes. In contrast, these fungicides have no inhibitory effects against fycomycetes. Contact fungicides, such as guazatine[6] [bis(8-guanidineoctyl)amine] (III), are used in agricultural practice where they are applied to exterminate fungi upon contact.



III

Additionally, foliar fungicide, dodine[1] [1-dodecylguanidiniumacetate] similar to the structure of guazatine was introduced to the market by American Cyanamid Co., which are applied as sprays.

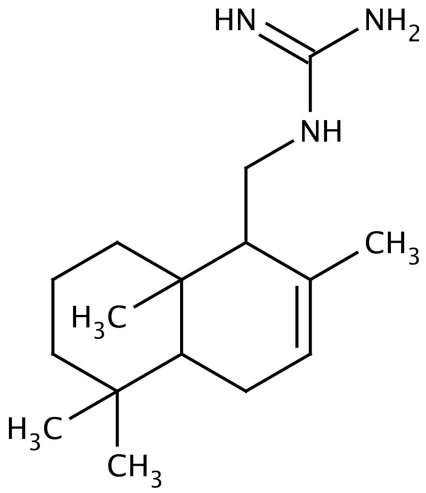
Research in this discipline, however, continues both in the group of alkyl and cycloalkylguanidine[4-9] derivatives and compounds with aromatic group[10-15] bonded to the guanidine group. Therefore, a first series of compounds[19] of similar structure was synthesized in our laboratory for biological evaluation. These compounds correspond to the structure IV, below, with a sulfanyl group on the 4th carbon in the benzene ring. These compounds have promising antifungal activity. Minimum inhibitory concentration (MIC) of the most active compounds on some strains is better than 2 μmol/l.



IV

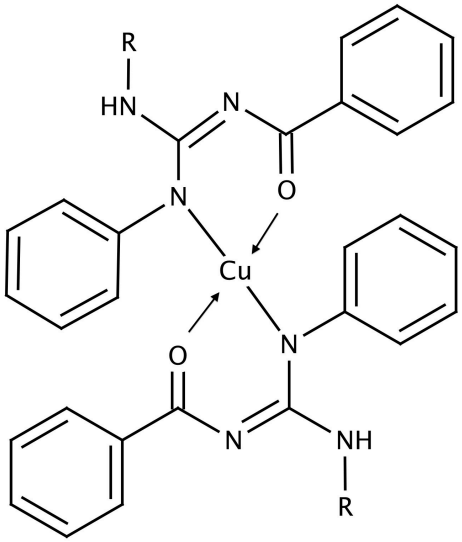
1.3 Other literature on arylguanidines

Literature on guanidines related to this thesis is limited. However, searches have been made on Sci-Finder, Science Direct, and scholar search engine Google Scholar, have been giving few interesting results. Keywords used in searches include: antifungal + guanidines, antifungal + phenylguanidines, antifungal + arylguanidines, phenyl + aryl + guanidines, guandines, phenylguanidines, and arylguanidines. All search were further categorized by dates: 2005-2012. In September 2011, Koffi-Nevry et al. wrote an article on polyhexamethylene-guanidine hydrochloride[20] (PHMGH) isolated from papaya fruit. Koffi-Nevry et al. conducted tests with positive indication that PHMGH is an effective fungicide and can be used as preservatives for fruits (papaya) after harvesting. An article written by Miguel Zarraga suggested that drimane sesquiterpenes are highly valuable due to their strong biological activity and concluded that antifungal activity of 11-guanidinodrimene[21] (see V) increased when tested against Candida albicans.



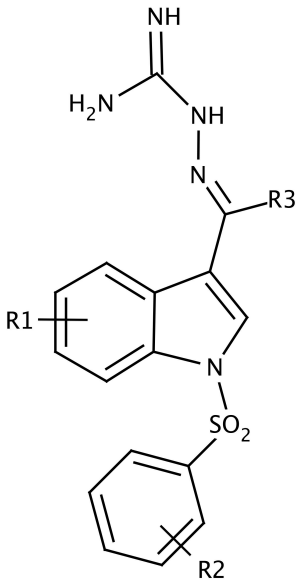
V

G. Murtaza et al. have synthesized a series of homoleptic copper(II) complexes with N, N',N''-trisubstituted guanidines[22] (see VI), which show a moderate level of cytotoxicity against these seven human cancer cell lines.



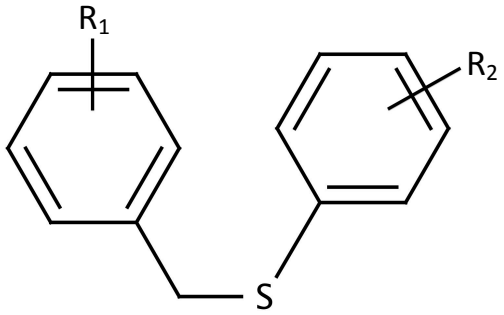
VI

In 2010, Hui Xu et al. synthesized aminoguanidine[23] derivatives of chemical structure shown in VII, which exhibit more potent antifungal activities than or comparable to hymexazol.



VII

S. Mo et al[24] cultured an antimicrobial sesterterpene bearing a guanidine group from cyanobacterium Scytonema sp. called Scytoscalarol, which showed antimicrobial activities against Bacillus anthracis, Staphylococcus aureus, Escherichia coli, Candida albicans, and Mycobacterium tuberculosis with MIC values in the range from 2 to 110 μM. In 2007, L. A. Vale-Silva et al. synthesized 19 antifungal compounds, in which newly synthesized guanidines and anilides[25] have similar potency to the level of amphotericin B. Moreover, guanidines are not just used in antifungals, they are also therapeutically beneficial for all sorts of treatments. In a study conducted by Bo Wu et al.[25], guanidines derivatives declare restoration of dystrophin expression in cardiac and skeletal muscles. Additionally, guanidines are being used for the inhibition of voltage-gated potassium channels subsequently stimulating the neuromuscular junction, or guanidine derivatives can be used as a protein-denaturing agent[26]. Most recent, a series of substituted benzylsulfanyl-phenylguanidine was synthesized by K. Thevissen[27], which showed potent fungicidal activity against strains of Candida albicans and Candida glabrata. When R_1 = 3,5-dibromine, and R_2 = p-1,2-Dicyclohexylguanidyl[27] or m-1,2-Dicyclohexylguanidyl (see VIII), it has potent fungicidal and bactericidal activity. Additionally, compound with R_2 = m-1,2-Dicyclohexylguanidyl exerts high activity against single C. albicans and mixed C. albicans/S. epidermidis species.



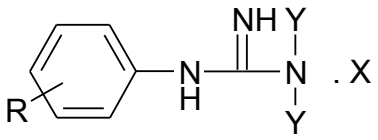
VIII

R_1 = 3,5-dibromine
R_2 = p-1,2-Dicyclohexylguanidyl, m-1,2-Dicyclohexylguanidyl

2. PROJECT GOAL

The goal of this project is to extend research on phenylguanidine compounds types: 1,1-diethyl-3-substituted phenylguanidines, alkylsulfanylphenylguanidines and 1,1-diethylbromophenyl-3-guanidines. More precisely, we will synthesize the following compounds; 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine, 3-(3-bromophenyl)-1,1-diethyl-guanidine, 3-(4-bromophenyl)-1,1-diethyl-guanidine, and to oxidize: 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate. To synthesize 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine, we will first need 1-chloro-4-nitrobenzene to react with dodecamethiol, dimethylformamide, potassium carbonate, and copper to produce 1-dodecylsulfanyl-4-nitro-benzene. That product is then reduced to produce 4-dodecylsulfanylaniline. Once reduced, we will form chlorides by adding dry hydrogen chloride to the mixture to form (4-dodecylsulfanylphenyl)ammonium chloride. In the final step, we will mix (4-dodecylsulfanylphenyl)ammonium chloride with N,N-diethylcyanamide to obtain the final product of 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine. To synthesize 3-(3-bromophenyl)-1,1-diethyl-guanidines, we will use the same procedure as previously mentioned by firstly producing chlorides and then mixing it with N,N-diethylcyanamide to give us the end product of 3-(3-bromophenyl)-1,1-diethyl-guanidine. Next, we will synthesize 3-(4-bromophenyl)-1,1-diethyl-guanidines in the same way. Finally, we will oxidize 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate to prepare sulfonyl derivative.

Possible alterations of the molecule are proposed in the figure below, IX.



IX

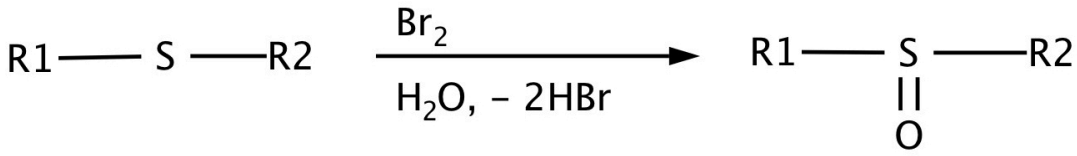
R = alkylsulfanyl, alkylsulfinyl, alkylsulfonyl
X = -, HNO_3, $C_6H_3N_3O_7$
Y = H, C_2H_5

3. THEORETICAL PART

3.1 Oxidation of sulfides

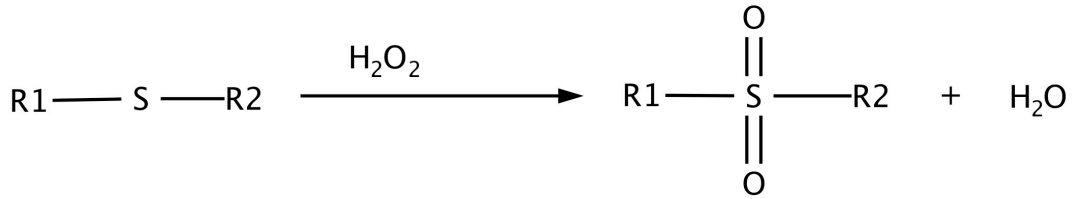
Organic sulfoxides play an important role as a therapeutic agent for the treatment of various diseases such as anti-atherosclerotic, antibacterial, antifungal and various heart related diseases. The oxidation of sulfides to sulfoxides can occur both organically and inorganically, through biological and/or chemical mechanisms. In this study, chemical mechanism is of high importance where sulfides are able to rapidly oxidize in the presence of dissolved oxygen, however, mechanisms rely on pH, redox potential, oxygen source and metal ions for catalysis and rate of oxidation. On the contrary, biological mechanisms depend on microbial activity, which is subject to environmental factors such as temperature, pH, food availability and an oxygen source. Over decades, vast numbers of procedures have been developed to oxidize sulfides to sulfoxides. Majority of these procedures however are toxic, harmful, or expensive for development, and many are over-oxidized to other compounds.

Halogens, such as bromine[28] or chlorine, have been widely used for oxidizing sulfides. Though, undesirable side reactions often do occur using this method. For example, using bromine for the oxidation of sulfides, byproducts such as sulfonic or sulfinic acid[29] are able to form in which hydrogen bromide is responsible. These byproducts, however, can be reversed using an aqueous acidic media resulting in high yield oxidized sulfides. The following is a scheme of the reaction for oxidization of sulfides using halogens:



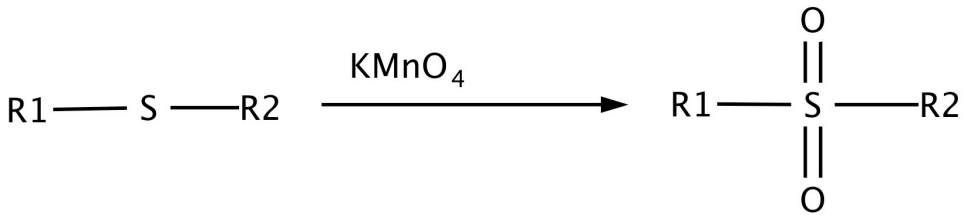
Scheme I

Hydrogen peroxide[30], recently, has been a promising oxidizing agent for the oxidation of sulfides. In contrast to the above-mentioned oxidizing agent, hydrogen peroxide is considered the green oxidant[31] since water is the theoretical by-product lacking of toxic by-products. Hydrogen peroxide is inexpensive, easily accessible, and easily stored. Moreover, hydrogen peroxide is known to oxidize aromatic and aliphatic sulfides to sulfoxides with high yields under neutral, acidic or alkaline condition with or without a catalyst. Hydrogen peroxide in the presence of zirconium tetrachloride[32] as a reagent is an efficient way to oxidize sulfides. The following is a scheme of the reaction for the oxidization of sulfides using hydrogen peroxide.



Scheme II

Potassium permanganate[33-34] is a strong inorganic oxidizing agent that is readily dissolved in water forming a purple colour after dissolution and does not generate toxic by-products. As an oxidant, potassium permanganate has various uses, such as oxidation of taste and odor, disinfectant and water treatment, organic synthesis, fruit preservation, etc. Potassium permanganate has been used extensively in the laboratory to oxidize 1-(4-tetradecylsulfanylphenyl)guanidine, see figure below. A. Shaabani et al. indicated in a study that addition of manganese dioxide[35] accelerates rate of oxidation.



Scheme III

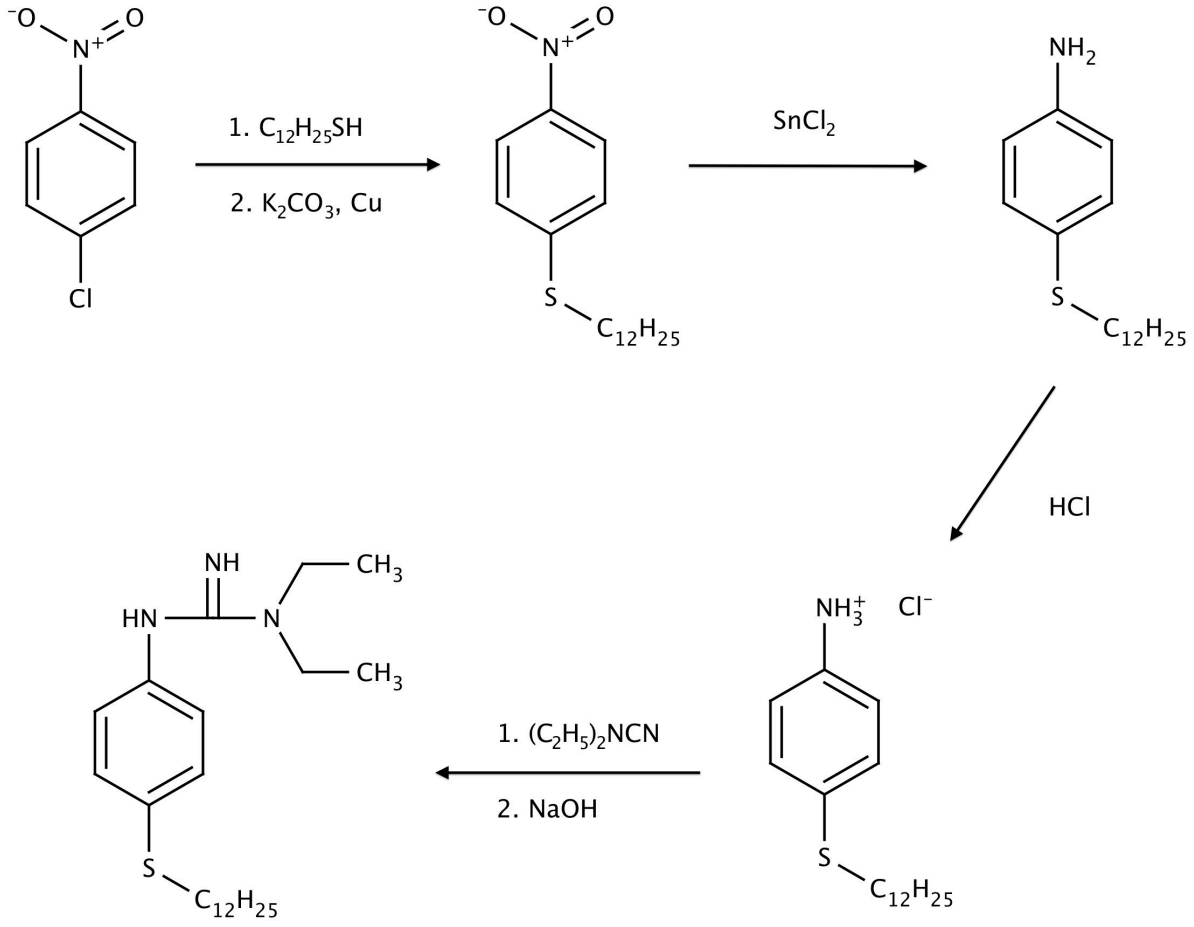
3.2 Guanidine: phenylguanidines

Substituted guanidine[36] is a broad group and subject, which contains many derivatives (i.e. nitroguanidine, aminoguanidine, organoguanidine, etc) and are synthesized using cyanamide or dicyandiamide with ammonium salts. This thesis mainly focuses on organoguanidine[7] such as alkyguanidine, arylguanidine or phenylguanidine. However, guanidine derivatives in general have been and are being used broadly as pharmaceuticals, fungicides, propellants, agrochemicals, in biotechnological engineering or biocides.

Organoguanidines[32] can be synthesized using cyanamide and adding any amines (i.e. polyamine, hydroxylamine). S-alkylisothiourea[37] is able to react with amines to form guanidines. Biocides, such as biguanides, are synthesized using dicyanamide or cyanoguanidines. Moreover, organoguanidines are the building blocks for agrochemicals and pharmaceuticals. They are also used for curing agents for plastics and rubbers.

3.3 Synthesis of guanidines

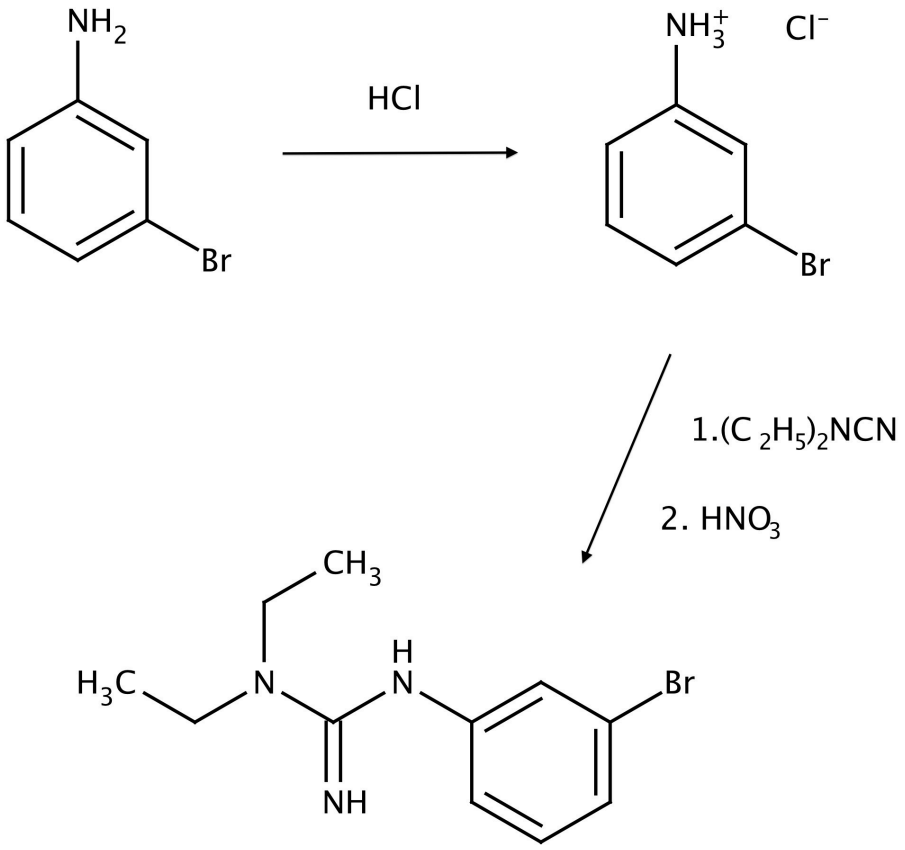
In this study, we synthesized the alkylsulfanyl derivatives as shown in a general reaction scheme shown below:



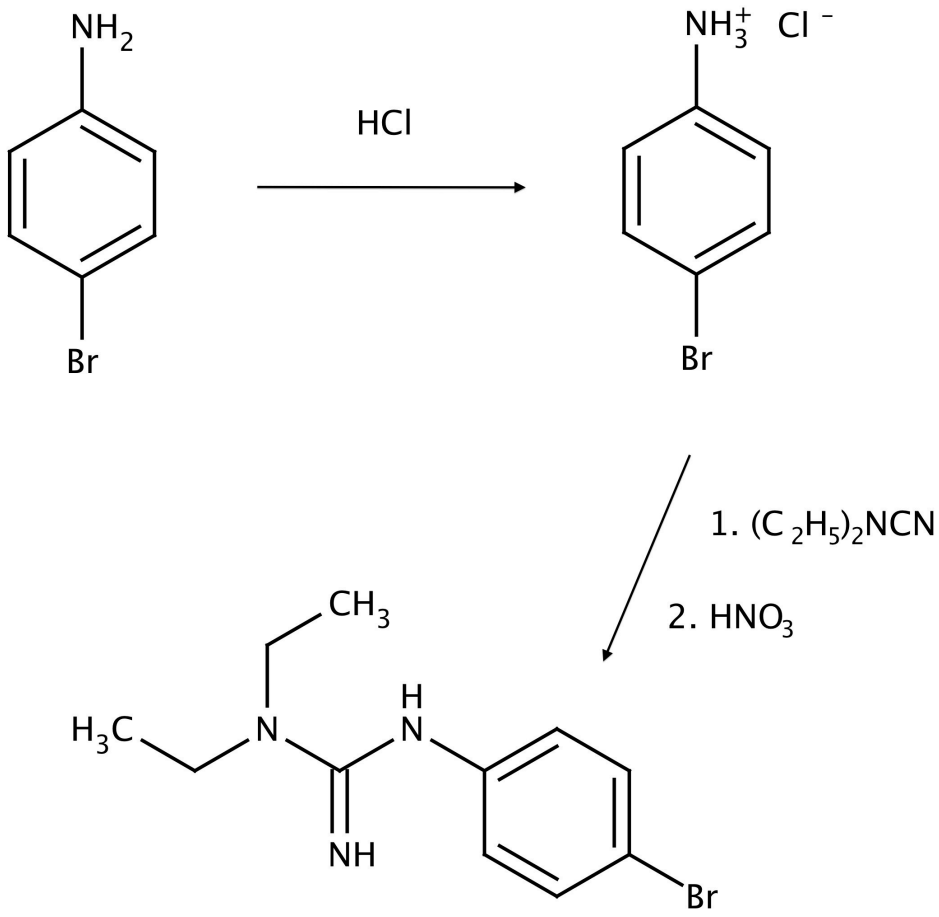
Scheme IV

The starting compound, needed to introduce the sulfanyl derivative, was 4-chloro-1-nitrobenzene. In the first step, the starting compound provided us with sulfanyl derivatives by reaction with the thiol group in alkaline conditions and by catalysis with the active copper[38]. The aforementioned reaction was followed by the reduction[39] of the nitro group, preparing the aniline derivative that was then transformed to anilinium chloride. Subsequently, this compound was used in the final step of the synthesis where it reacted with cyanamide[40,41,42] forming guanidines. Diethylguanidine derivatives were prepared by the reaction of amine with N,N-diethylcyanamide. Sulfonyl derivatives were prepared by the oxidation[17] of sulfanyl derivatives.

The following is the scheme followed to synthesize 3-(3-bromophenyl)-1,1-diethyl-guanidines, 3-(4-bromophenyl)-1,1-diethyl-guanidines:



Scheme V: 3-(3-bromophenyl)-1,1-diethyl-guanidine



Scheme VI: 3-(4-bromophenyl)-1,1-diethyl-guanidine

To synthesize 3-(3-bromophenyl)-1,1-diethyl-guanidines and 3-(4-bromophenyl)-1,1-diethyl-guanidines we first prepared the aniline derivative that was then transformed to anilinium chloride. Subsequently, this compound was used in the final step of the synthesis where it reacted with cyanamide[40,41,42] forming guanidines. N,N-Diethylguanidine derivatives were prepared by the reaction of ammonium chlorides with N,N-diethylcyanamide.

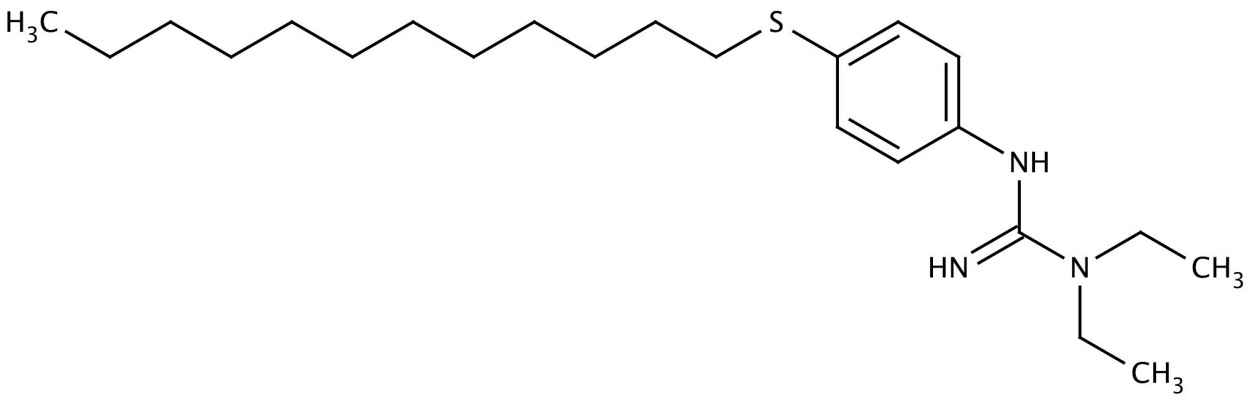
The schemes for the oxidation of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate are located in their respective categories.

4. EXPERIMENTAL PART

4.1 General Methods

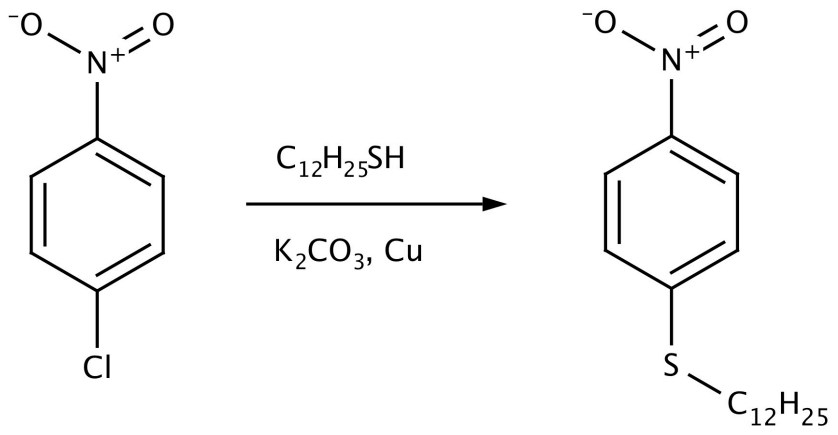
All chemicals, which were used during the experiments, were not further purified and were used as received from different commercial sources, such as Aldrich. The end products components and structure were identified using melting points (MP), literature data, thin-layer chromatography (TLC), infrared (IR), nuclear magnetic resonance (NMR), and mass spectra (MS). The melting points were determined on a Kofler apparatus. The samples for the analysis tests were dried over P_2O_5 at 61 °C and 66 Pa for 24 hours. The standard IR spectra were measured on germanium ATR crystal on a Nicolet 6700 FTIR apparatus; the wavenumbers are given in cm^{-1}. The ^{1}H and ^{13}C NMR spectra of new compounds were recorded in DMSO-d_6 solutions at room temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts were recorded as δ values in parts per million (ppm), and were indirectly referenced to tetramethylsilane *via* the solvent signal (2.49 for ^{1}H or 39.7 for ^{13}C for DMSO-d_6). TLC was performed on silica gel plates precoated with a fluorescent indicator Silufol UV 254 (RP-18 F_{254s} of Kavalier). Mixture of hexane (16 parts), ethanol (8 parts), triethylamine (1 part) was used as the mobile phase. The synthetic routes leading to the desired compounds, please review the scheme IV located under **3.3 Synthesis of Guanidines**. The synthesis was divided into two parts: the oxidation of phenylguanidines and the synthesis of phenylguanidines.

4.2 Synthesis of 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine



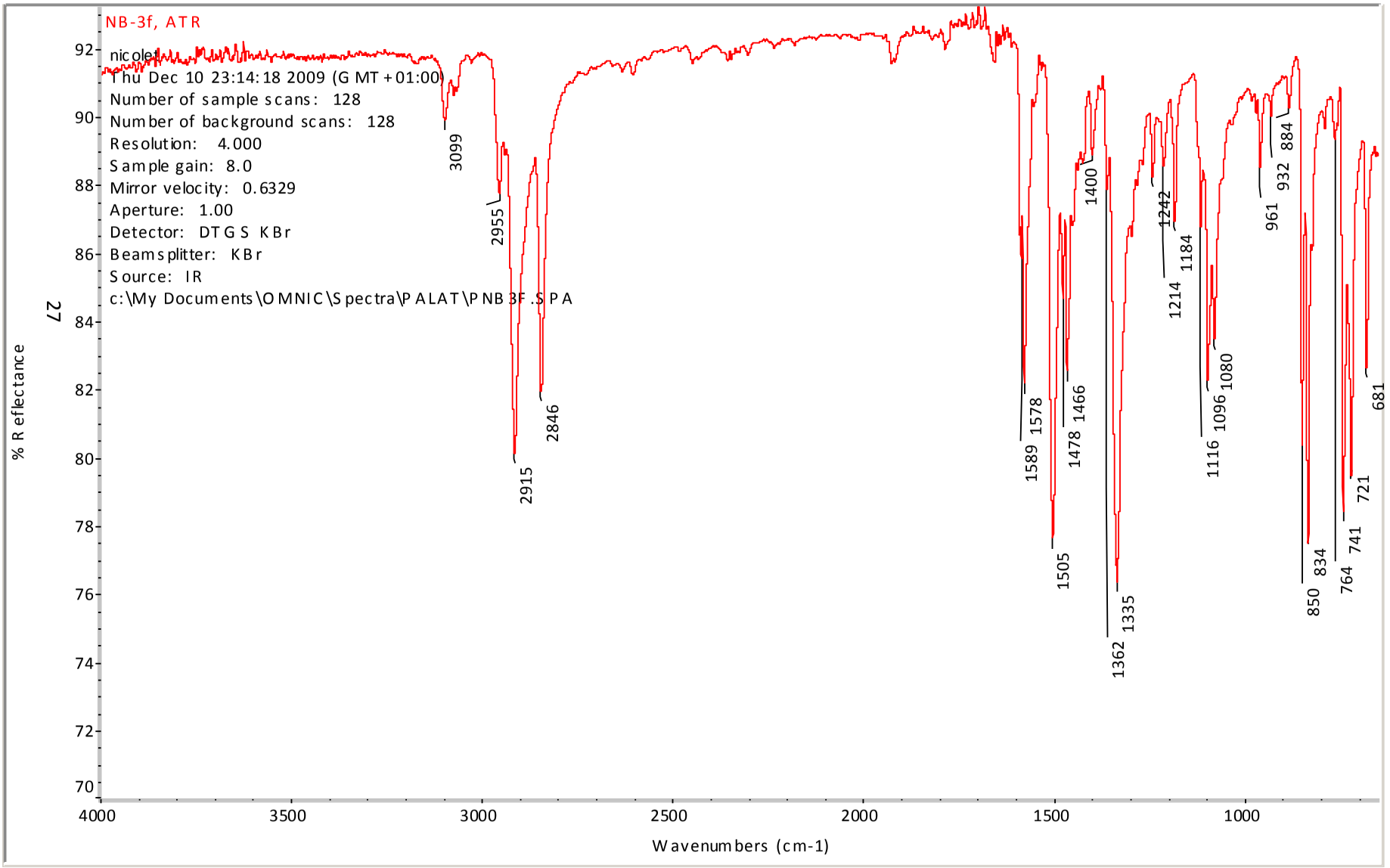
3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine
MW = 363.56 g/mol

4.2.1 Procedure to synthesize 1-dodecylsulfanyl-4-nitro-benzene

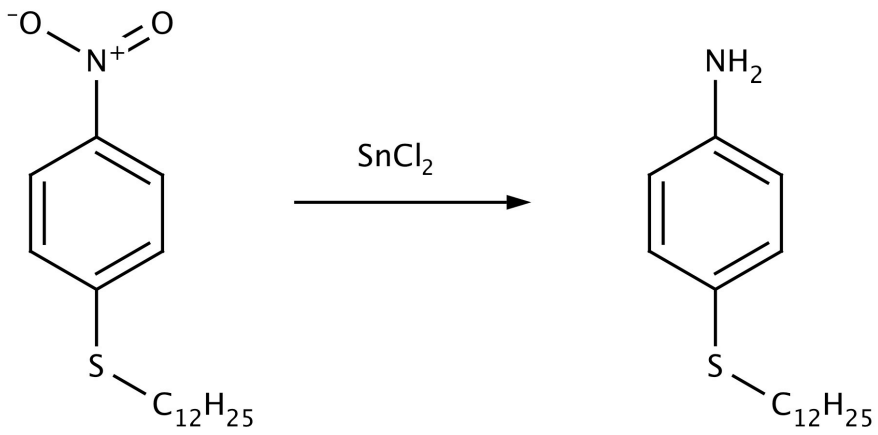


1-dodecylsulfanyl-4-nitro-benzene
MW = 319.46 g/mol

15.38 g of dodecamethiol (18.22 ml, 0.0976 mol, MW = 202.40 g/mol) was dissolved in 75 ml of dimethylformamide. Following dissolution, 33.68 g (0.2440 mol) of potassium carbonate was added to the mixture. Subsequently, 5.16 g (0.0406 mol) of copper and 30.00 g (0.095 mol) of 4-chloro-1-nitrobenzene was added to the mixture under nitrogen gas. The mixture was stirred and heated in oil bath at 150 °C for 5 hours. The mixture was filtered, then water was added to the filtrate causing formation of crystals and the mixture was cooled to 5 °C and crystals were filtered off. Melting point of the crystals was measured to be 34-38 °C. The crystals were then dissolved in hot ethanol with the addition of small amount of charcoal and subsequently filtered the mixture then stored in fridge for 24 hours. The mixture contained crystals which was filtered to obtain crystals, m = 18.26 g, and MP = 49.0–51.0 °C. The practical yield was calculated to be 89.6% of the theoretical yield. [Ref. 19: MP = 49.0–51.5 °C, 68%]

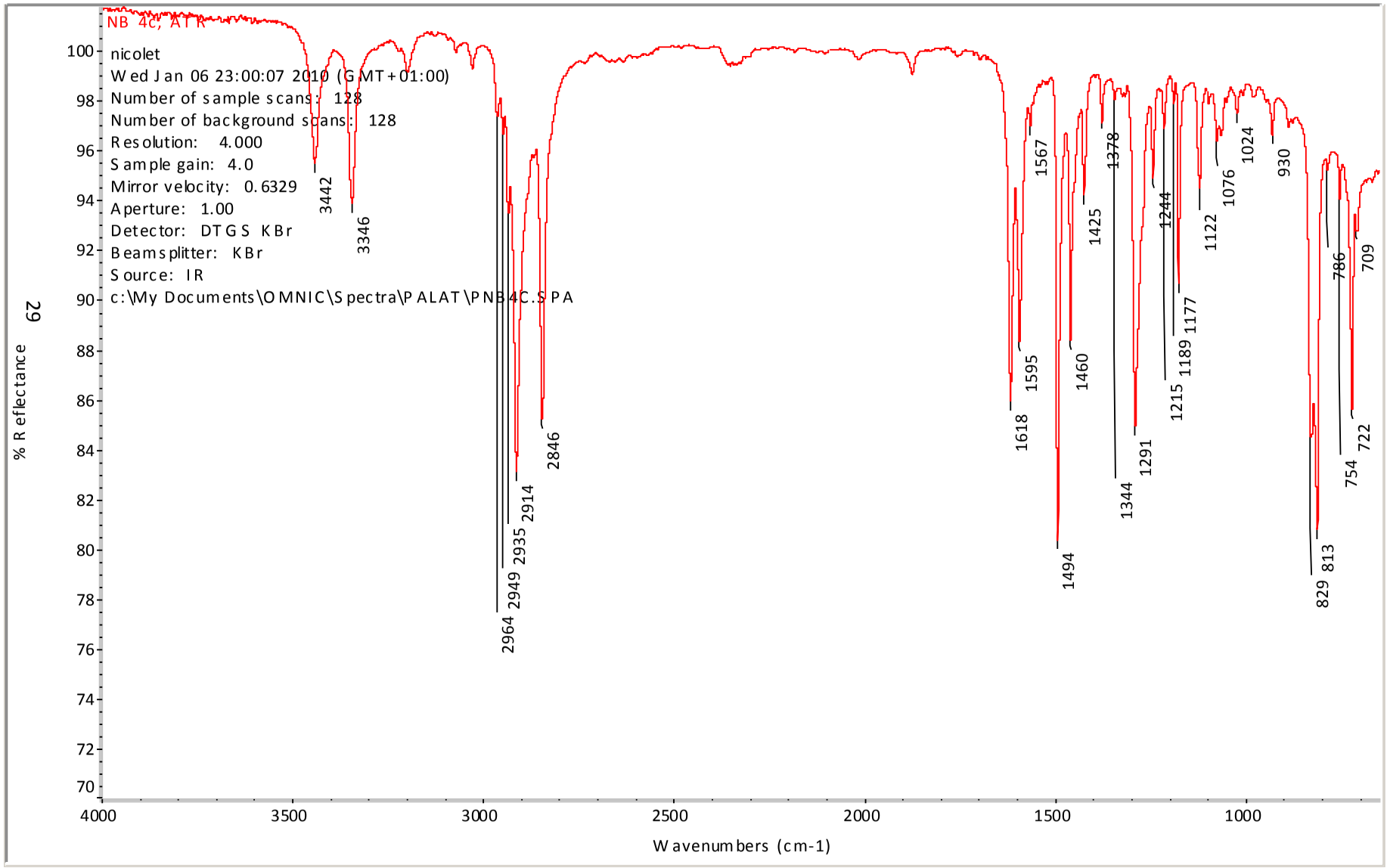

NB-3f, ATR
nicolet
Thu Dec 10 23:14:18 2009 (GMT+01:00)
Number of sample scans: 128
Number of background scans: 128
Resolution: 4.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 1.00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
c:\My Documents\OMNIC\Spectra\PALAT\PNB3F.SPA
% Reflectance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
92
90
88
86
84
82
80
78
76
74
72
70
3099
2955
2915
2846
1589
1578
1505
1478
1466
1400
1362
1335
1242
1214
1184
1116
1096
1080
961
932
884
850
834
764
741
721
681

4.2.2 Procedure to synthesize 4-dodecylsulfanylaniline

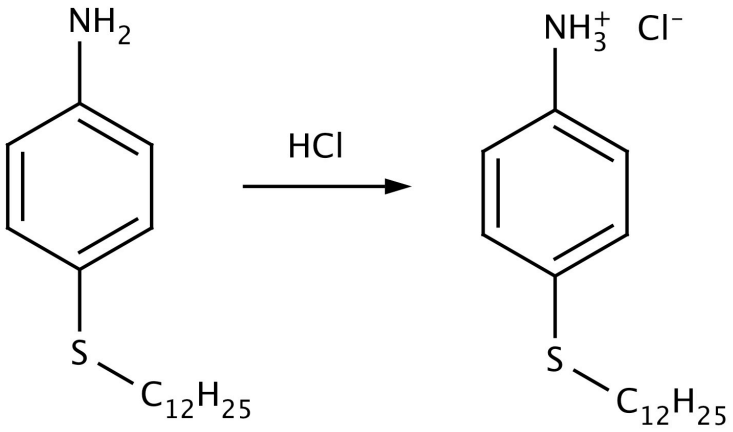


4-dodecylsulfanylaniline
MW = 289.47 g/mol

10.00 g (0.01 mol) of 1-dodecylsulfanyl-4-nitrobenzene was mixed with 35.00 g (0.05 mol) of tin-dichloride and 40 ml of dry ethanol. The mixture was then refluxed under nitrogen at 70 °C for 4 hours. The reaction was checked using thin-layer chromatography. Following reflux, the mixture was cooled and alkalized by solution of sodium hydroxide and 5 times extracted with ethyl acetate. The extracts were collected and dried with sodium sulfate and solvent was distilled off. The crystals were dissolved in hot ethanol, then added charcoal and subsequently filtered and stored in fridge. After cooling, the mixture was vacuum filtered to collect crystals, m = 6.54 g, and MP = 34.6 – 36.8 °C. The practical yield was calculated to be 72.2% of theoretical yield. [Ref. 19: MP = 34.6–36.8 °C, 73%]


NB 4C, ATR
nicolet
Wed Jan 06 23:00:07 2010 (GMT+01:00)
Number of sample scans: 128
Number of background scans: 128
Resolution: 4.000
Sample gain: 4.0
Mirror velocity: 0.6329
Aperture: 1.00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
c:\My Documents\OMNIC\Spectra\PALAT\PNB4C.SPA
% Reflectance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
98
96
94
92
90
88
86
84
82
80
78
76
74
72
70
3442
3346
2964
2949
2935
2914
2846
1618
1595
1567
1494
1460
1425
1378
1344
1291
1244
1215
1189
1177
1122
1076
1024
930
829
813
786
754
722
709

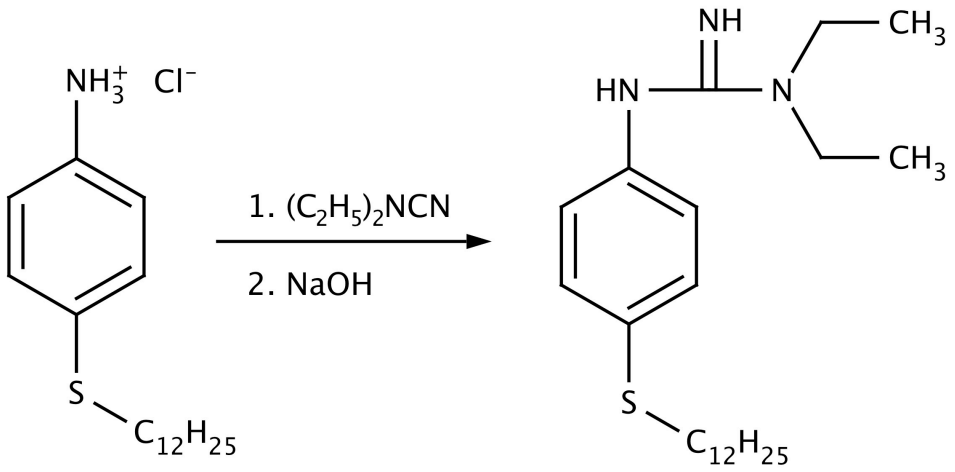
4.2.3 Procedure to synthesize (4-dodecylsulfanylphenyl)ammonium chloride



4-dodecylsulfanylphenylammonium chloride
MW = 325.93 g/mol

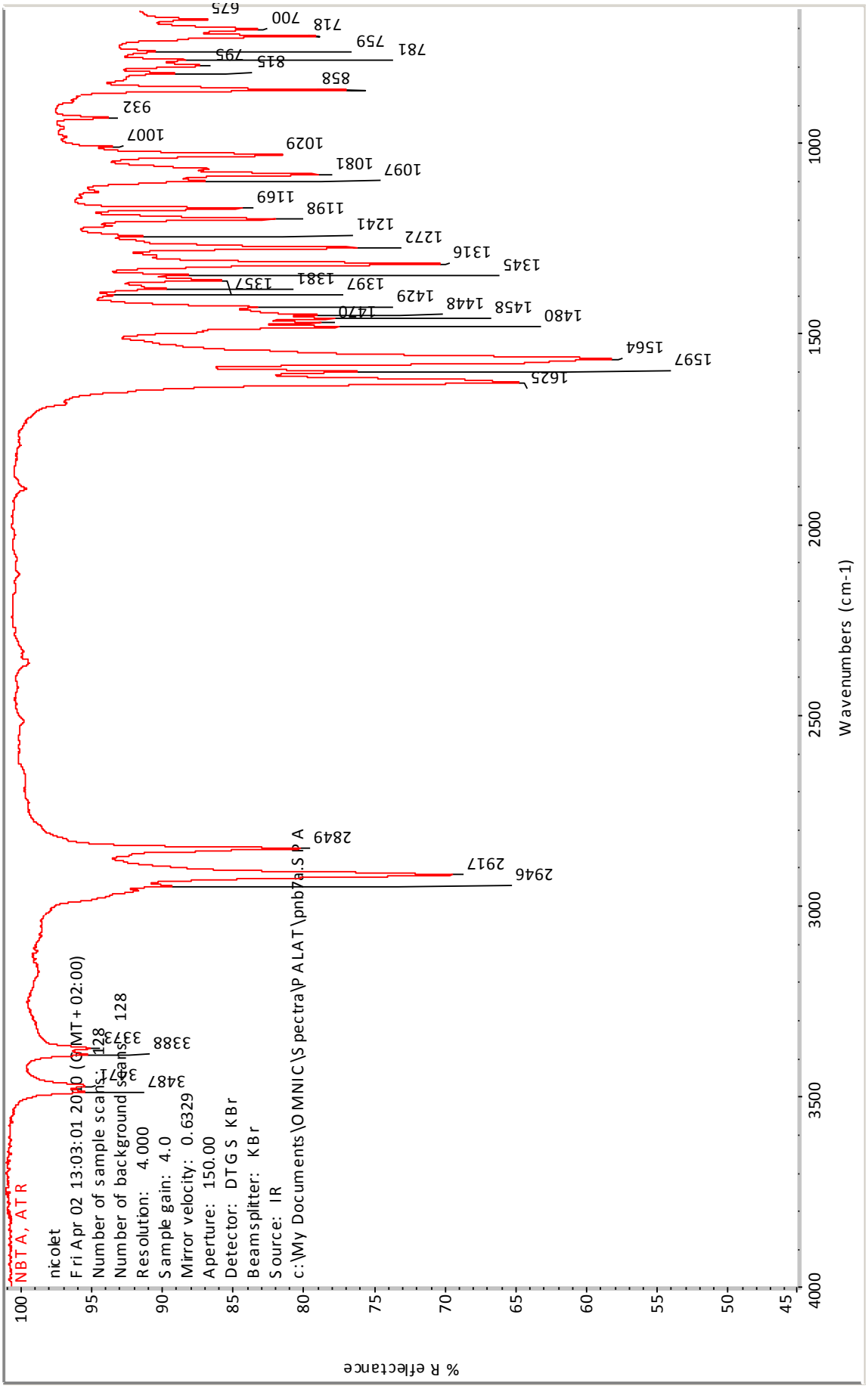
To synthesize 4-dodecylsulfanylphenylammonium chloride, we dissolved 1.00 g (0.00303 mol) of 4-dodecylsulfanylaniline with 50 ml of ether and was cooled in an ice bath. After cooled, dry hydrogen chloride was let into the mixture. Crystals were formed, which were subsequently collected and filtered off. 1.00 g of 4-dodecylsulfanylaniline crystals were collected, 88.8% yield.

4.2.4 Procedure to synthesize 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine



3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine
MW = 363.56 g/mol

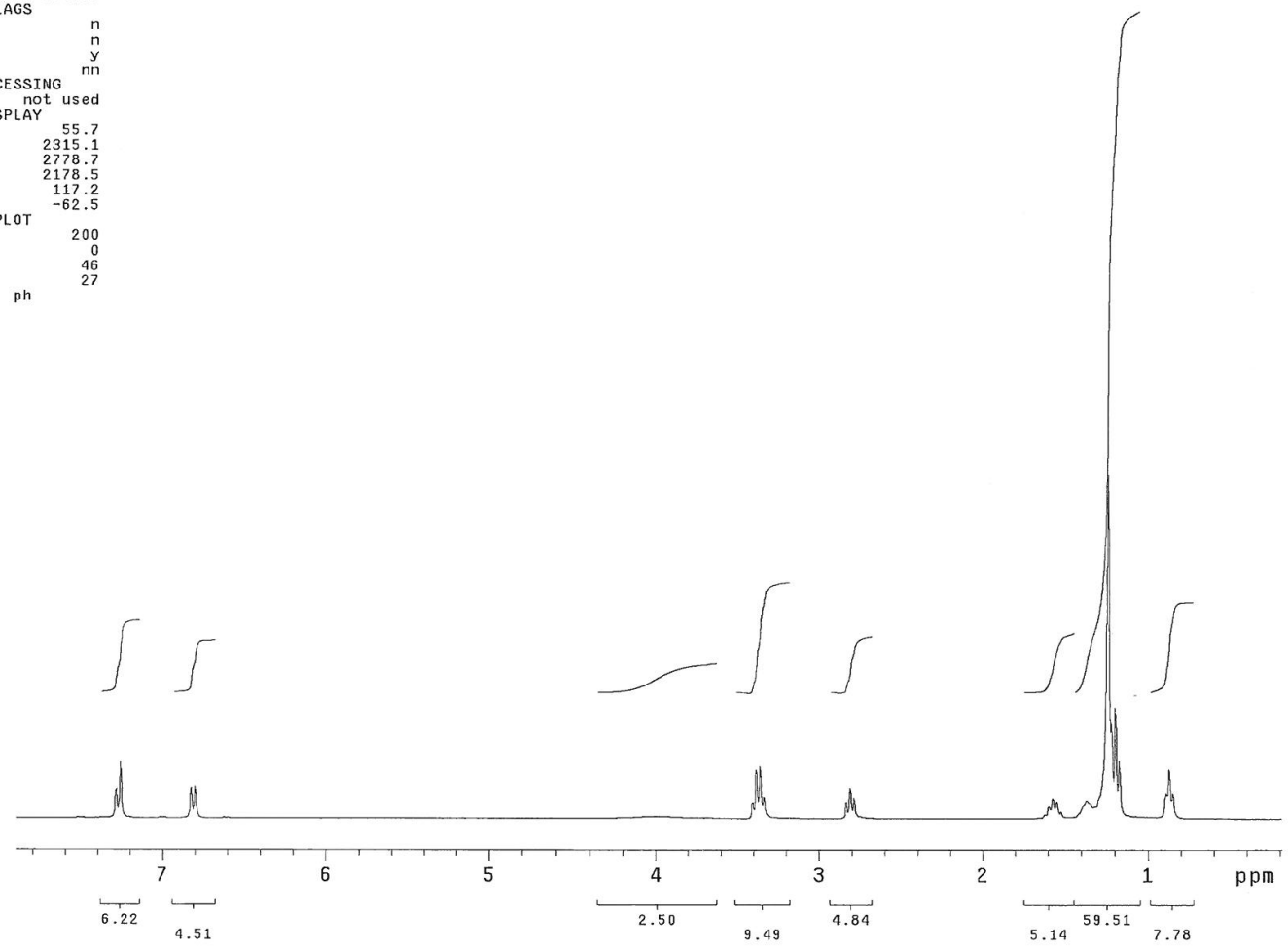
1.00 g (0.0030 mol) of 4-dodecylsulfanylphenylammonium chloride and 0.45 g (0.00455 mol, 0.53 ml) of N,N-diethylcyanamide were mixed and heated to 130 °C for 60 minutes. After 60 minutes, 0.12 g (0.0012 mol, 0.14 ml) of N,N-diethylcyanamide was added to the mixture. The reaction was complete after 90 minutes. The mixture was then dissolved in water and alkalized by 5% solution of sodium hydroxide. The product was extracted with diethylether and dried with sodium sulfate. The solvent was distilled off and the product was recrystallized from hexane, m = 0.54 g, and MP = 46.7–47.6 °C. The practical yield was calculated to be 49.1%. [Ref. 19: MP = 115.9–117.3 °C, 82%]


NBTA, ATR
nicolet
Fri Apr 02 13:03:01 2010 (GMT+02:00)
Number of sample scans: 128
Number of background scans: 128
Resolution: 4.000
Sample gain: 4.0
Mirror velocity: 0.6329
Aperture: 150.00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
c:\My Documents\OMNIC\Spectra\PALAT\pnb7a.SPA
% Reflectance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
100
95
90
85
80
75
70
65
60
55
50
45
3487
3388
2946
2917
2849
1625
1597
1564
1480
1458
1448
1429
1397
1381
1357
1345
1316
1272
1241
1198
1169
1097
1081
1029
1007
932
858
815
795
781
759
718
700
675

NB7A
STANDARD 1H OBSERVE

exp1 s2pul

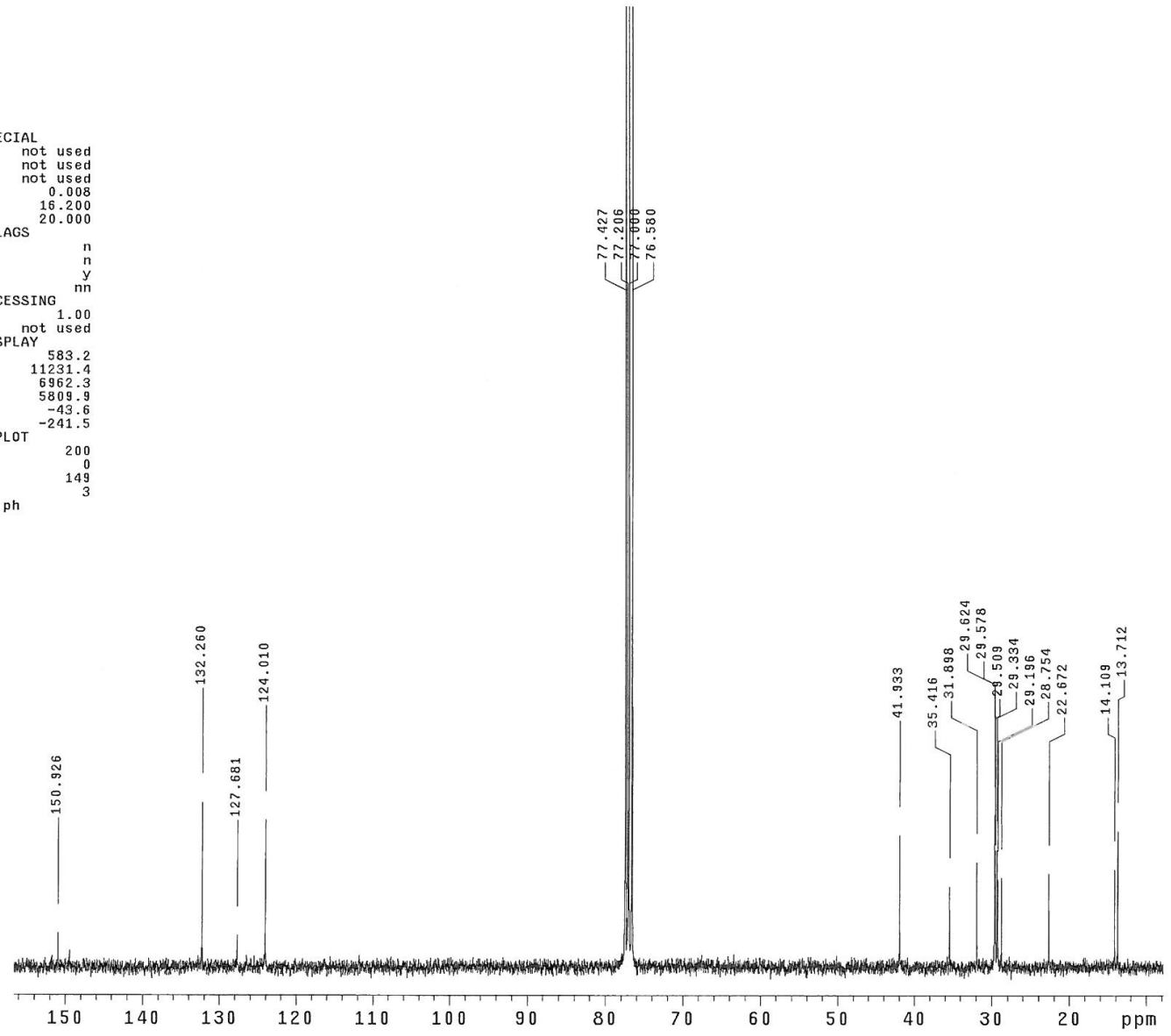
SAMPLE		SPECIAL	
date	May 25 2010	temp	not used
solvent	cdcl3	gain	not used
file	/export/home/~	spin	not used
vnmr1/abc/abc/auto~		hst	0.008
_25.05.10/NB7A_H.f~		pw90	13.300
	id	alfa	20.000
ACQUISITION		FLAGS	
sw	4800.8	il	n
at	1.706	in	n
np	16384	dp	y
fb	2600	hs	nn
bs	16	PROCESSING	
d1	5.000	fn	not used
nt	16	DISPLAY	
ct	16	sp	55.7
TRANSMITTER		wp	2315.1
tn	H1	rfl	2778.7
sfrq	300.075	rfp	2178.5
tof	255.9	rp	117.2
tpwr	56	lp	-62.5
pw	6.650	PLOT	
DECOUPLER		wc	200
dn	C13	sc	0
dof	0	vs	46
dm	nnn	th	27
dmm	c	ai	cdc ph
dpwr	0		
dmf	0		



NB7A
13C OBSERVE

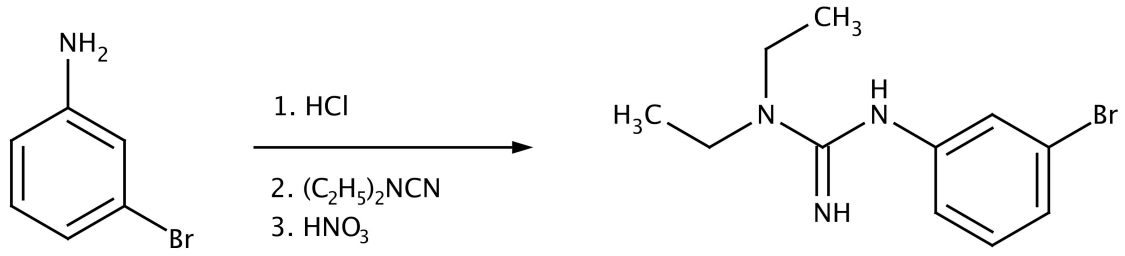
exp1 s2pul

SAMPLE		SPECIAL	
date	May 25 2010	temp	not used
solvent	cdcl3	gain	not used
file	/export/home/~	spin	not used
vnmr1/abc/abc/auto~		hst	0.008
_25.05.10/NB7A.fid		pw90	16.200
ACQUISITION		alfa	20.000
sw	18867.9	FLAGS	
at	1.737	il	n
np	65536	in	n
fb	10400	dp	y
bs	64	hs	nn
d1	5.000	PROCESSING	
nt	1000	lb	1.00
ct	1000	fn	not used
TRANSMITTER		DISPLAY	
tn	C13	sp	583.2
sfrq	75.462	wp	11231.4
tof	725.9	rfl	6962.3
tpwr	50	rfp	5809.9
pw	8.100	rp	-43.6
DECOUPLER		lp	-241.5
dn	H1	PLOT	
dof	0	wc	200
dm	yyy	sc	0
dmm	w	vs	149
dpwr	37	th	3
dmf	8400	ai no ph	



4.3 Synthesis of bromophenylguanidines

4.3.1 3-(3-bromophenyl)-1,1-diethyl-guanidine

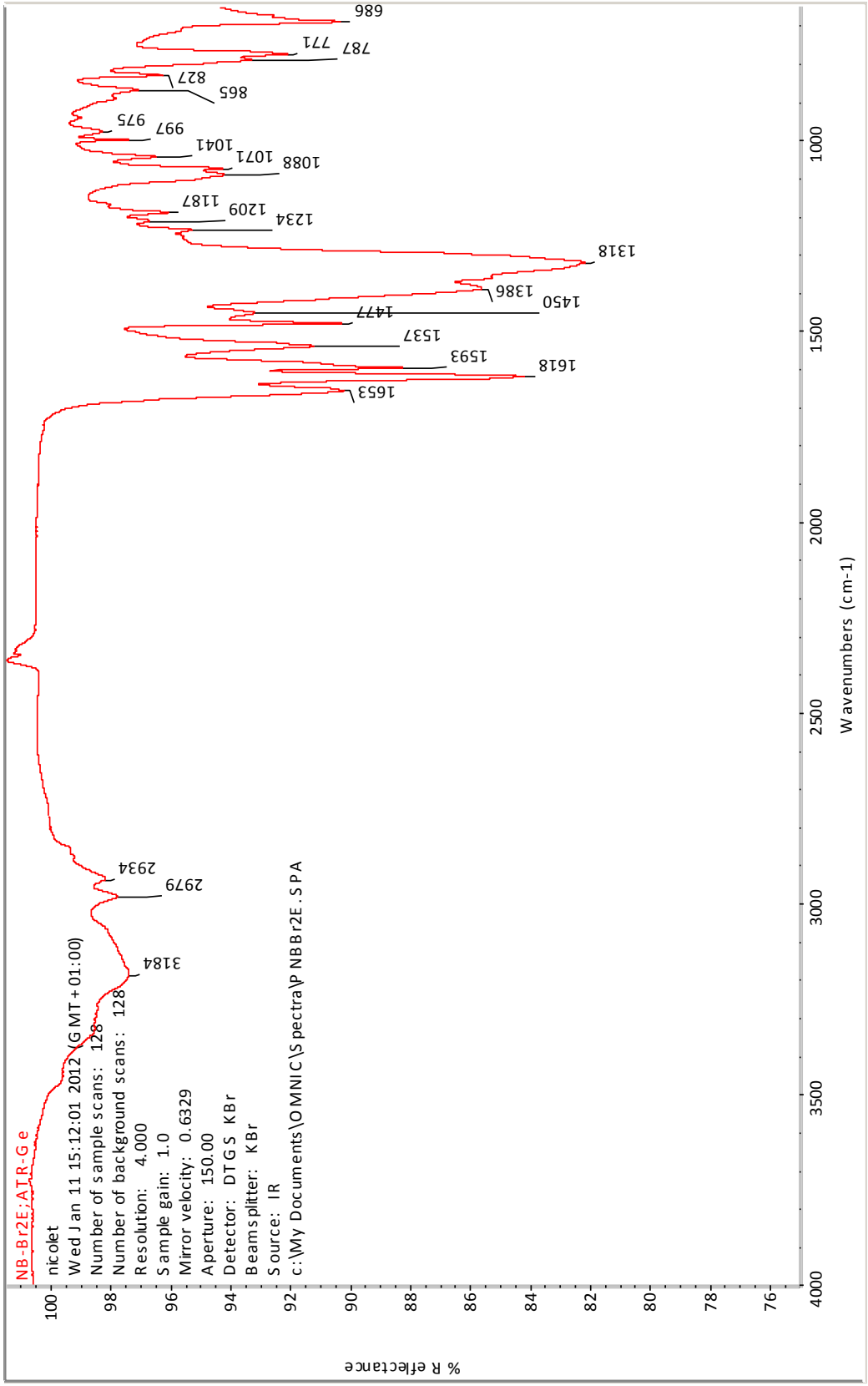


3-(3-bromophenyl)-1,1-diethyl-guanidine
MW: 270.17 g/mol

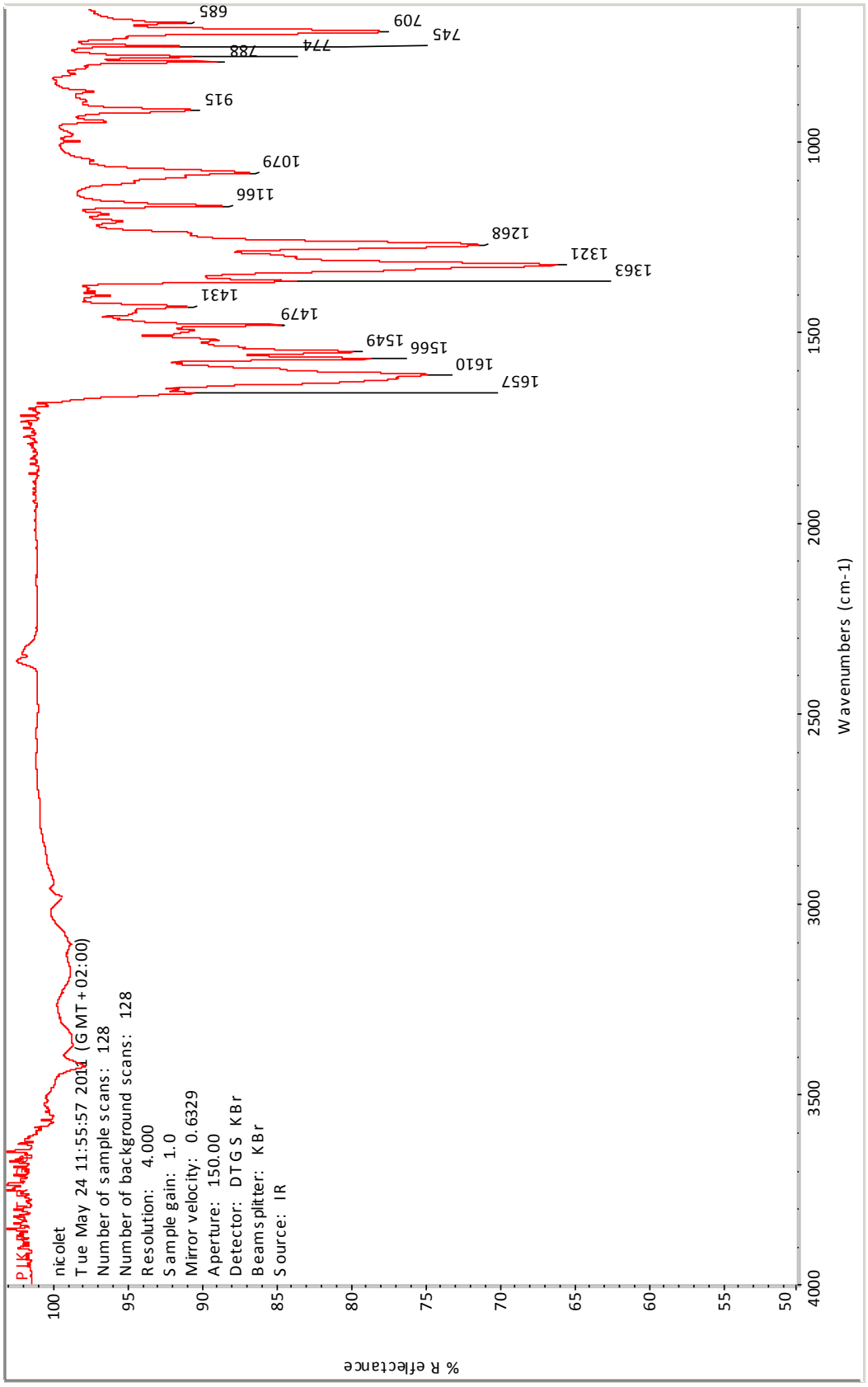
10.00 g (0.058 mol, 6.34 ml) of 3-bromaniline (MW = 172,3 g/mol, d = 1.58) was added to 50 ml of dry ether and was cooled in ice bath. While cooling, hydrogen chloride is let into the mixture to prepare crystals (m = 9.96, yield = 81.6%). 6.00 g (0.0288 mol) from the crystals was mixed with 1.55 g (0.0192 mol, 1.83 ml) of substituted N,N-diethylcyanamide and heated to 130 °C for 60 minutes. After 60 minutes, 0.23 g (0.00237 mol, 0.27 ml) of N,N-diethylcyanamide was added to the mixture. The reaction was complete after 90 minutes. The mixture was then dissolved in water and alkalized by 5% solution of sodium hydroxide. The product was extracted with diethylether and dried with sodium sulfate. The product was in liquid form, m = 4.49 g (34.0% yield)

A sample of the product was dissolved with ethanol and picric acid (2,4,6-trinitrophenol (TNP), MP = 122.5 °C) was added to the mixture. Crystals of the picrate was formed then filtered off and MP was measured to be 102.3-103.1 °C.

3-(3-bromophenyl)-1,1-diethyl-guanidine liquid:



3-(3-bromophenyl)-1,1-diethyl-guanidine picrate:

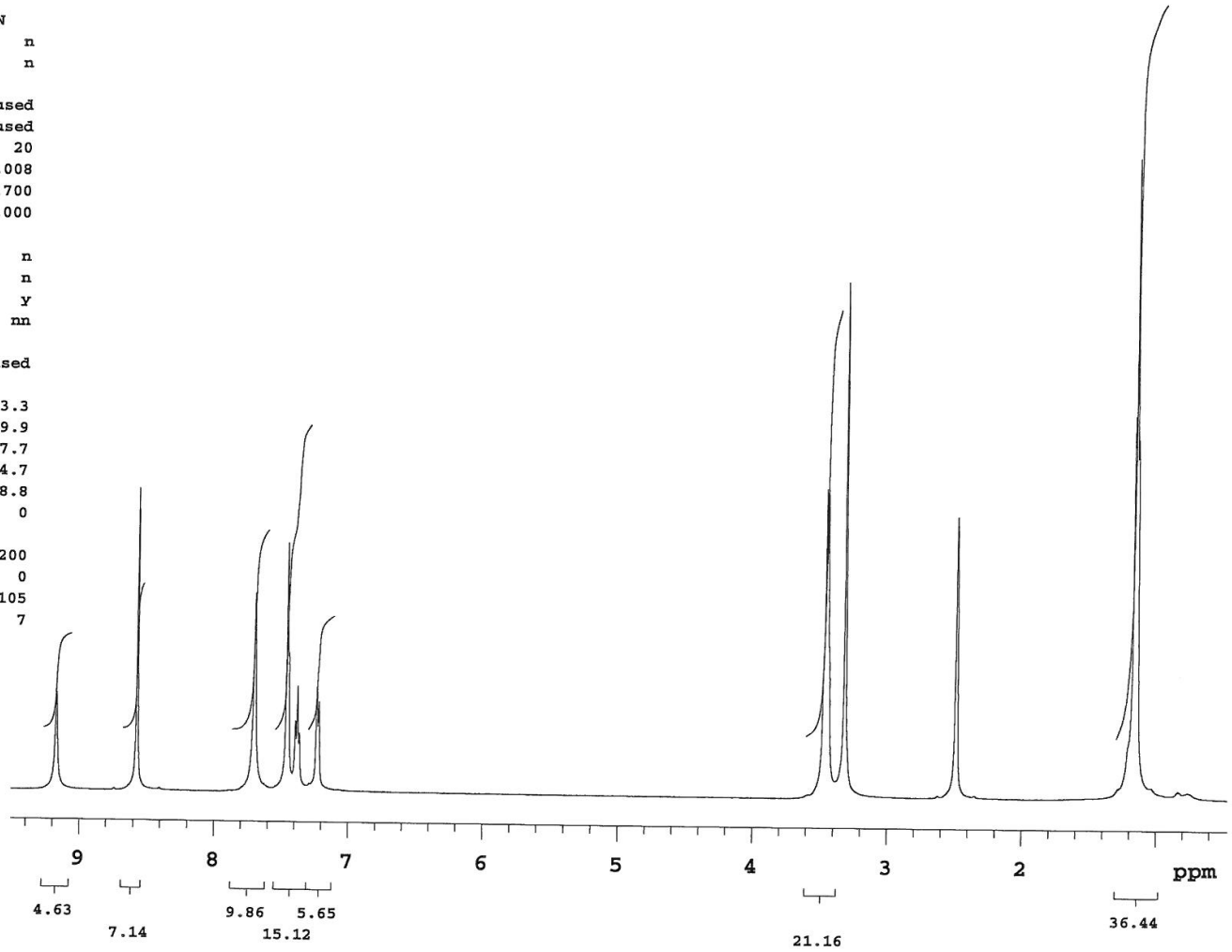


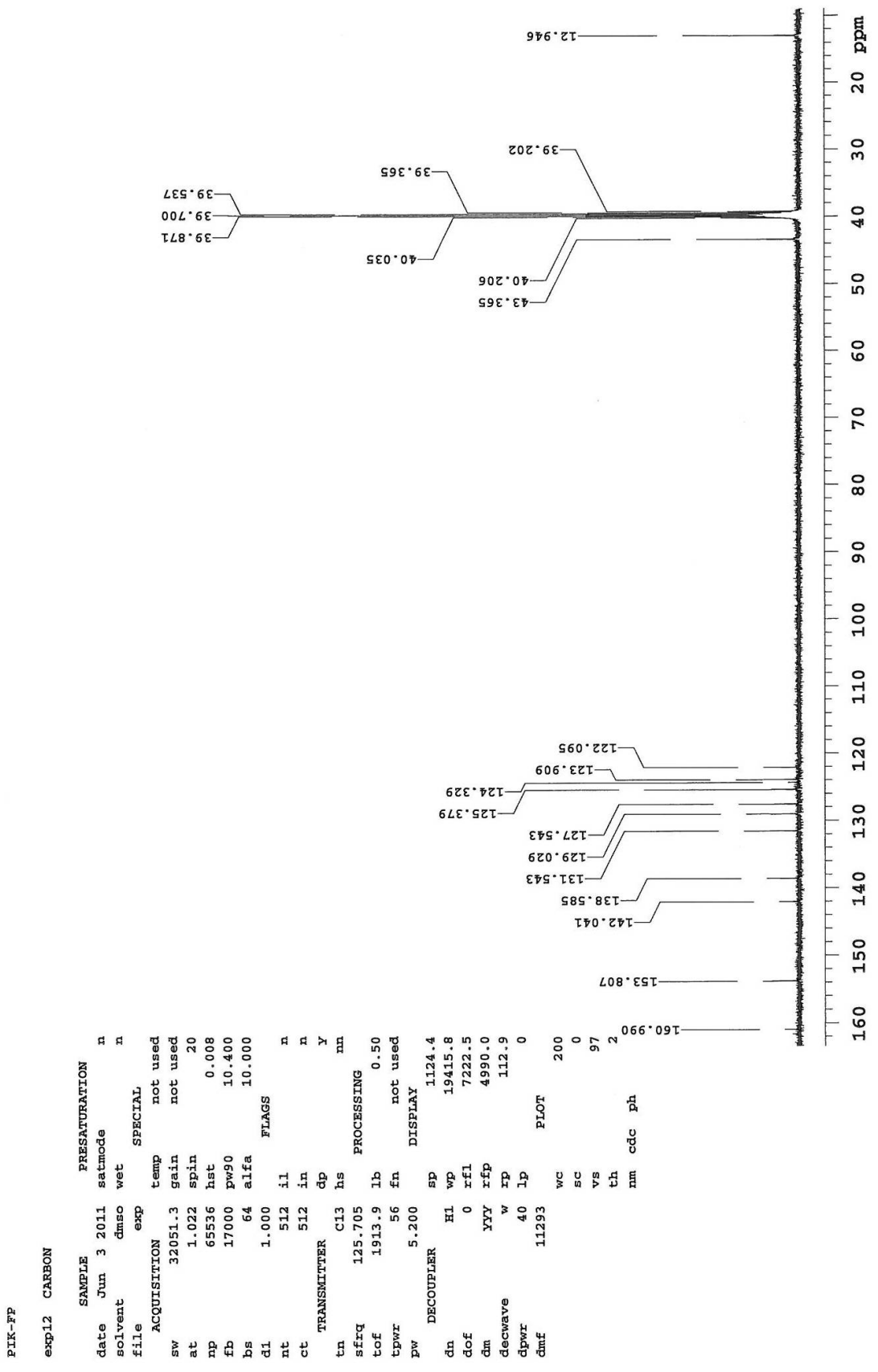
PIK-FP

exp11 PROTON

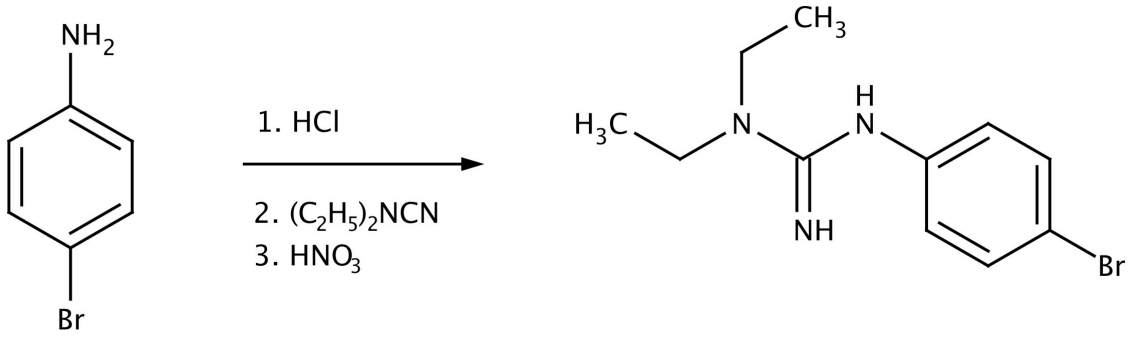
SAMPLE	
date	Jun 3 2011
solvent	dmso
file	exp
ACQUISITION	
sw	8012.8
at	2.045
np	32768
fb	4000
bs	32
d1	1.000
nt	8
ct	8
TRANSMITTER	
tn	H1
sfrq	499.870
tof	499.8
tpwr	60
pw	4.350
DECOUPLER	
dn	C13
dof	0
dm	nnn
decwave	W40_OneNMR
dpwr	39
dmf	32258

PRESATURATION	
satmode	n
wet	n
SPECIAL	
temp	not used
gain	not used
spin	20
hst	0.008
pw90	8.700
alfa	10.000
FLAGS	
il	n
in	n
dp	y
hs	nn
PROCESSING	
fn	not used
DISPLAY	
sp	233.3
wp	4519.9
rfl	2247.7
rfp	1244.7
rp	78.8
lp	0
PLOT	
wc	200
sc	0
vs	105
th	7
nm	cdc ph



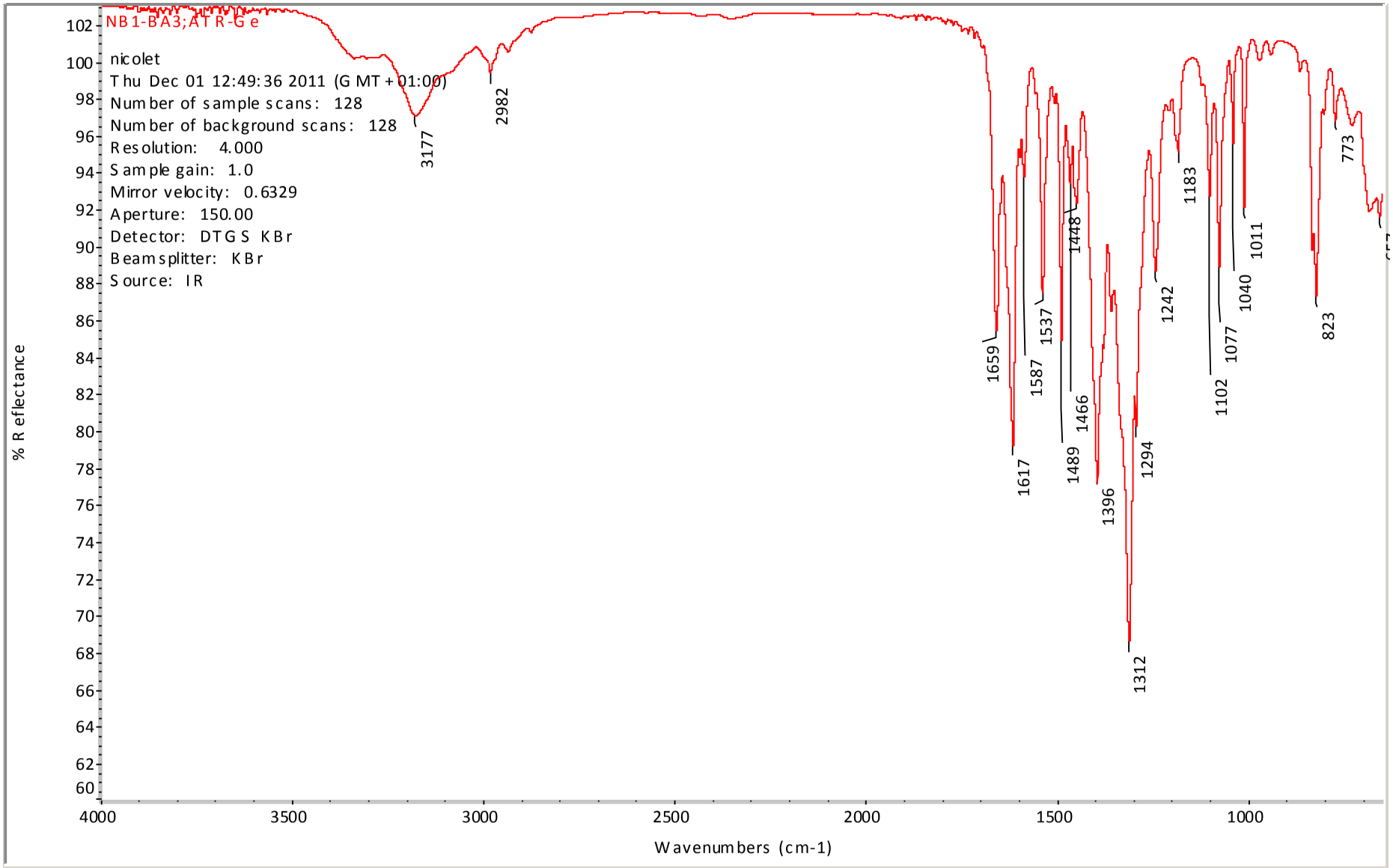

PIK-FP
exp12 CARBON
SAMPLE
date Jun 3 2011
solvent dmso
file exp
ACQUISITION
sw 32051.3
at 1.022
np 65536
fb 17000
bs 64
d1 1.000
nt 512
ct 512
TRANSMITTER
tn C13
sfrq 125.705
tof 1913.9
tpwr 56
pw 5.200
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 40
dmf 11293
PRESATURATION
satmode n
wet n
SPECIAL
temp not used
gain not used
spin 20
hst 0.008
pw90 10.400
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp 1124.4
wp 19415.8
rfl 7222.5
rfp 4990.0
rp 112.9
lp 0
PLOT
wc 200
sc 0
vs 97
th 2
nm cdc ph
12.946
39.202
39.365
39.537
39.700
39.871
40.035
40.206
43.365
122.095
123.909
124.329
125.379
127.543
129.029
131.543
138.585
142.041
153.807
160.990
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

4.2.2.2 3-(4-bromophenyl)-1,1-diethyl-guanidine

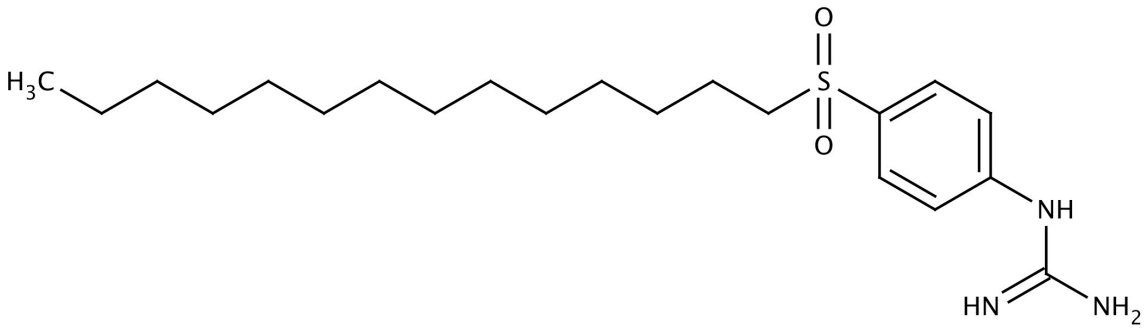


3-(4-bromophenyl)-1,1-diethyl-guanidine
MW: 270.17 g/mol

In the synthesis of p-bromophenylguanidine, 5.00 g (0.029 mol) of p-bromanilin, MW = 172.03 g/mol, d = 0.846 was added to 50 ml of dry ether and was cooled in ice bath. While cooling, hydrogen chloride is let into the mixture to prepare crystals. 5.00 g (0.0239 mol) of the crystals was dissolved in 10% excess with 2.85 g (0.029 mol, 3.37 ml) of substituted N,N-diethylcyanamide and heated to 130 °C for 60 minutes. After 60 minutes, 0.47 g (0.0048 mol, 0.56 ml) of N,N-diethylcyanamide was added to the mixture. The reaction was complete after 90 minutes. The mixture was then dissolved in water and alkalized by solution of sodium hydroxide. The product was extracted with diethylether and dried with sodium sulfate. The product was dissolved in ethanol and added a few drops of nitric acid. Crystals were formed after being cooled in the fridge for 48 hours, m = 2.99 g (18.7 % of theoretical yield) and the MP = 119.8-122.1°C

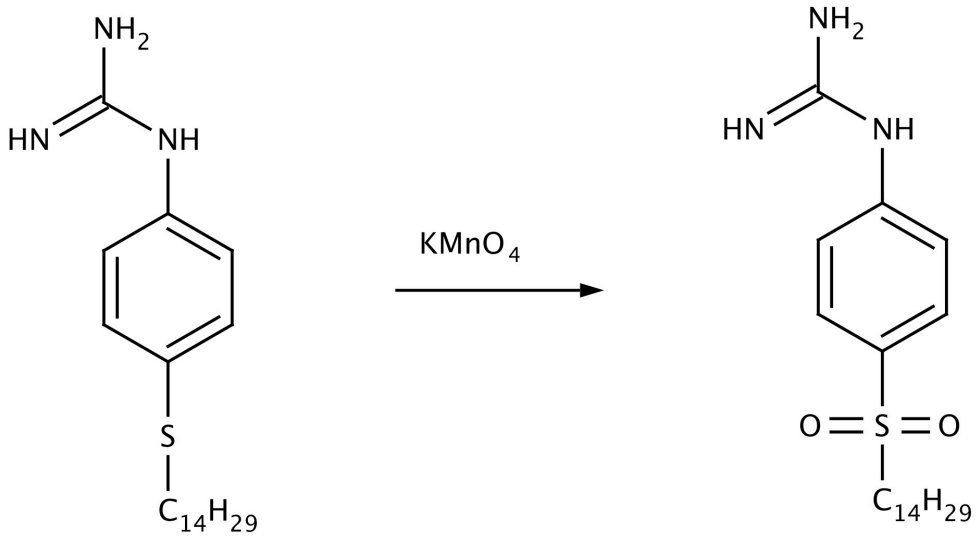

NB1-BA3;ATR-Ge
nicolet
Thu Dec 01 12:49:36 2011 (GMT+01:00)
Number of sample scans: 128
Number of background scans: 128
Resolution: 4.000
Sample gain: 1.0
Mirror velocity: 0.6329
Aperture: 150.00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
% Reflectance
Wavenumbers (cm-1)
3177
2982
1659
1617
1587
1537
1489
1466
1448
1396
1312
1294
1242
1183
1102
1077
1040
1011
823
773

4.4 Preparation of 1-(4-tetradecylsulfonylphenyl)guanidinium nitrate



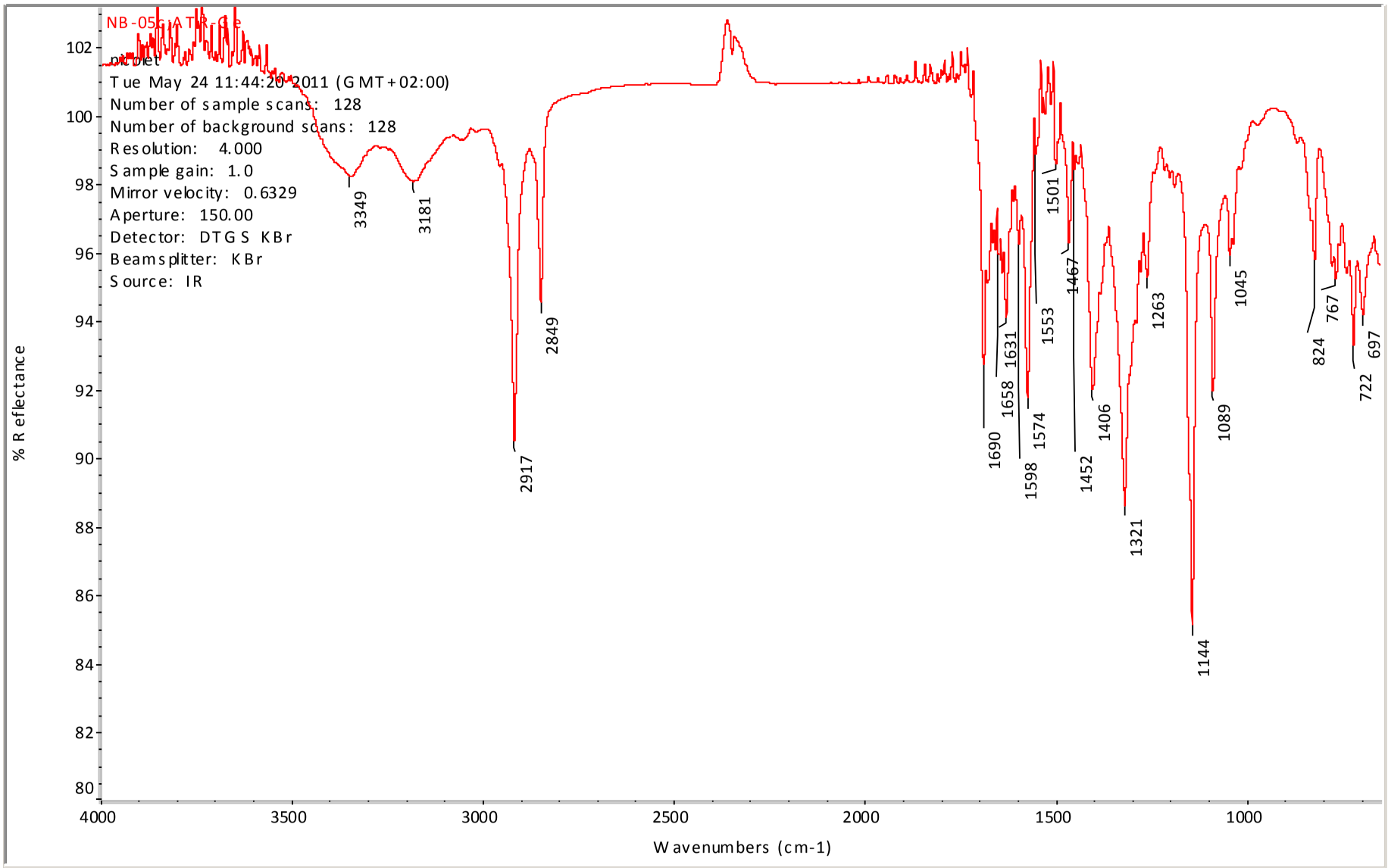
1-(4-tetradecylsulfonylphenyl)guanidine
MW = 396.7 g/mol

4.4.1 Oxidation of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate with potassium permanganate



1-(4-tetradecylsulfonylphenyl)guanidinium nitrate
MW = 458.6 g/mol

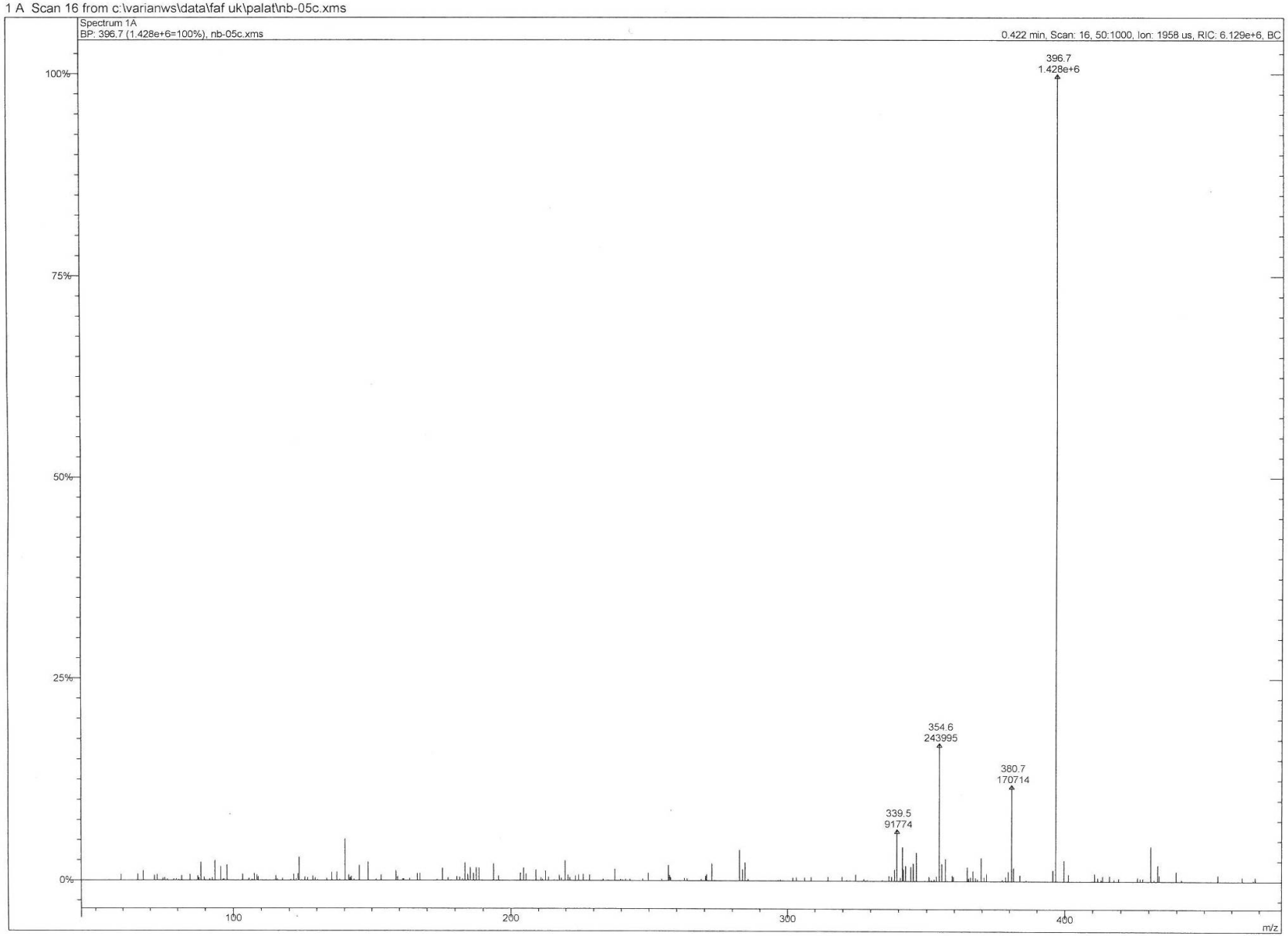
0.50 g ($1.17x10^{-3}$ mol) of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate was dissolved in 200 ml of water. After dissolution, the first portion 0.074 g ($4.69x10^{-4}$ mol) of potassium permanganate was added to the mixture. The second portion 0.064 g ($4.06x10^{-4}$) was added followed by acidification using hydrochloric acid and stored in fridge for 3 days. Following acidification, the mixture was filtered and alkalized then extracted with ethylacetate. The residue after evaporation of ethylacetate was recrystallized from water with few drops of nitric acid, m = 0.24 g (22.2% yield), MP = 115.0-117.8 °C.


NB-05
Tue May 24 11:44:20 2011 (GMT+02:00)
Number of sample scans: 128
Number of background scans: 128
Resolution: 4.000
Sample gain: 1.0
Mirror velocity: 0.6329
Aperture: 150.00
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
% Reflectance
Wavenumbers (cm-1)
3349
3181
2917
2849
1690
1658
1631
1598
1574
1553
1501
1467
1452
1406
1321
1263
1144
1089
1045
824
767
722
697

Print Date: 15 Jun 2011 15:22:43

Spectrum Plot - 6/15/2011 3:22 PM

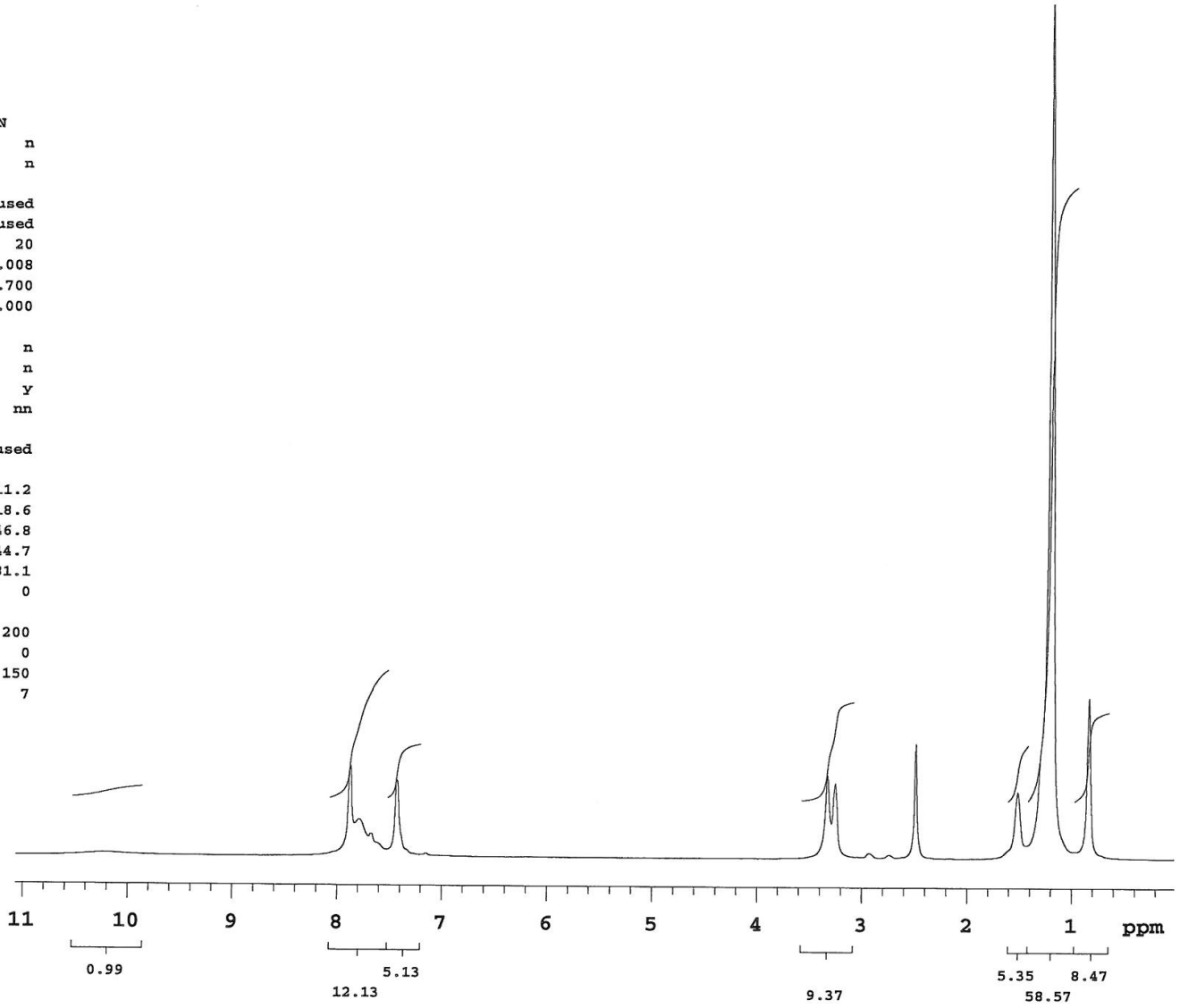
1 A Scan 16 from c:\varianws\data\faf uk\palat\nb-05c.xms



NB-05c

exp11 PROTON

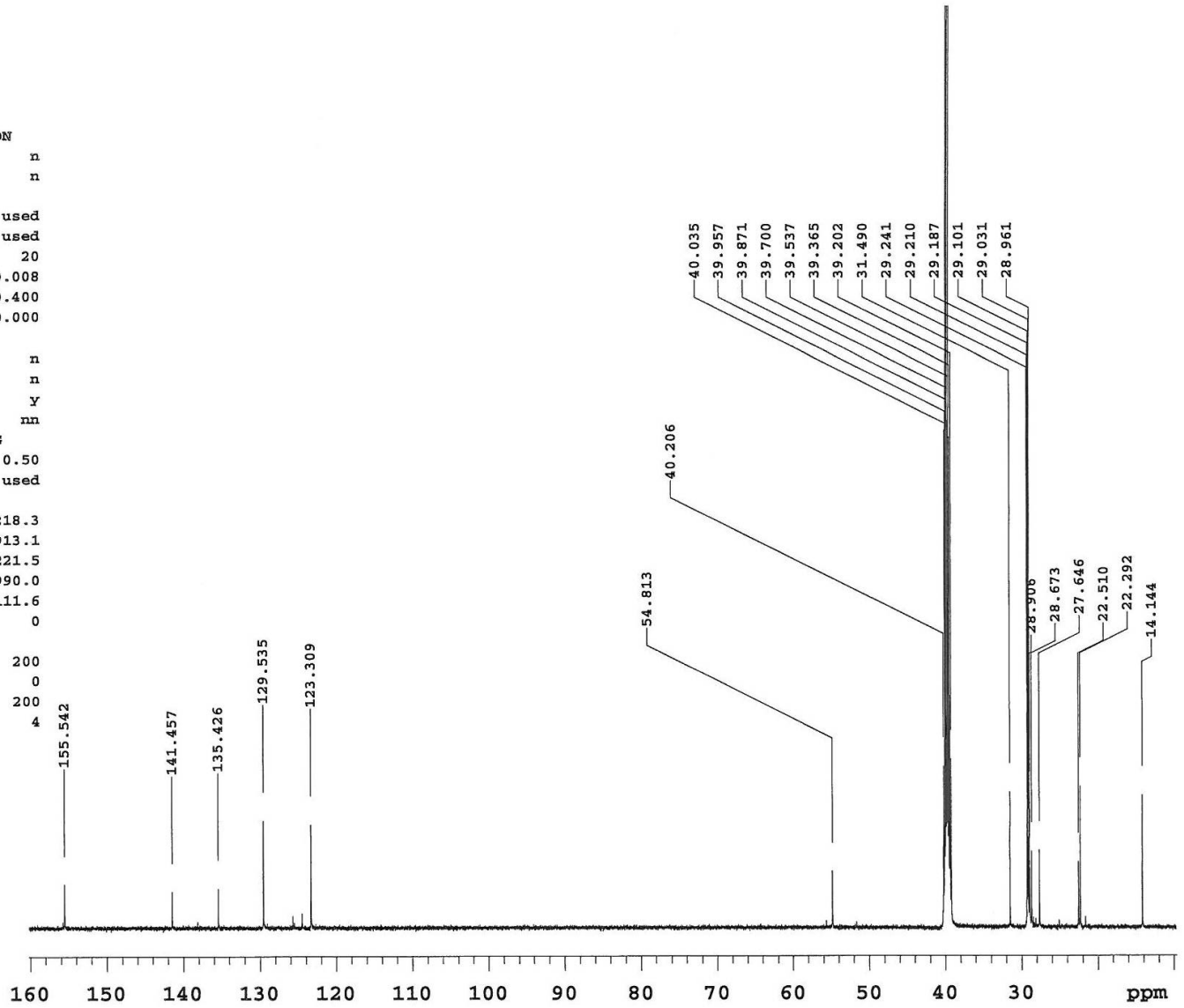
SAMPLE		PRESATURATION	
date	Jun 3 2011	satmode	n
solvent	dmso	wet	n
file	exp	SPECIAL	
ACQUISITION		temp	not used
sw	8012.8	gain	not used
at	2.045	spin	20
np	32768	hst	0.008
fb	4000	pw90	8.700
bs	32	alfa	10.000
d1	1.000	FLAGS	
nt	8	il	n
ct	8	in	n
TRANSMITTER		dp	y
tn	H1	hs	nn
sfrq	499.870	PROCESSING	
tof	499.8	fn	not used
tpwr	60	DISPLAY	
pw	4.350	sp	11.2
DECOUPLER		wp	5518.6
dn	C13	rf1	2246.8
dof	0	rfp	1244.7
dm	nnn	rp	81.1
decwave	W40_OneNMR	lp	0
dpwr	39	PLOT	
dmf	32258	wc	200
		sc	0
		vs	150
		th	7
		nm	cdc ph



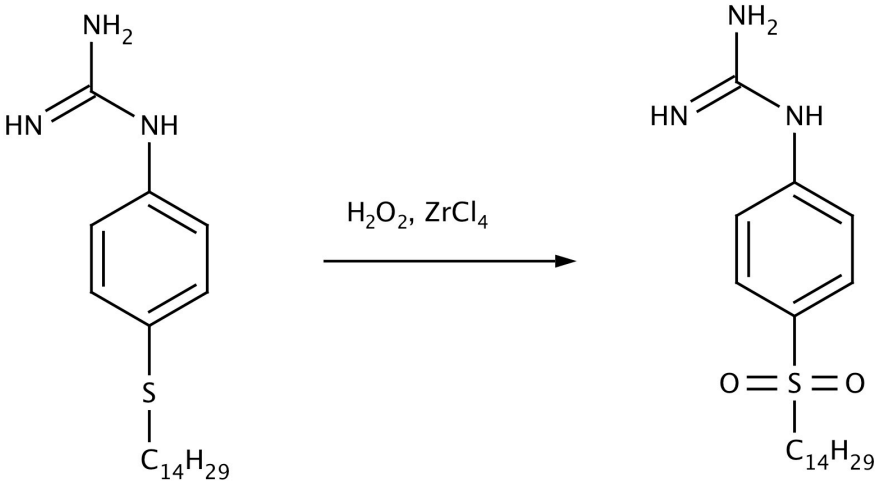
NB-05c

exp12 CARBON

SAMPLE		PRESATURATION	
date	Jun 3 2011	satmode	n
solvent	dmso	wet	n
file	exp	SPECIAL	
ACQUISITION		temp	not used
sw	32051.3	gain	not used
at	1.022	spin	20
np	65536	hst	0.008
fb	17000	pw90	10.400
bs	64	alfa	10.000
d1	2.000	FLAGS	
nt	2000	il	n
ct	2000	in	n
TRANSMITTER		dp	Y
tn	C13	hs	nn
sfrq	125.705	PROCESSING	
tof	1913.9	lb	0.50
tpwr	56	fn	not used
pw	5.200	DISPLAY	
DECOUPLER		sp	1218.3
dn	H1	wp	18913.1
dof	0	rfl	7221.5
dm	yyy	rfp	4990.0
decwave	w	rp	111.6
dpwr	40	lp	0
dmf	11293	PLOT	
		wc	200
		sc	0
		vs	200
		th	4
		nm cdc ph	



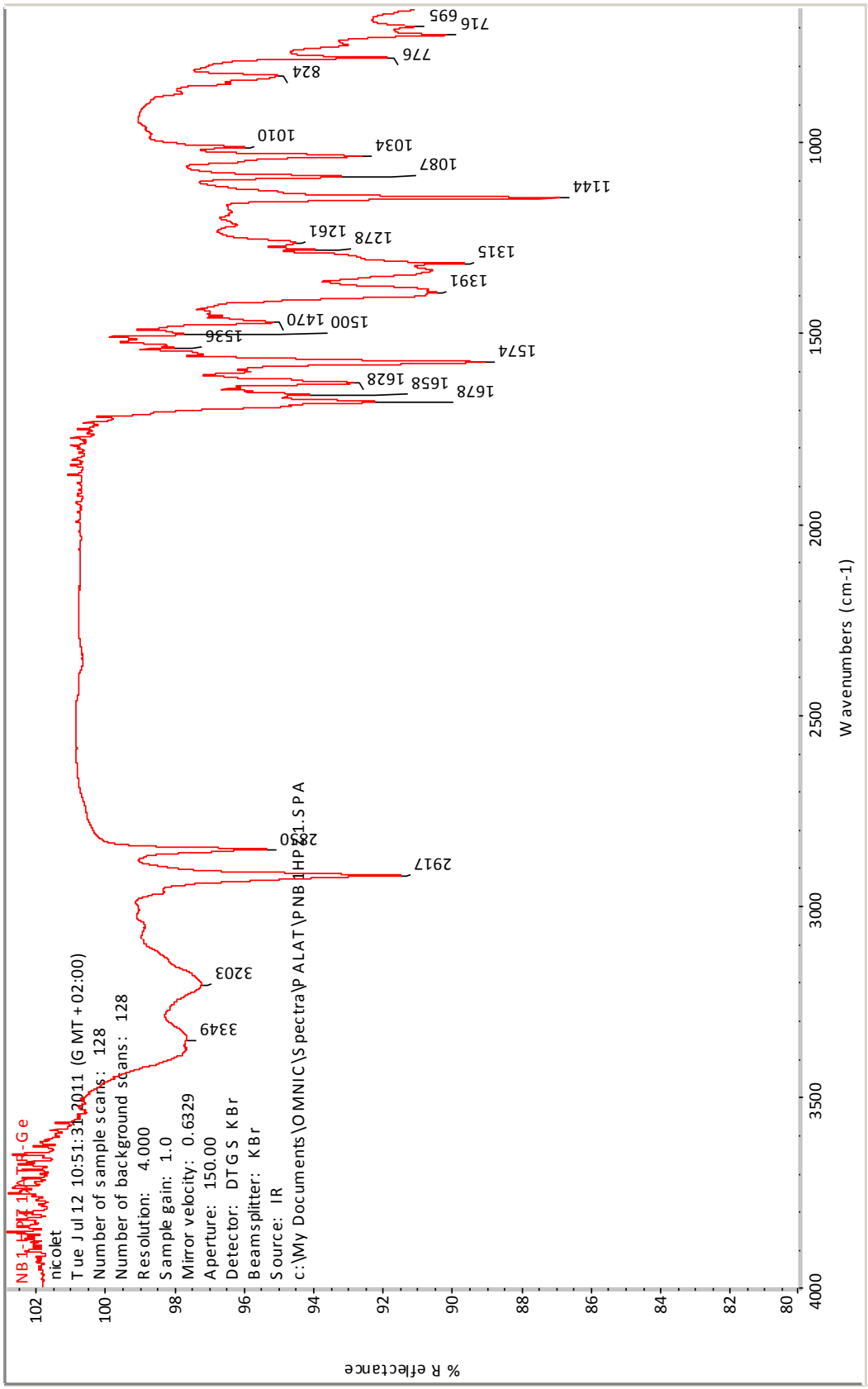
4.4.2 Oxidation of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate with hydrogen peroxide



1-(4-tetradecylsulfonylphenyl)guanidinium nitrate
MW = 458.6 g/mol

To prepare 1-(4-tetradecylsulfonylphenyl)guanidinium nitrate, 0.20 g (4.69×10^{-4} mol) of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate compound was dissolved in 7.5 ml of ethanol. After dissolution, 0.33 ml of 35% hydrogen peroxide was added following the addition of 0.22 g of zirconium tetrachloride. The product was acidified with nitric acid and cooled over night in the fridge. Crystals formed, m = 0.20 g (18.3% yield), MP = 114.5-118.4 °C. This product is the same as the product synthesized in section 4.4.1.

Oxidation with hydrogen peroxide and zirconium tetrachloride:



5. DISCUSSION

The goal of this thesis was to synthesize 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine, 3-(3-bromophenyl)-1,1-diethyl-guanidine, 3-(4-bromophenyl)-1,1-diethyl-guanidine, and to find methods in oxidizing 1-(4-tetradecylsulfanylphenyl)guanidine.

There were many steps involved in preparing the 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine compound and each step had its trails and tribulations. However, for the synthesis, dodecanethiol, was dissolved in dimethylformamide, then added potassium carbonate, copper, and 4-chloro-1-nitrobenzene to the mixture. After filtration and collection of crystals, the mass obtained was 18.26 g of 1-dodecylsulfanyl-4-nitro-benzene, MP = 49-51 °C, and the yield was calculated to be 89.6%. This result is identical to the result by G. Braunerová et al.[19] MP = 49.0–51.5 °C but the yield by G. Braunerová et al. 68% is lower.

10.00 g of 1-dodecylsulfanyl-4-nitro-benzene was used to reduce to 4-dodecylsulfanylaniline, which involved addition of tin-dichloride, dry ethanol and then refluxed under nitrogen. After filtration and collection of crystals, the mass of aniline crystals obtained m = 6.54 g, and MP = 34.6 – 36.8 °C. The practical yield was calculated to be 72.2% of theoretical yield. This result is also identical to the result by G. Braunerová et al.[19] MP = 34.6 – 36.8 °C, 73% yield.

1.00 g of 4-dodecylsulfanylaniline was used for final step for the preparation of 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine, which involved addition of N,N-diethylcyanamide. After the reaction of the aniline crystals with N,N-diethylcyanamide was complete, the product was dissolved in hot hexane and silica gel was added. 0.54 g of the final

crystalline product was obtained after filtration, cooling and purification, MP = 46.7 – 47.6°C and the yield of 49.1%. In the second trail, same procedure as the first trail was followed, however, 3.00 g of the aniline crystals was used instead of 1.00 g. 1.84 g of crystals was left after reaction with N,N-diethylcyanamide, which was dissolved in hexane and used to perform column chromatography to obtain more the final product. However, low yield of the final product was obtained therefore making column chromatography column with silica[43] not a good option to obtain the product. This can be due to the absorptive capabilities of silica to the final product. 1.50 g of aniline crystals was used in the third trail. Following the reaction with N,N-diethylcyanamide, the product was dissolved in water and ethanol. Dissolving the product in water and ethanol to obtain a crystalline product was not a good option thus very low yield of final product was found. In the fourth trial, 1.00 g of aniline crystals was used. Following reaction with N,N-diethylcyanamide, the product was dissolved in water and the crystals obtained after filtration was dissolved in hexane to perform a column chromatography using cellulose. However, very low yield of the final product was obtained.

The synthesis of 3-(3-bromophenyl)-1,1-diethyl-guanidine was prepared by using 3-bromaniline liquid. 6.34 ml of 3-bromanilin was used to prepare 9.96 g of 3-bromoanilinium chloride. 6.00 g of 3-bromoanilinium chloride was used to react with N,N-diethylcyanamide and the mass of the final product was 4.49 g (34.0% yield) in liquid form. Samples of the final product were taken to perform reactions with nitric acid, carbon dioxide, pthalic acid, or trinitrophenol to obtain 3-bromophenylguanidine in crystalline form. Since the reaction was started in liquid form, it was difficult for the 3-(3-bromophenyl)-1,1-diethyl-guanidine to form crystalline salts. However, only trinitrophenol was effective in the reaction with 3-(3-

bromophenyl)-1,1-diethyl-guanidine to form a picrate crystalline product, MP of crystals were 102.3-103.1 °C.

p-Bromaniline (5.00 g) was used to synthesize 3-(4-bromophenyl)-1,1-diethyl-guanidine. The starting compound was dissolved in ether and while cooling in an ice bath, hydrogen chloride is let into the mixture to form crystals. These crystals were heated with N,N-diethylcyanamide and then dissolved in water, alkalized with sodium hydroxide, and extracted with diethylether. To form the product, the crystals were dissolved in ethanol and acidified with nitric acid. Mass obtained after reaction is 2.99 g and the MP = 119.8-122.1°C.

We oxidized 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate using potassium permanganate and hydrogen peroxide with zirconium tetrachloride to prepare 1-(4-tetradecylsulfonylphenyl)guanidinium nitrate. In the first trail, 0.50 g ($1.17x10^{-3}$ mol) of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate was dissolved in 200 ml of water. First portion of potassium permanganate, 0.074 g ($4.69x10^{-4}$ mol) was added to the mixture. The second portion 0.064 g ($4.06x10^{-4}$) was added followed by acidification using hydrochloric acid and stored in fridge for 3 days. The mixture was filtered and alkalized then extracted with ethylacetate. After extraction, the mixture was evaporated to dryness. The remaining residue was recrystallized from water with few drops of nitric acid, m = 0.24 g (22.2% yield), MP = 115.0-117.8 °C. In the second trail, 0.20 g ($4.69x10^{-4}$ mol) of 1-(4-tetradecylsulfanylphenyl)guanidinium nitrate compound was dissolved in 7.5 ml of ethanol. After dissolution, 0.33 ml of 35% hydrogen peroxide was added following the addition of 0.22 g of zirconium tetrachloride. The product was cooled and then acidified with nitric acid to form crystals, m = 0.20 g with 18.3% yield. The MP of the product is 114.5-118.4 °C.

6. SUMMARY

In summary, we synthesized the following: 3-(4-dodecylsulfanylphenyl)-1,1-diethyl-guanidine, 3-(3-bromophenyl)-1,1-diethyl-guanidine, 3-(4-bromophenyl)-1,1-diethyl-guanidine, and we oxidized: 1-(4-tetradecylsulfanylphenyl)guanidine.

7. REFERENCES

1. P.R. Murray.; K. Rosenthal.; M. Pfaller.: Medical Microbiology 6th ed. (2008) 730-748
2. G. S. de Hoog.: Mycosis 39 (11) (2009) 407-417
3. L.A. Vale-Silva.; V. Buchta.; E. Valentova.: Folia Microbiol. 52 (1) (2007) 39–43
4. U.S. 3,541,213 (1966).
5. U.S. 3,852,460 (1967).
6. A. Schachnai, I. Barash: Plant. Dis. 66, 733 (1982).
7. Kukharev, B. F.; Lopyrev, V. A.; Klimenko, G. R.; Belozerov, L. E.; Antonik, L. M.; Shelupaev, A. P.; Kolesnikov, S. I.; Barkova, N. P.: Russ. RU 2144024 (2000).
8. Calis, U.; Koksal, M.; Ozalp, M.: FABAD J. Pharm. Sci. 26(3), 119 (2001).
9. Gossnitzer, E.; Malli, R.; Schuster, S.; Favre, B.; Ryder, N. S.: Arch. Pharm. (Weinheim, Ger.) 2002, 335(11-12), 535 (2003).
10. Gembitskii, P. A.; Efimov, K. M.; Martynenko, S. V.: Russ. RU 2217417 (2003).
11. Gembitskii, P. A.; Efimov, K. M.; Martynenko, S. V.: Russ. RU 2230734 (2004).
12. Kobori, T.; Yoshioka, N.; Haramoto, M.; Urihara, I.; Arai, S.: PCT Int. Appl. WO 2006118283; ref. Chem. Abstr. 145:488924 (2006).
13. Stephens, C. E.; Tanious, F., Kim, S.; Wilson, W. D.; Schell, W. A.; Perfect, J. R.; Franzblau, S. G.; Boykin, D. W.: J. Med. Chem. 44(11), 1741 (2001).
14. Jana, G. H.; Jain, S.; Arora, S. K.; Sinha, N.: Bioorg. Med. Chem. Lett. 15(15), 3592 (2005); Erratum in: Bioorg. Med. Chem. Lett. 16(3) 751 (2006).
15. Matolcsy, G.; Andriska, V.; Oros, G.; Komives, T.: PCT Int. Appl. WO 9615107 (1996).
16. Naik, P. R.; Pandeya, S. N.; Pandey, A.: Acta Pharm. Turcica 38(2), 37 (1996); ref. Chem. Abstr. 125:195528.
17. Liebeschuetz, J. W.; Katz, R. B.; Duriatti, A. D.; Arnold, M. L.: Pestic. Sci. 50(3), 258 (1997).
18. Gour Hari; Jain, Sanjay; Arora, Sudershan K.; Sinha, Neelima: Bioorg. Med. Chem. Lett.15, (2005) 3592
19. G. Braunerová.; V. Buchta.; Luis Silva.; J. Kuneš.; K. Palát Jr.: IL FARMACO 59 (2004) 443–450
20. R. Koffi-Nevry.; A. L. Manizan.; K. Tano.; Y. C. Yué Bi.; M. K. Oulé.; M. Koussémon.: Afr. J. Microbiol. Res. 5(24) (2011) 4162-4169
21. M. Zárraga.; A. M. Zárraga.; B. Rodríguez.; C. Pérez.; C. Paz.; P. Paz.; C. Sanhueza.: Tetrahedron Letters 49, (2008) 4775-4776
22. G. Murtaza.; M. K. Rauf.; A. Badshah.; M. Ebihara.; M. Said.; M. Gielen.; D. de Vos.; E. Dilshad.; B. Mirza.: Eur. J. Med. Chem. 1-10 (2011)
23. H. Xu.; Y.-Y. Wang.: Bioorg. Med. Chem. Lett., 20, (2010) 7274-7277
24. S. Mo.; A. Krunic.; S. D. Pegan.; S. G. Franzblau.; J. Orjala.: J. Nat. Prod 72, (2009) 2043–2045
25. L.A. Vale –Silva.; V. Buchta.; E. Valentová.; Folia Microbiol. 52 (1), 39–43 (2007)
26. O. D. Monera.; C. M. Kay.; R. S. Hodges.: protein science 3(11) (2008)
27. K. Thevissen .; K. Pellens.; K. De Brucker.; I. François.: Bioorg. Med. Chem. Lett. 21, (2011) 3686–3692
28. M. H. Ali.; G. J. Bohnert.: Synthesis (1998) 1238-1240
29. P. Kowalski.; K. Mitka.; K. Ossowskab.; Z. Kolarska.: Tetrahedron 61 (2005) 1933–1953
30. K. Jeyakumar.; D. K. Chand.: Tetrahedron Lett. 47 (2006) 4573–4576
31. A. Shaabani.; P. Mirzaei.; S. Naderia.; D. G. Lee.: Tetrahedron 60 (2004) 11415–11420
32. K. Bahrami Tetrahedron Lett. 47 (2006), 2009–2012
33. G. W. Gokel.; H. M. Gerdes.; D. M. Dishong.: J. Org. Chem. 45 (1980) 3634-3639
34. S. Dash.; S. Patel.; B. K. Mishra.: Tetrahedron 65 (2009) 707–739
35. A. Shaabani.; P. Mirzaei.; D.G. Lee.: Catalysis Letters (97) (2004) 119-123
36. C. Grambow.; S. Weiss.; R Youngman.; B. Antelmann.; B. Mertschenk.; K. P. Stengele.: Ullmann's (2001) 11283-11297
37. J. Li.; G. Zhang.; Z. Zhang.; E. Fan.: J. Org. Chem. 68 (2003) 1611-1614
38. M. Rajšner, J. Metyšová, Svátek E., F. Mikšík, M. Protiva: Collect. Czech. Chem. Commun. 40, 719 (1975)
39. F. D. Belamy, K. Ou: Tetrahedron Lett. 25, 839 (1984).
40. F. Arndt, B. Rosenau: Ber. Dtsch. Chem. Ges. 50, 1248 (1917).
41. F. Arndt: Ber. Dtsch. Chem. Ges. 46, 3522 (1913).
42. J. Miller.: J. Chem. Soc. (1949) 2722.
43. M. H. Ali.; G. J. Bohnert.: Synthesis 1238 (1998) 1238-1240