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New synthetic transformations of 1-benzyl, 3,5-dibromo, 1h-1,2,4-triazole /c

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY ADAM M. FIVUSH ENTITLED "New Synthetic Transformations of 1-Benzyl, 3,5-Dibromo, 1H-1,2,4-Triazole" BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS OF THE DEGREE OF Master of Science FROM THE COLLEGE OF Arts & Sciences

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NEW SYNTHETIC TRANSFORMATIONS OF 1-BENZYL, 3,5-DIBROMO, 1H-1,2,4-TRIAZOLE

BY

ADAM MICHAEL FIVUSH
B.S., Emory University, 1986

THESIS

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ABSTRACT

This report details the study of the nucleophilic substitution of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole. A variety of nucleophiles have been studied to date. The nucleophiles studied primarily fall into the categories of Phosphorous, Oxygen and Sulfur species. Some of the initially formed substitution products are thermally unstable and undergo unique rearrangements.

The report describes the physical properties, ^{1}H NMR, ^{13}C NMR, IR and Mass spectra for all of the synthesized compounds. Possible mechanistic pathways are presented for the formation of the prepared compounds. Recommendations are made in order to suggest future research opportunities in this area.

ACKNOWLEDGEMENTS

I would like to thank the faculty and staff of the Department of Chemistry at the University of Central Florida for giving me the opportunity to continue my studies in chemistry. I would especially like to thank Dr. John T. Gupton III, for his wisdom, encouragement, and patience. I would also like to thank Dr. Seth Elsheimer for his time, comments and efforts in assisting me with this work. I also extend my appreciation to Dr. Howard Miles and Dr. Michael Hampton for their time and effort. I would like to comment that this institution has supplied me with invaluable teaching and research experience.

In addition, I would like to thank Dr. Jim Sikorski of the Monsanto Agricultural Products Company for providing the funding for this project and for his solid advice.

I wish to thank my grandmother, Helen Fivush, for all her support and love throughout the years. Finally, I wish to thank my parents, Donald and Georgette Fivush, for their support, love and encouragement.

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LIST OF ABBREVIATIONS

bp	boiling point
^{o}C	degrees Centigrade
$CDCl_3$	deuterated chloroform
cm^{-1}	wavenumber
^{13}C NMR	Carbon-13 NMR
δ	delta (NMR spectrum)
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
eq.	equivalents
g	grams
HMPA	Hexamethylphosphoramide
^{1}H NMR	Proton NMR
IR	infrared
J	coupling constant in Hertz (NMR spectrum)
q	quartet (NMR spectrum)
m	multiplet (NMR spectrum)
m/e	mass to charge ration
mp	melting point
mL	milliliters
M^{+}	molecular ion

mol	moles
MHz	megahertz
ppm	parts per million
r.t.	room temperature
s	singlet (NMR spectrum)
t	triplet (NMR spectrum)
TLC	thin layer chromatography
v/v	volume/volume
w/w	weight/weight
xs	excess

INTRODUCTION

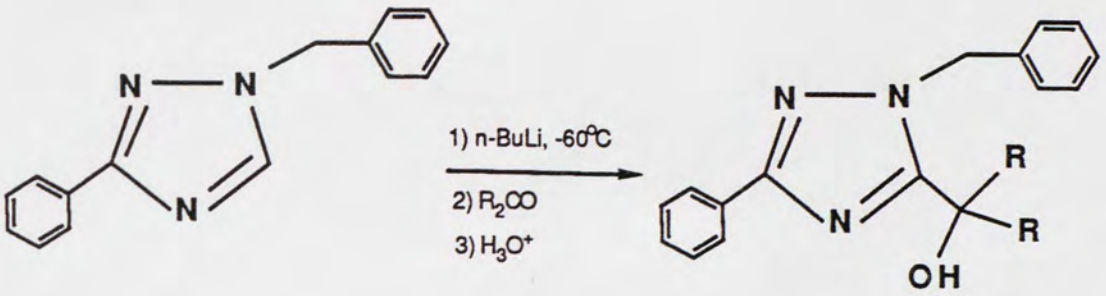
The use of organometallic reagents in organic synthesis had its origin in the early 1900's with Victor Grignard's work. He discovered that aryl and alkyl halides reacted with magnesium metal to produce nucleophilic organomagnesium compounds. Based upon this discovery, organolithium compounds, which have been shown to be more reactive than Grignard's organomagnesium compounds, have become synthetically useful reagents. Alpha-lithiation, where the carbon that is alpha to the heteroatom undergoes facile metallation has been utilized mainly for substituting on five-membered heterocycles, particularly thiazoles and thiophenes. The alpha-lithiation of 1H-1,2,4-triazole rings, however, has been overlooked until recently. In fact, only four reports of such metallations have appeared in the literature.[1-4]

Burgess and Sanchez[1], and Behringer and Ramert[2] treated 1-benzyl-3-phenyl-1H-1,2,4-triazole with n-butyllithium at low temperatures and then quenched with benzophenones or formaldehyde to yield the corresponding 1-benzyl-3-phenyl- 1H-1,2,4-triazol-5-yl carbinols as seen in Figure 1. Jutzi and Gilge[3] treated 1-methyl-1H-1,2,4-

triazole with n-butyllithium at low temperatures and then quenched with trimethylstannyl chloride to yield the trimethylstannane (Figure 2).

The most recent article on alpha-lithiation, authored by Anderson, Sikorski, Reitz, and Pilla[4], of the Monsanto Agricultural Products Company, was an in-depth study of the electrophilic substitution of 1-substituted-1H-1,2,4-triazoles via lithiated triazole intermediates. In particular, the researchers were interested in synthesizing the previously unknown 1-substituted-1H-1,2,4-triazol-5-yl phosphonate. The 5-phosphono-1H-1,2,4-triazol-3-one was predicted to have potential use as an inhibitor of EPSP synthase, a plant growth hormone, since it was similar spatially and had the same functional group orientation as the potent herbicide N-phosphonomethyl-glycine. The method chosen for preparing the 5-substituted phosphonate utilized a lithiated triazole which would be quenched with a chlorophosphate. In order to avoid isomer formation, the metallation reaction had to proceed in a regioselective manner to produce the 5-substituted product. The literature indicated that the lithiation at C-5 would predominate but possibility of C-3 lithiation could not be ignored.

The first step in the inquiry was to determine whether a carbon-phosphorous bond could be formed via a lithiation reaction. 1-Benzyl-3-phenyl-1H-1,2,4-triazole was used for



R	% Yield
H	78
C_6H_5-	92
4-CH_3O-C_6H_4-	94
4-$(CH_3)_2N$-C_6H_4-	91

Figure 1. Preparation of 1-benzyl-3-phenyl-1H-1,2,4-triazol-5-yl carbinols from 1-benzyl-3-phenyl-1H-1,2,4-triazole and the corresponding benzophenone or formaldehyde.

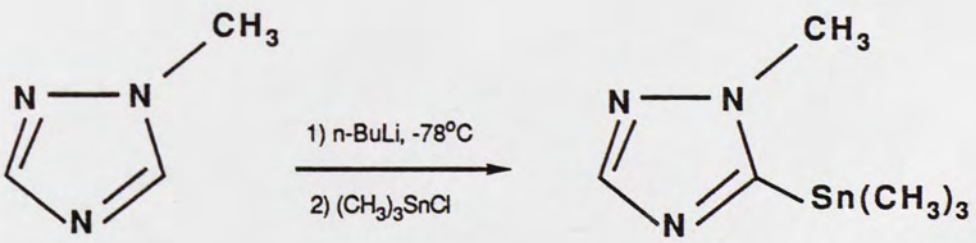


Figure 2. Preparation of 1-methyl-5-trimethylstannane-1H-1,2,4-triazole from 1-methyl-1H-1,2,4-triazole and trimethylstannyl chloride.

this initial study because the only available site for lithiation was at C-5. When treated with n-butyllithium at minus seventy-eight degrees Centigrade and quenched with diethyl chlorophosphate the desired 1-benzyl-3-phenyl-1H-1,2,4-triazol-5-yl phosphonic diethyl ester (Figure 3) was produced in good yield. The 3-phenyl-4-benzyl-4H-1,2,4-triazole reacted similarly to give the 3-phenyl-4-benzyl-4H-1,2,4-triazol-5-yl phosphonic acid diethyl ester. A side product of this reaction was revealed as N-cyano, N-benzylaminophosphonic acid diethyl ester, presumably caused by an anion mediated ring opening upon quenching with the diethyl chlorophosphonate (Figure 4). Treatment of the substituted phosphonate esters with excess trimethylsilyl bromide and subsequent hydrolysis gave the corresponding substituted phosphonic acids.

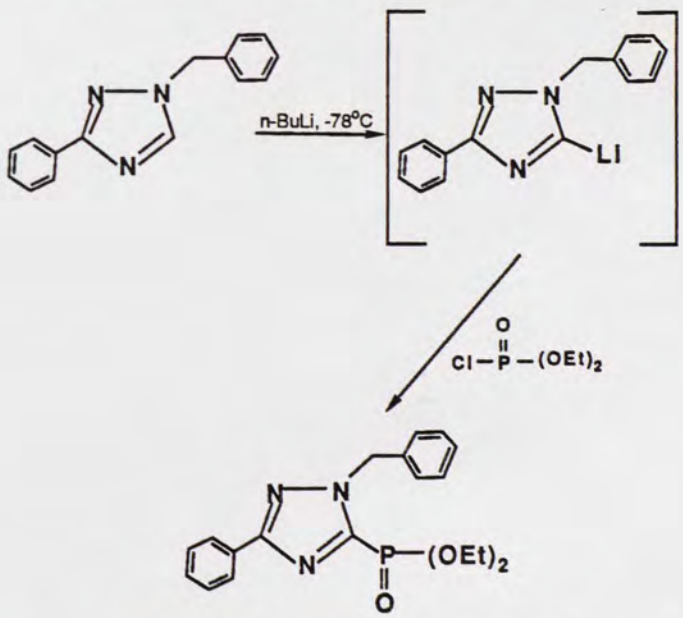


Figure 3. Preparation of 1-benzyl-3-phenyl-1H-1,2,4-triazol-5-yl phosphonic acid diethyl ester.

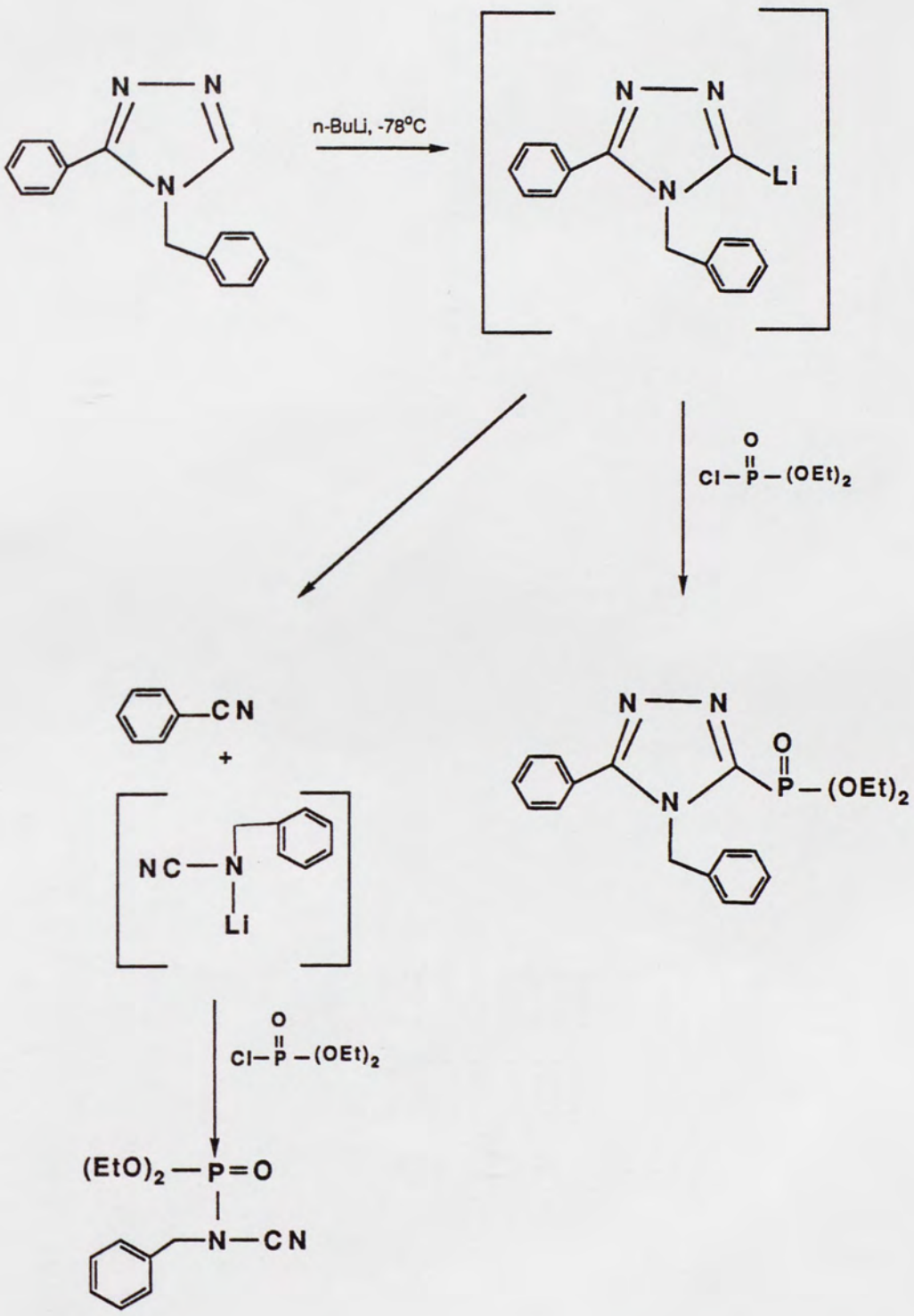


Figure 4. Preparation of 3-phenyl-4-benzyl-4H-1,2,4-triazol-5-yl phosphonic acid diethyl ester.

Since a triphenylmethyl protecting group can be cleaved easily, the 1-triphenylmethyl-1H-1,2,4-triazole was treated with n-butyllithium and then quenched with perdeuterio-methanol or benzophenone to give the 5-substituted products in good yields. However, when quenched with diethyl chlorophosphate, none of the desired phosphonate was produced. The reaction led to recovered starting material evidentally due to the shielding of the lithiated 5-position which inhibited attack by the bulky chlorophosphate. As reported by Burgess and Sanchez[1], the N-benzyltriazoles are deprotected quite easily by treatment of sodium metal in ammonia. However, in the case of the 5-substituted phosphonates, no debenzylation occurred. Hydrogenolysis using a palladium-carbon catalyst also failed because hydrogenolysis of such compounds requires acid catalysis. Unfortunately, the phosphonates are not stable under acidic conditions, resulting in carbon-phosphorous bond cleavage.

In order to illustrate the versatility of the electrophilic substitution of the lithiated triazoles, other electrophiles were studied. Several are shown in Figure 5.

Since the original objective was to prepare the 5-phosphono-1H-1,2,4-triazol-3-one, the next step in the synthesis was to activate the C-3 position of the 1-benzyl-5-phosphono-1H-1,2,4-triazole by another lithiation.

the product did not exhibit the expected inhibition of the EPSP synthase. This result was attributed to the flexibility of the glyphosate backbone and the rigidity of the triazole backbone.

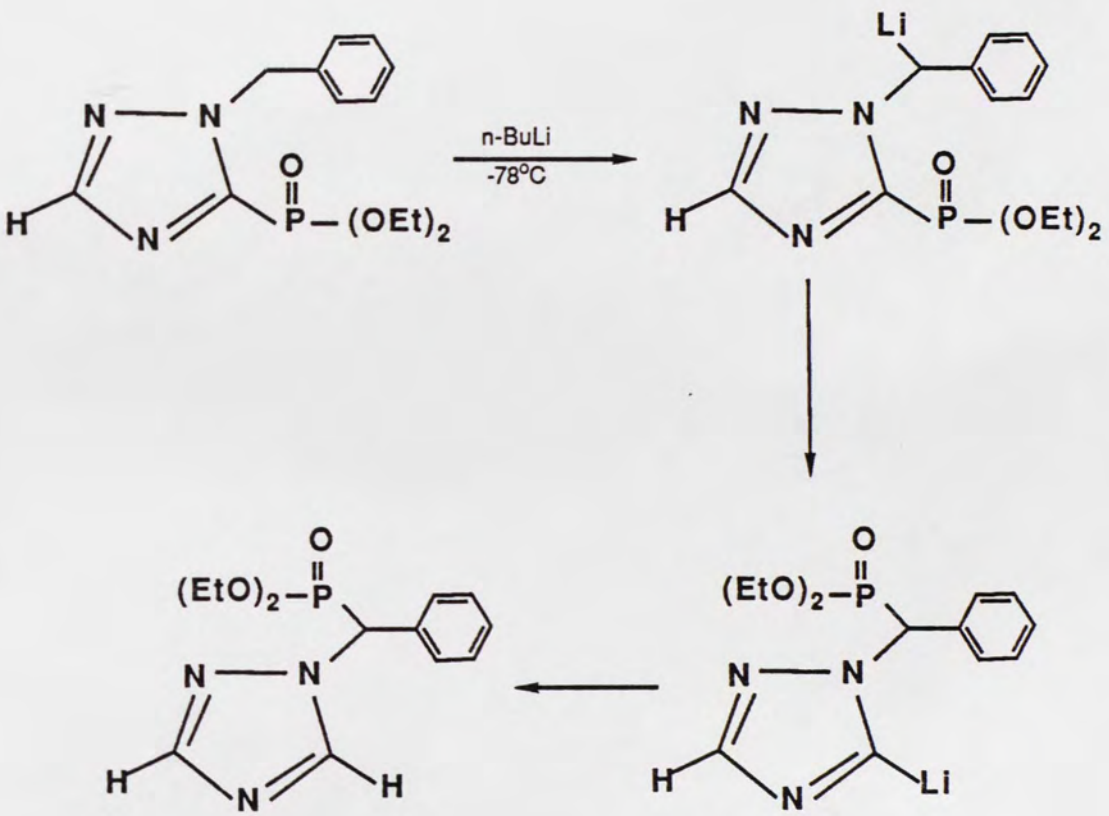


Figure 6. Lithiation and subsequent rearrangement of 1-benzyl-5-phosphono-1H-1,2,4-triazole.

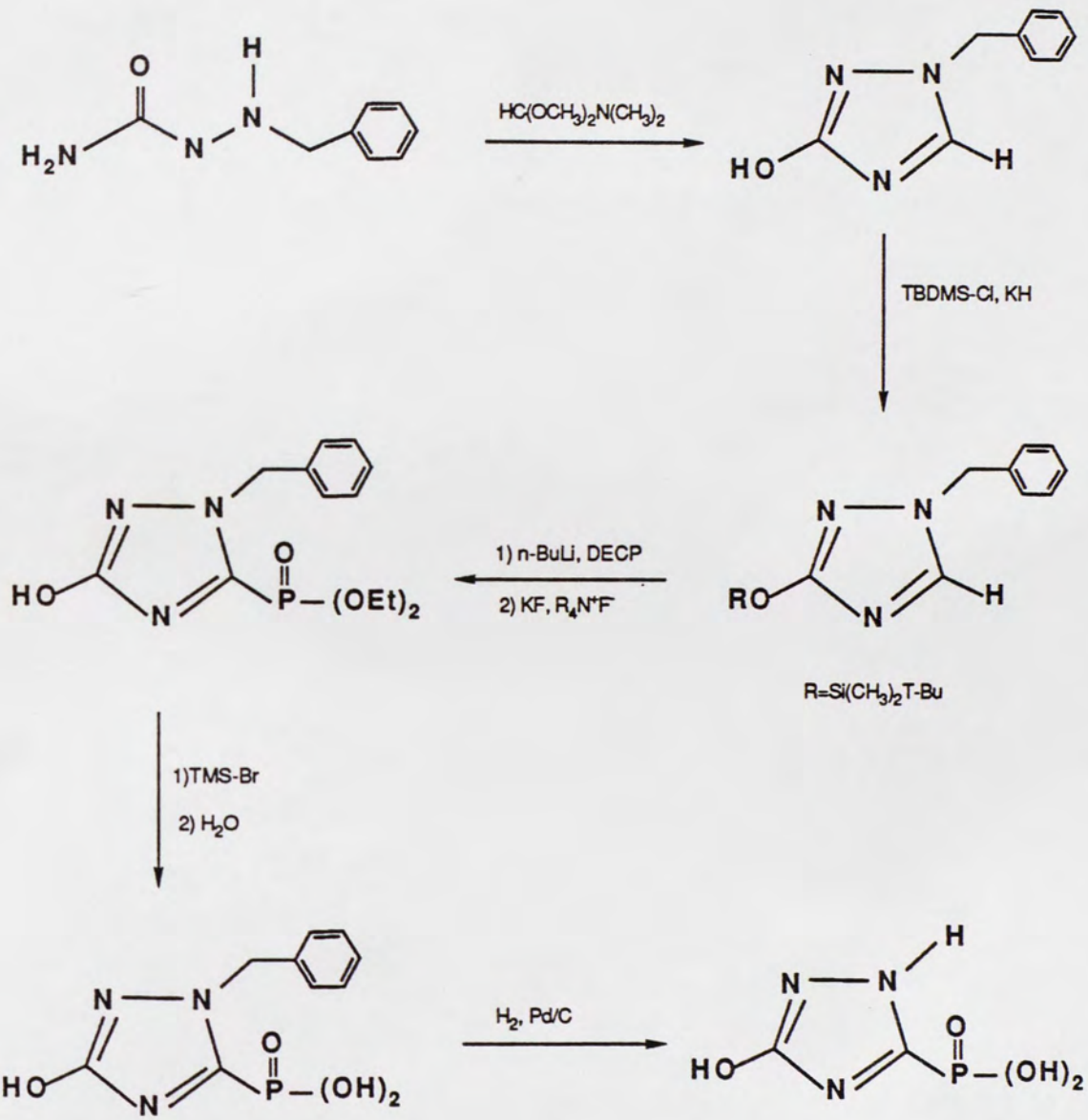


Figure 7. Synthesis of 5-phosphono-1H-1,2,4-triazol-3-one.

The Sikorski group at Monsanto Agricultural Products was also interested in synthesizing unsymmetrical 3-phosphono-5-substituted-1H-1,2,4-triazoles. Since lithiation at C-3 had already been proven unsatisfactory, a possible solution was to substitute C-3 nucleophilically and then substitute C-5 via lithiation chemistry. In particular, we proposed to use Arbuzow chemistry[5] to produce the 3-phosphono-1H-1,2,4-triazole. The Arbuzow reaction (Figure 8) proceeds by two successive S_N2 steps. An unstable phosphonium ion forms initially and then the halide displaces one of the alkyl groups. We proposed (1) to investigate the reactions of triethyl phosphite with 1-benzyl-3,5-dibromo- 1H-1,2,4-triazole; (2) to investigate the reactions of the sodium salt of diethyl phosphite with 1-benzyl-3,5-dibromo- 1H-1,2,4-triazole; and (3) to investigate the nucleophilic substitution reactions of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole.

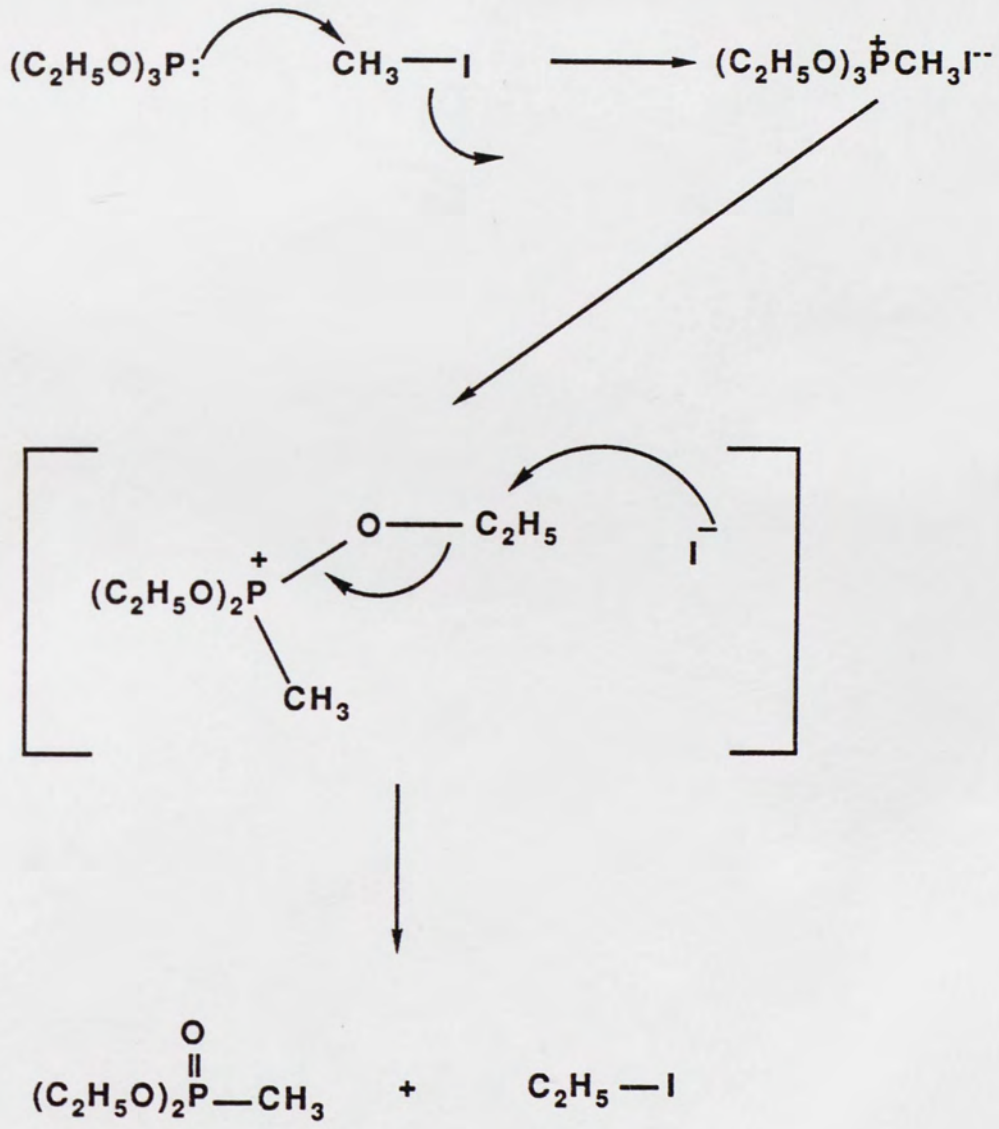


Figure 8. Mechanism of the Arbuzow reaction.

EXPERIMENTAL

A. General

Proton and carbon NMR spectra were obtained at 200 MHz on a Varian Gemini-200 NMR spectrometer. Chemical shifts were reported in ppm (δ) downfield from tetramethylsilane, which was used as the internal standard. Solvents used to dissolve samples for the purpose of obtaining NMR spectra included $CDCl_3$ and DMSO-d_6.

Infrared spectra were recorded on a Perkin-Elmer Model 1420 ratio recording infrared spectrometer and absorptions are reported in cm^{-1}. Samples were run as thin films, nujol mulls, $CHCl_3$ solutions, or KBr pellets.

Melting points were determined using a Fischer-Johns melting point apparatus and were corrected. Boiling points were determined using a Kugelrohr distillation apparatus (1.5-0.5 mm Hg).

Removal of solvents *in vacuo* was performed using a Buchi Rotovapor-R rotary evaporator and a thermostatically controlled hot water bath. Anhydrous magnesium sulfate was used as the drying agent in reaction workups.

Analytically pure samples of liquids were prepared by Kugelrohr distillation or a Harrison Research Chromatotron

(preparative, accelerated thin-layer chromatograph). Solids were purified by recrystallization.

B. Preparation of 3,5-dibromo-1H-1,2,4-triazole

3,5-Dibromo-1H-1,2,4-triazole was prepared as described in the literature.[6] To a 1000-mL three-necked round bottom flask immersed in an ice bath and equipped with a thermometer, mechanical stirrer, and an addition funnel were added 23.0 g (0.333 mol) of 1,2,4-triazole, 40 g (1.0 mol) of sodium hydroxide pellets, and 350 mL of water. The cooled mixture was treated dropwise with 35 mL (0.666 mol) of bromine in such a manner that the reaction temperature remained below 30°C. The reaction was then allowed to proceed at room temperature for 1 hour. The mixture was then acidified, while cooling in an ice bath, with concentrated hydrochloric acid, to pH 3. The resulting white precipitate was collected by vacuum filtration and dried in vacuo to afford 65.74 g (89% yield) of a white solid: mp 202-204°C; lit. mp 211-212°C; IR (nujol) 1510, 1340, 1200-1300 (broad), 1125, 1010, 980, 790-850 (broad), 725, and 700 cm^{-1}.

C. Preparation of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole

1-Benzyl-3,5-dibromo-1H-1,2,4-triazole was prepared as described in a private correspondence with James A. Sikorski.[7] To a 500-ml three-necked round bottom flask

equipped with a reflux condenser, thermometer, magnetic stirring bar and a glass stopper were added 15 g (0.0066 mol) of 3,5-dibromo, 1H-1,2,4-triazole, 10.5 g (0.099 mol) of sodium carbonate, 8.4 g (0.0066 mol) of benzyl chloride, and 75 mL of anhydrous N,N-dimethylformamide. The reaction mixture was stirred under nitrogen for 20 hours. The reaction was then heated to 100°C for 1 hour. After cooling, 75 mL of chloroform was added and the precipitated salts were filtered off by gravity. The chloroform and the N,N-dimethylformamide were removed under vaccum. The residue was dissolved in chloroform, washed with 100 mL water, and 100 mL brine, and dried over anhydrous magnesium sulfate. The drying agent was removed by gravity filtration and the solution concentrated in vacuo to afford 17.0 g (81% yield) of an off-white solid: mp 48-51°C; 1H NMR ($CDCl_3$) δ 5.30 (s,2H) and 7.35 (m,5H); ^{13}C NMR (CDCL3) δ 54.1, 128.6, 129.4, 129.7, 130.1, 134.3, and 140.9; IR ($CHCl_3$) 3000, 1490, 1430, 1450, 1350, 1220-1290 (broad), 1050-1090, 990, and 715 cm^{-1}.

D. Preparation of 1-benzyl-3-bromo-1H-1,2,4-triazole

To a dry 250-mL three-necked round bottom flask equipped with magnetic stirrer, reflux condenser, thermometer and rubber septum were added 1.50 g (0.00473 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole and 25 mL of dry tetrahydrofuran. The system was flushed with nitrogen

and the mixture cooled in an ice/salt-water bath, after which 4.15 mL (0.0118 mol) of methyl magnesium bromide in tetrahydrofuran was added via syringe. The reaction mixture was allowed to stir at room temperature for 1 hour. The reaction was then quenched with water while cooling in an icebath. The tetrahydrofuran was stripped off <u>in vacuo</u> and 50 mL of chloroform was added. The chloroform was then washed with 3 x 50 mL of water and the organic layer was dried over anhydrous magnesium sulfate. The drying agent was removed by gravity filtration and the mixture concentrated <u>in vacuo</u> to give an off-white solid which was recrystallized from cyclohexane to afford 0.510 g (45.3% yield) of a white solid: mp 52-53°C; ^{1}H NMR ($CDCl_3$) δ 5.25 (s,2H), 7.35 (m,5H), and 7.9 (s,1H); ^{13}C NMR ($CDCl_3$) δ 54.7, 128.9, 129.6, 129.8, 134.3, 140.8, and 145.2; IR (nujol) 3120, 1730, 1580-1600, 1310, 1230-1280 (broad), 1140-1210, 1020, 870, 710-750 (broad), and 700 cm^{-1}.

<u>E. Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with triethyl phosphite</u>

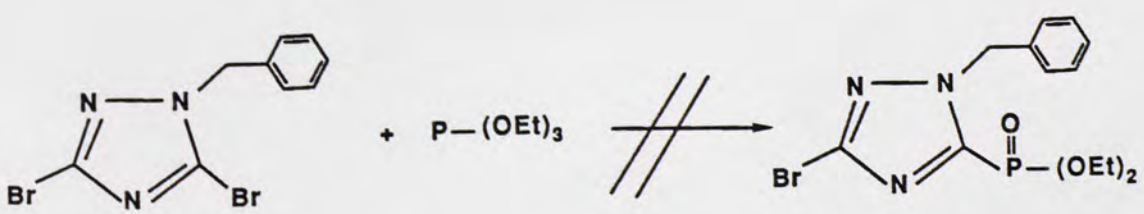


Table I

Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with triethyl phosphite.

Entry	eq. $P(OEt)_3$	Solvent	Temp°C	Time-h	Results[a]
1	1	toluene	110	24	A
2	1	neat	160	2	C
3	1	DMF	135	24	A + B
4	xs	neat	130	1	A + B
5	1	DMSO	100	4	A + B

[a] The projected product by Arbuzov chemistry: 1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl phosphonic diethyl ester, was not produced. Instead, indicated by ^1H NMR and TLC, the results were determined to be A: 1-benzyl-3,5-dibromo-1H-1,2,4-triazole, B: 1-benzyl-3-bromo-1H-1,2,4-triazole and C: decomposition (where no methylene H's from the benzyl substituent appear in the ^1H NMR spectrum).

Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with triethyl phosphite

A 50-mL one-necked round bottom flask was equipped with a magnetic stirring bar and a reflux condenser. Into the flask were placed 1.00 g (0.00316 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole and excess triethyl phosphite. The reaction mixture was heated to 130°C for 1 hour. The excess triethyl phosphite was then stripped off on the Kugelrohr to afford a dark liquid.

F. Attempted reaction of 2-chlorolepidine with triethyl phosphite

A 50-mL one-necked round bottom flask was equipped with a magnetic stirring bar and a reflux condenser. Into the flask were placed 1.00 g (0.00563 mol) of 2-chlorolepidine and excess triethyl phosphite. The reaction mixture was heated to 150°C for 2 hours. The excess triethyl phosphite was then stripped off on the Kugelrohr to afford a dark liquid. ^{1}H NMR and TLC indicated unreacted starting material.

G. Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with the sodium salt of diethyl phosphite

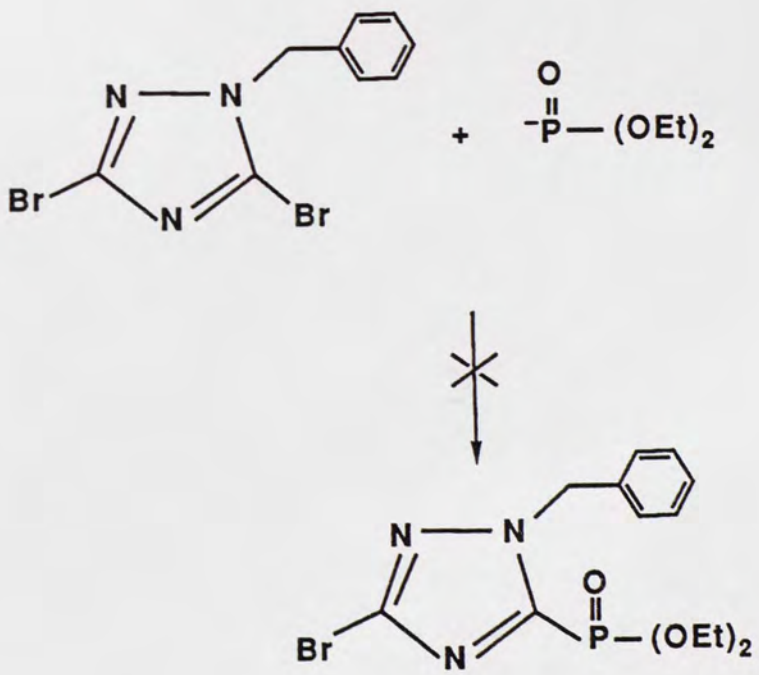


Table II

Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with the sodium salt of diethyl phosphite.

Entry	eq. $P(OEt)_2OH$	Solvent	Temp°C	Time-h	Results[a]
1	1.25	dioxane	100	0.5	A
2	1.25	DMSO	60	0.5	A + B
3	1.25	DMF	100	0.5	A + B
4	1.25	HMPA	160	1	B
5	1.25	HMPA	90	1.5	B
6	1.25	HMPA	30	48	B
7	2.5	DMF	150	24	B

[a] The predicted product: 1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl phosphonic diethyl ester was not produced under any of the conditions. Instead, indicated by ^1H NMR and TLC, the products were determined to be A: 1-benzyl-3,5-dibromo-1H-1,2,4-triazole and B: 1-benzyl-3-bromo-1H-1,2,4-triazole.

Attempted reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with the sodium salt of diethyl phosphite

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, reflux condenser and two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 0.0126 g (.00316 mol) of sodium hydride (60% dispersion in mineral oil) and

50 mL of hexane. The mixture was stirred for several minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 0.436 g (0.00316 mol) of diethyl phosphite and 30 mL of N,N-dimethylformamide were added to the dry sodium hydride. The mixture was stirred for several minutes and 1.0 g (0.00316 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was heated to 100°C for 30 minutes. After the mixture was cooled to room temperature, the solvent was removed in vacuo and the residue partitioned between chloroform (50 mL) and water (50 mL). The aqueous phase was extracted with additional chloroform (15 mL) and the combined chloroform layers were washed with 3 x 50 mL water. The organic layer was then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solution concentrated in vacuo to afford a brown liquid.

H. Preparation of 4,5-dihydro-1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazol-5-one

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser, and two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 0.56 g (0.014 mol) of sodium hydride (60% dispersion in mineral oil) and 50 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula

syringe and vacuum. Once the mineral oil was removed by the hexane wash, 0.81 g (0.0253 mol) of methanol and 100 mL of N,N-dimethylformamide were added to the dry sodium hydride. The mixture was stirred for several minutes and 2.0 g (0.0063 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was refluxed for 24 hours. After the mixture was cooled to room temperature, the solvent was removed in vacuo and the residue partitioned between chloroform (150 mL) and water (100 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The organic layer was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The solution was concentrated in vacuo to give a yellow solid which upon recrystallization from methanol afforded 1.09 g (64.5% yield) of a white solid: mp 114-116°C; ^{1}H NMR ($CDCl_3$) δ 3.28 (s,3H), 4.93 (s,2H), and 7.35 (m,5H); ^{13}C NMR ($CDCl_3$) δ 29.6, 50.0, 122.7, 128.7, 129.0, 129.3, 136.4, and 153.6; IR (nujol) 3100-3650 (broad), 1600-1740 (broad), 1520, 1320, 1270, 1260, 1100, 1020, 750, 730, and 700 cm^{-1}; mass spectrum m/e 267, 269 (M^+).

I. Preparation of 1-benzyl-3-bromo-5-methoxy-1H-1,2,4-triazole

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser and

two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 0.56 g (0.014 mol) of sodium hydride (60% dispersion in mineral oil) and 50 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 50 mL of methanol was added to the dry sodium hydride. The mixture was stirred for several minutes and 2.0 g (0.0063 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was stirred overnight. The solvent was removed <u>in vacuo</u> and the residue partitioned between chloroform (150 mL) and water (100 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The organic layer was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The solution was concentrated <u>in vacuo</u> to give a yellow solid which upon recrystallization from methanol afforded 1.277 g (75.5% yield) of white crystals: mp 52-53°C; ^{1}H NMR ($CDCl_3$) δ 4.02 (s,3H), 5.0 (s,2H), and 7.15 (m,5H); ^{13}C NMR ($CDCl_3$) δ 50.7, 59.3, 128.5, 128.9, 129.5, 135.6, 136.3, and 159.9; IR (nujol) 1555, 1500, 1250-1310 (broad), 1115, 980-1020, 720, and 695 cm^{-1}; mass spectrum m/e 267, 269 (M^{+}).

J. Preparation of 1-benzyl-3-bromo-5-alkoxy-1H-1,2,4-triazoles.

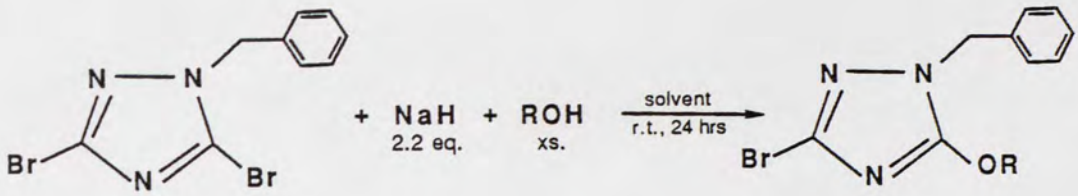


Table III

Preparation of 1-benzyl-3-bromo-5-alkoxy-1H-1,2,4-triazoles

Entry	R	Solvent	%Yield[a]	bp (mm Hg) mp (°C)
1	ethyl	ethanol	85.4[c]	bp 144 (1.2)
2	n-propyl	n-propanol[b]	79.94[d]	bp 150 (1.0)
3	n-butyl	1-butanol[b]	87.6[e]	mp 48-52
4	isopropyl	isopropanol[b]	--[f]	--
5	isobutyl	isobutanol	--[f]	--
6	tert-butyl	tert-butanol	--[g]	--
7	sec-butyl	sec-butanol	--[g]	--

[a] The percent yield is based on the purified yield where the purification involved distillation or recrystallization.

[b] When the reaction was done in DMF with 4.4 equivalents of the alcohol, the reaction products were 1-benzyl-3,5-dibromo-1H-1,2,4-triazole, 1-benzyl-3-bromo-1H-1,2,4-triazole, and a minute amount of the 5-substituted alkoxy

as indicated by ^1H NMR and TLC. Subsequent attempts at purification using a Harrison Chromatotron failed.

[c] See the experimental procedure for spectral data.

[d] 1H NMR ($CDCl_3$) δ 0.93 (t,J=7.9,3H), 1.8 (m,J=7.9,2H), 4.35 (t,J=7.9,2H), 5.0 (s,2H), and 7.3 (m,5H); ^{13}C NMR ($CDCl_3$) δ 10.3, 22.5, 50.7, 74.3, 128.6, 128.9, 129.4, 135.6, 136.2, and 159.4; IR (neat) 2800-3100, 1550, 1490, 1450, 1380, 1240-1310 (broad), 1110, 980, 960, 720, and 700 cm^{-1}; mass spectrum m/e 295, 297 (M^+).

[e] 1H NMR ($CDCl_3$) δ 0.90 (t,J=7.7,3H), 1.35 (m,J=7.7,2H), 1.72 (m,J=7.7,2H), 4.4 (t,2H), 5.05 (s,2H), and 7.30 (m,5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.1, 31.1, 50.7, 72.6, 128.6, 128.9, 129.4, 135.7, and 136.2; IR (nujol) 1510-1570 (broad), 1495, 1240-1300 (broad), 1225, 1115, 1060, 1030, 990, 940, 880, 730, and 700 cm^{-1}; mass spectrum m/e 309, 311 (M^+).

[f] TLC and ^1H NMR indicated pure 1-benzyl-3,5-dibromo-1H-1,2,4-triazole as the reaction product.

[g] TLC and ^1H NMR indicated both 1-benzyl-3,5-dibromo-1H-1,2,4-triazole and 1-benzyl-3-bromo-1H-1,2,4-triazole as the reaction products.

Preparation of 1-benzyl-3-bromo-5-ethoxy-1H-1,2,4-triazole

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser, and two glass stoppers. A nitrogen atmosphere was maintained

at all times. Into the flask were placed 0.84 g (0.021 mol) of sodium hydride (60% dispersion in mineral oil) and 50 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 50 mL of ethanol was added to the dry sodium hydride. The mixture was stirred for several minutes and 3.0 g (0.0095 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was stirred overnight. The solvent was removed in vacuo and the residue partitioned between chloroform (150 mL) and water (100 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The organic layer was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The solution was concentrated in vacuo to give a yellow liquid which upon distillation (Kugelrohr) afforded 2.279 g (85.4% yield) of a pale yellow liquid: bp 144°C (1.2 mm Hg); ^{1}H NMR ($CDCl_3$) δ 1.40 (t,J=7.0,3H), 4.45 (q,J=7.0,2H), 5.03 (s,2H), and 7.3 (m,5H); ^{13}C NMR ($CDCl_3$) δ 14.9, 50.6, 68.7, 128.5, 128.8, 129.4, 135.7, 136.3, and 159.3; IR (neat) 2800-3300, 1550, 1490, 1385, 1355, 1240-1310 (broad), 1225, 1115, 1020, 980, 880-920, 720, and 700 cm^{-1}; mass spectrum m/e 281, 283 (M+).

K. Preparation of 1-benzyl-3-bromo-5-benzyloxy-1H-1,2,4-triazole

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser and two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 0.356 g (0.0089 mol) of sodium hydride (60% dispersion in mineral oil) and 50 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 3.04 g (.00884 mol) of benzyl alcohol and 100 mL of N,N-dimethylformamide were added to the dry sodium hydride. The mixture was stirred for several minutes and 2.0 g (0.0063 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was stirred overnight. The solvent was removed in vacuo and the residue partitioned between chloroform (150 mL) and water (100 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The organic layer was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The solution was concentrated in vacuo to give a yellow liquid which upon purification on a Harrison chromatotron with a 1-mm silica gel plate using ethyl acetate/hexane (v/v 20/80) afforded 1.563 g (72.0% yield) of a white solid: mp 64-67^{o}C; ^{1}H NMR ($CDCl_3$) δ 5.05 (s,2H), 5.45 (s,2H), and 7.3 (m,10H);

^{13}C NMR ($CDCl_3$) δ 50.9, 74.2, 128.6, 128.9, 129.0, 129.2, 129.4, 129.5, 129.6, 135.3, 135.5, 136.3, and 159.2; IR ($CHCl_3$) 2900-3100, 1550, 1500, 1450, 1370, 1250-1300, 1100-1130, 700 and 670 cm^{-1}; mass spectrum m/e 343, 345 (M^+).

L. Preparation of 1-benzyl-3-bromo-5-fluoroalkoxy-1H-1,2,4-triazoles

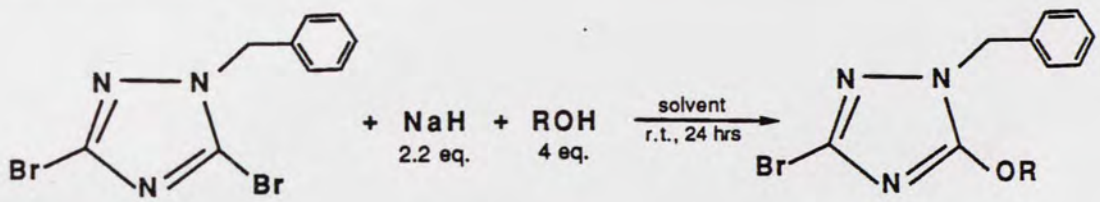


Table IV

Preparation of 1-benzyl-3-bromo-5-fluoroalkoxy-1H-1,2,4-triazoles

Entry	R	Solvent	Temp°C	%Yield[a]	mp (°C)
1	$-CH_2CF_3$	Dioxane	100	76.6[b]	61-63
2	$-CH_2CF_3$	DMF	150	65.6	60-62
3	$-CH_2CF_3$	DMF	30	57.6	61-63
4	$-C(CH_3)_2CF_3$	DMF	150	--[c]	--
5	$-CH_2CF_2CF_2CF_3$	DMF	150	--[c]	--
6	$-CH_2CF_2CF_2CF_3$	HMPA	230	--[d]	--

[a] The percent yield is based on the purified yield where the purification was recrystallization from ethanol.

[b] See the experimental procedure for spectral data.

[c] The products of this reaction as indicated by TLC and

^{1}H NMR are 1-benzyl-3,5-dibromo-1H-1,2,4-triazole-1-benzyl 3-bromo-1H-1,2,4-triazole, and a very minute amount of the expected product.

[d] Analysis by ^{1}H NMR indicated an unidentified decomposition product evidenced by the absence of the benzyl methylene peak.

Preparation of 1-benzyl-3-bromo-5-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazole

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser and two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 1.12 g (0.028 mol) of sodium hydride (60% dispersion in mineral oil) and 75 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 5.28 g (0.0528 mol) of 2,2,2-trifluoroethanol and 150 mL of dioxane were added to the dry sodium hydride. The mixture was stirred for several minutes and 4.0 g (0.0126 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was heated to 100^{o}C and stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between chloroform (200 mL) and water (150 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The

organic layer was dried over anhydrous magnesium sulfate and the drying agent was removed by filtration. The solution was concentrated <u>in vacuo</u> to give a yellow-white solid which upon recrystallization from ethanol afforded 3.406 g (76.6% yield) of a white solid: mp 61-63°C; ^{1}H NMR ($CDCl_3$) 4.75 (q,J=9,2H), 5.1 (s,2H), and 7.35 (m,5H); ^{13}C NMR ($CDCl_3$) 51.2, 67.7 (q,J=37.7), 122.7 (q,J=276.6), 128.7, 129.2, 129.5, 134.7, 136.0, and 157.5; IR (nujol) 1530-1570 (broad), 1500, 1410, 1350, 1240-1310 (broad), 1130-1210 (broad), 1120, 1045, 990, 960, 870, 780-830, and 680-740 cm^{-1}; mass spectrum m/e 335, 337 (M^{+}).

M. Preparation of 1-phenylmethylene semicarbazide

1-Phenylmethylene semicarbazide was prepared as described in a private correspondence with James A. Sikorski.[7] A suspension of 27.86 g (0.25 mol) of semicarbazide hydrochloride in 500 mL of ethanol in a 1000-mL three-necked round bottom flask equipped with a mechanical stirrer, reflux condenser and an addition funnel was treated with 50% (w/w) aqueous sodium hydroxide to adjust the pH to 9. Then ammonium chloride was added to adjust the pH to 7.5. The suspension was then treated dropwise with 26.4 g (0.250 mol) of benzaldehyde over several hours. The reaction mixture was stirred overnight at room temperature. The resulting solid was collected by vacuum filtration, washed several times with water and

recrystallized from hot ethanol to afford 31.36 g (76.90% yield) of a white crystalline solid: mp 230-233°C; ^{1}H NMR (DMSO-d_6) δ 6.595 (broad s,2H), 7.377 (s,1H), 7.410 (s,1H), 7.728 (s,1H), 7.767 (s,1H), 7.896 (s,1H), and 10.379 (s,1H); ^{13}C NMR (DMSO-d_6) δ 126.8, 128.9, 135.1, 139.7, and 157.3; IR (KBr pellet) 3430, 3000-3300, 1680, 1550-1650, 1400-1460, 1220, 1020, 970, 760, 700-730, 680, and 630 cm^{-1}.

N. Preparation of 2-phenylmethyl hydrazinecarboxamide

2-Phenylmethyl hydrazinecarboxamide was prepared by a modification of the procedure described in a private correspondence with James A. Sikorski.[7] To a 250-ml three-necked round bottom flask equipped with a stirring bar, reflux condenser and two glass stoppers were added 1.0 g (0.0061 mol) of 1-phenylmethylene semicarbazide, 0.50 g (0.0077 mol) of sodium cyanoborohydride and 50 mL of acetic acid. The reaction mixture was stirred at room temperature overnight. While cooling in an ice bath, excess sodium hydroxide (pellets) was added to adjust the pH to 6. After stirring for 1 hour, the solid was collected by vacuum filtration and washed several times with cold water. Drying in vacuo gave 0.492 g (48.7% yield) of a white solid which required no further purification: mp 150-153°C ; ^{1}H NMR (DMSO-d_6) δ 3.8 (broad s,2H), 5.0 (very broad s,1H), 5.85 (broad s,2H) 7.08 (s,1H), and 7.35 (m,5H); ^{13}C NMR

(DMSO-d_6) 55.6, 127.2, 128.4, 129.0, 138.8, and 160.4; IR (nujol) 3450, 1540-1690, 1200, 1090, 960, 890, and 670-770 cm^{-1}.

O. Preparation of 2,3-dihydro-1-benzyl-1H-1,2,4-triazol-3-one

2,3-Dihydro-1-benzyl-1H-1,2,4-triazole-3-one was prepared as described in a private correspondence with James A. Sikorski.[7] To a 500-mL three-necked round bottom flask, equipped with a stirring bar, reflux condenser and two glass stoppers, containing 1.65 g (0.0100 mol) of 2-phenylmethyl hydrazinecarboxamide in 100 mL of anhydrous tetrahydrofuran were added 1.45 g (0.0120 mol) of dimethylformamide dimethyl acetal and a catalytic amount of trifluoroacetic acid. The reaction mixture was refluxed under nitrogen for 20 hours, cooled and concentrated in vacuo. The solid residue was triturated several times with water and then recrystallized from ethanol/tetrahydrofuran to yield 1.08 g (61.6% yield) of a light tan solid: mp 207-209°C; ^1H NMR (DMSO-d_6) δ 5.2 (s,2H), 7.35 (m,5H), and 8.25 (s,1H); ^{13}C NMR (DMSO-d_6) δ 52.3, 128.2, 128.9, 136.8, 143.0, and 167.6; IR (nujol) 2300-2700 (very broad), 1500-1670 (broad), 1400-1470, 1330-1390, 1150-1230, 1020, 980, 870, 750, 700, and 675 cm^{-1}.

P. Preparation of 1-benzyl-3-methoxy-1H-1,2,4-triazole

1-Benzyl-3-methoxy-1H-1,2,4-triazole was prepared as described in a private correspondence with James A. Sikorski.[7] To a 100-mL one-necked round bottom flask, equipped with a stirring bar, was added 1.024 g (0.018 mol) of powdered potassium hydroxide in 20 mL of dimethyl sulfoxide. The mixture was stirred for 20 minutes at room temperature and 0.80 g (0.0046 mol) of 2,3-dihydro-1-benzyl-1H-1,2,4-triazol-3-one and 7.70 g (0.0540 mol) of methyl iodide were added. The reaction mixture was stirred at room temperature for 1 hour, then poured into water (200 mL) and extracted with 75 mL of methylene chloride. The organic layer was then washed with 3 x 50 mL water, dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting tan oil was purified on a Harrison chromatotron with a 1-mm silica gel plate using ethyl acetate/hexane (v/v 50/50) as the eluant affording 0.50 g (59% yield) of a colorless oil: ^{1}H NMR (CDCl3) δ 3.95 (s,3H), 5.18 (s,2H), 7.35 (m,5H) and 7.75 (s,1H); ^{13}C NMR ($CDCl_3$) δ 54.0, 57.1, 128.6, 129.1, 129.5, 135.1, 142.9, and 170.1; IR (neat) 2800-3160, 1550, 1490, 1410, 1330, 1150-1250, 1040-1100, 1020, 715-760, and 700 cm^{-1}.

Q. Preparation of 1-benzyl-3-bromo-5-alkyl and arylthio-1H-1,2,4-triazole

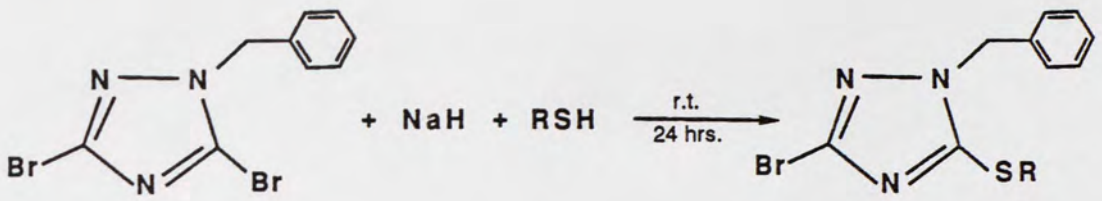
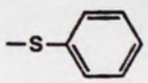
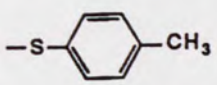


Table V

Preparation of 1-benzyl-3-bromo-5-alkythio-1H-1,2,4-triazole

Entry	R	eq. NaH or eq. RSH	Solvent	%Yield[a]	mp (°C) bp (mm Hg)
1		1.2	DMF	73.5[b]	mp 46-48
2		1.2	DMF	--[c]	--
3		1.0	DMF	78.74[d]	bp 163 (1)

[a] The percent yield is based on the purified yield where the purification involved distillation or recrystallization.

[b] 1H NMR ($CDCl_3$) δ 5.35 (s,2H) and 7.3 (m,10H); ^{13}C NMR ($CDCl_3$) δ 53.7, 128.6, 129.2, 129.4, 129.5, 130.3, 130.4, 132.3, 134.9, 140.6, and 151.9; IR (nujol) 1565, 1490, 1220-1280 (broad), 1040-1090, 1020, 990, 720, and 690 cm^{-1};

mass spectrum m/e 345, 347 (M^+).

[c] The expected product was not produced. Instead, p-tolyl disulfide was produced in 64.41% yield. This product was identified by ^1H NMR and IR spectra.[8,9]

[d] See the experimental procedure for spectral data.

Preparation of 1-benzyl-3-bromo-5-butylthio-1H-1,2,4-triazole

A dry 250-mL three-necked round bottom flask was equipped with a magnetic stirrer, a reflux condenser and two glass stoppers. A nitrogen atmosphere was maintained at all times. Into the flask were placed 0.1264 g (0.00316 mol) of sodium hydride (60% dispersion in mineral oil) and 50 mL of hexane. The mixture was stirred for a few minutes, after which the hexane was removed using a cannula syringe and vacuum. Once the mineral oil was removed by the hexane wash, 0.282 g (0.00316 mol) of n-butylthiol and 100 mL of N,N-dimethylformamide was added to the dry sodium hydride. The mixture was stirred for several minutes and 1.00 g (0.00316 mol) of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was added. The resulting mixture was stirred overnight. The solvent was removed in vacuo and the residue partitioned between chloroform (100 mL) and water (100 mL). The aqueous phase was extracted with additional chloroform (25 mL) and the combined chloroform extracts were washed with 3 x 100 mL water. The organic layer was dried over anhydrous magnesium sulfate and the drying agent

was removed by filtration. The solution was concentrated in vacuo to give a yellow liquid which upon distillation (Kugelrohr) afforded 0.81 g (79% yield) of a pale yellow liquid: bp 163°C (1 mm Hg); ^{1}H NMR ($CDCl_3$) δ 0.88 (t,J=7.4,3H), 1.38 (m,J=7.4,2H), 1.65 (m,J=7.4,2H), 3.18 (t,2H), 5.18 (s,2H), and 7.3 (m,5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.0, 31.7, 33.9, 128.6, 129.1, 129.5, 135.0, 139.8, and 155.1; IR (neat) 2800-3100, 1490, 1400-1470, 1260, 1080, 990, and 720 cm^{-1}; mass spectrum m/e 325, 327 (M^+).

DISCUSSION OF RESULTS

The study of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole chemistry was conducted in four phases: synthesis, reaction with triethyl phosphite, reaction with the sodium salt of diethyl phosphite, and reaction with various nucleophiles. All products obtained were characterized by ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy.[10-14] Four infrared absorption assignments were used to identify the presence of the 1,2,4-triazole ring. These ring stretching vibrations were 1525-1490, 1450-1340, 1370-1260 and 1190-1120 cm^{-1}. In order to obtain an analytically pure sample, distillation, recrystallization or the use of a chromatotron was employed.

The 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was prepared in a two-step synthesis. The first step was the bromination of the triazole to give the 3,5-dibromo-1H-1,2,4-triazole. This was identified by the very broad singlet centered at 8.70 ppm corresponding to the N-H, in the ^{1}H NMR spectrum and the aforementioned ring stretching vibrations in the IR spectrum. This compound was benzylated to give the 1-benzyl-3,5-dibromo-1H-1,2,4-triazole which was characterized by a sharp singlet at 5.30

ppm corresponding to the benzyl methylene and a multiplet at 7.35 ppm corresponding to the five aromatic hydrogens in the ^{1}H NMR spectrum. Refer to Figure 9 for the ^{13}C NMR spectrum assignments.

The 1-benzyl-3,5-dibromo-1H-1,2,4-triazole was reacted with triethyl phosphite under several conditions indicated in Table I. Under none of the experimental conditions was the desired product (1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl phosphonic acid diethyl ester) produced. Instead, as indicated by ^{1}H NMR and TLC, the reaction mixture contained starting material, an unidentified decomposition product (where no methylene protons from the benzyl substituent appear in the ^{1}H NMR), and 1-benzyl-3-bromo-1H-1,2,4-triazole. The 1-benzyl-3-bromo-1H-1,2,4-triazole was synthesized independently for structural proof (see the experimental section). Since in the literature there had been no examples of Arbuzow chemistry with heterocycles, it was decided to try reacting a simpler heterocycle: 2-chlorolepidine, with triethyl phosphite. The product of this reaction was, as in the case of the 1-benzyl-3,5-dibromo- 1H-1,2,4-triazole, starting material.

The experimental data for the reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with the sodium salt of diethyl phosphite appear in Table II. As was the case with the triethyl phosphite, these reactions did not produce the desired 1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl phosphonic

acid diethyl ester. Instead, as indicated by ^{1}H NMR and TLC, the mixture contained starting material and 1-benzyl-3-bromo-1H-1,2,4-triazole. In fact, in several cases there was almost 96% yield of the dehalogenated product. A proposed mechanism for production of the 1-benzyl-3-bromo-1H-1,2,4-triazole is shown in Figure 10. The triazole ring is a good leaving group because it can stabilize the negative charge produced. The charged species is then protonated during the workup.

The identification and characterization of the products formed by the reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with sodium methoxide posed some interesting problems. In one procedure, the reaction was done in N,N-dimethylformamide at reflux, whereas the other procedure was performed in methanol at room temperature. The reactions proceeded to yield two different products, both having the same molecular weight (from the mass spectral analysis) indicating elimination of bromine and incorporation of the oxygen and methyl group of the methoxy into the molecule. The major difference in the ^{1}H NMR spectra is the methyl group shifts. In the case of the high temperature product, the methyl singlet appears at 3.28 ppm, whereas the methyl singlet for the room temperature product appears at 4.02 ppm. The ^{13}C NMR spectra for the two compounds differ drastically. After viewing the ^{1}H NMR and ^{13}C NMR spectra, the products were

tentatively identified as compound A: 1-benzyl-3-bromo- 5-methoxy-1H-1,2,4-triazole and compound B: 1-benzyl-3-methoxy-5-bromo, 1H-1,2,4-triazole, where "A" was the product from the low temperature reaction and "B" was the product from the high temperature reaction.

A proposed mechanism for the production of "A" involved an S_NAr process (Figure 11). Conceivably, "B" could be produced by a three-step mechanism, whereby "A" is first produced by an S_NAr process and then undergoes a 1,5-sigmatropic rearrangement (Figure 12). These 1,5-alkyl shifts are allowed processes.[15] However, the IR data did not fit the identification of "B." The IR spectrum for "B" indicated a strong carbonyl absorption at 1600-1740 cm^{-1}, and in the ^1H NMR spectrum, the upfield shift of the methyl group (as compared to the methyl shift in "A") indicated substititution of the methyl on a less electronegative atom. Thus "B" could not possibly be 1-benzyl-3-methoxy-5-bromo- 1H-1,2,4-triazole. Instead, "B" has been identified as 4,5-dihydro-1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazole. This may be explained by a formal concerted 1,3-methyl shift of "A" to give "B," as shown in Figure 13. This type of rearrangement has been seen in the literature. Gehlen and Stein[16,17] indicated that upon heating, the 3-methyl-5-(2-chloroethoxy)-1H-1,2,4-triazole rearranged to give the 3-methyl-4-(2-chloroethyl)-1H-1,2,4-triazol-5-one (Figure 14). Additional proof of a three-step mechanism was

achieved by refluxing isolated "A" in N,N-dimethylformamide overnight, to give "B" in 91% yield. The typical ring stretching vibrations in the IR spectra appear for both "A" and "B". Assignment of the ^{13}C NMR spectra is shown in Figure 15.

The multistep independent synthesis of 1-benzyl-3-methoxy-1H-1,2,4-triazole was performed in order to give further proof of the structures for "A" and "B." The first step is the preparation of 1-phenylmethylene semicarbazide from the semicarbazide hydrochloride by addition of benzaldehyde. The product is characterized by the presence in the ^{1}H NMR spectrum of five aromatic hydrogens at 7.377, 7.410, 7.728, 7.767, and 7.896 ppm, and a singlet at 10.379 for the N-H. The ^{13}C NMR spectrum indicates four aromatic carbons at 126.842, 128.864, 135.105, and 139.703 ppm, and a carbonyl carbon at 157.294 ppm. The 1-phenylmethylene semicarbazide was reduced by sodium cyanoborohydride to give 2-phenylmethyl hydrazinecarboxamide. This product was identified by the very broad singlet at 5.0 ppm in the ^{1}H NMR for the hydrazine N-H. The ^{13}C NMR spectrum indicates an alkyl carbon at 55.573 ppm for the benzyl methylene carbon, four aromatic carbons at 127.210, 128.388, 128.974, and 138.842 ppm, and a carbonyl carbon at 160.393 ppm.

Dimethylformamide dimethyl acetal was then reacted with the 2-phenylmethyl hydrazine carboxamide to give the

2,3-dihydro-1-benzyl-1H-1,2,4-triazol-3-one. The ^{1}H NMR spectrum indicates a singlet at 5.2 ppm for the benzyl methylene, a multiplet at 7.35 ppm accounting for the five aromatic hydrogens, and a singlet at 8.25 ppm accounting for the N-H. The ^{13}C NMR spectrum assignments appear in Figure 16. The 2,3-dihydro-1-benzyl-1H-1,2,4-triazol-3-one was reacted with methyl iodide in the presence of potassium hydroxide to give 1-benzyl-3-methoxy-1H-1,2,4-triazole. The ^{1}H NMR and ^{13}C NMR spectra assignments can be found in Figure 17. The ^{1}H NMR spectrum of the compound is quite similar to the ^{1}H NMR spectrum of the 1-benzyl, 3-bromo-5-methoxy-1H-1,2,4-triazole. This is because the electronic environment of the methoxy substituent does not change much from C-3 to C-5. However, the ^{13}C NMR spectrum is slightly different, as would be expected, due to the different substitution pattern and the presence of the bromine in the 1-benzyl-3-bromo-5-methoxy-1H-1,2,4-triazole.

The 1-benzyl-3-bromo-5-alkoxy-1H-1,2,4-triazoles that were isolated from the reactions listed in Table III were easily characterized by the ^{1}H NMR spectra which indicated in all cases a singlet centered at 5.0 ppm corresponding to the benzyl methylene protons and a multiplet centered at 7.3 ppm corresponding to the five aromatic hydrogens. Other peaks depended upon the particular alkoxy nucleophile. A typical ^{1}H NMR and ^{13}C NMR spectrum for the

5-alkoxy compounds is presented in Figure 18. The IR ring stretching absorptions were present in all the compounds. The reaction results in the table indicate that the straight chain alcohols reacted to give the 5-substituted products. These reactions proceeded in excellent yields. However, the branched chain alcohols yielded none of the 5-substituted products. This can possibly be explained by the difference in the nucleophilicity of branched versus straight chain alcohols coupled with the slight steric hindrance of branched chain alkoxy attack at C-5 by the benzyl group at C-1.

The preparation of 1-benzyl-3-bromo-5-benzyloxy-1H-1,2,4-triazole is similar to the preparation of the 5-alkoxy compounds in that the reaction proceeded in excellent yields. However, the reaction was performed in N,N-dimethylformamide instead of the straight alcohol. An interesting development in the ^{1}H NMR spectrum of this compound is the fact that all ten aromatic hydrogens appear under the same multiplet at 7.3 ppm. The rest of the spectral data are similar to the spectral data for the 5-alkoxy compounds.

The 1-benzyl, 3,5-dibromo, 1H-1,2,4-triazole was reacted with several fluoroalcohols under the conditions shown in Table IV. The only fluoroalcohol to give the 5-substituted product, however, was the 2,2,2-trifluoroethanol. The 1-benzyl-3-bromo-5-(2,2,2-

trifluoroethoxy)-1H-1,2,4-triazole was produced in good yields under all the conditions. The 2-trifluoromethylpropan-2-ol did not react to give the desired 5-substituted product because it is sterically hindered from attack due to its bulky nature. The 1H, 1H-heptafluorobutan-1-ol did not react to give the desired product because it is much less nucleophilic than the analogous 1-butanol. The ^{1}H NMR and ^{13}C NMR spectra assignments for 1-benzyl-3-bromo-5-(2,2,2-trifluoroethoxy)-1H-1,2,4-triazole can be found in Figure 19. The IR spectra indicate the typical ring stretching absorptions.

Table V lists the experimental data for the preparation of 1-benzyl-3-bromo-5-alkyl and arylthio, 1H-1,2,4-triazoles. Both the n-butylthiol and the thiophenol gave good yields of the 5-substituted alkylthio product. However, the p-thiocresol reacted to give p-tolyl disulfide. This product was identified by standard ^{1}H NMR and IR.[8,9] A proposed mechanism for the formation of p-tolyl disulfide may be found in Figure 20. The assignments for the ^{1}H NMR and ^{13}C NMR spectrum for the 1-benzyl-3-bromo-5-butylthio-1H-1,2,4-triazole may be found in Figure 21. The IR spectra for the 5-substituted alkyl or arylthio compounds indicate the typical ring stretching absorbances.

Peak assignments

Carbons	Chemical shifts ppm
a	129.4
b	128.6, 129.7
c	130.1
d	54.1
e	140.9
f	134.3

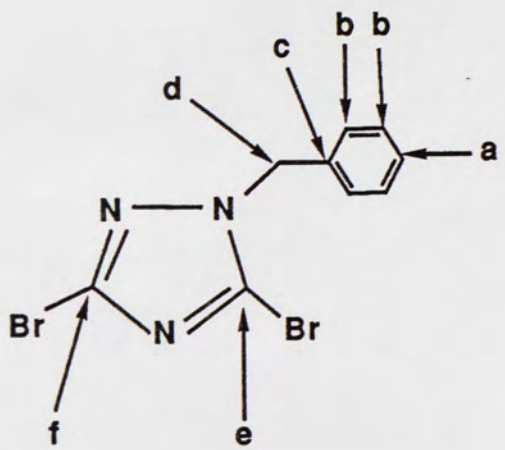


Figure 9. Chemical shift assignments for the ^{13}C NMR spectrum of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole.

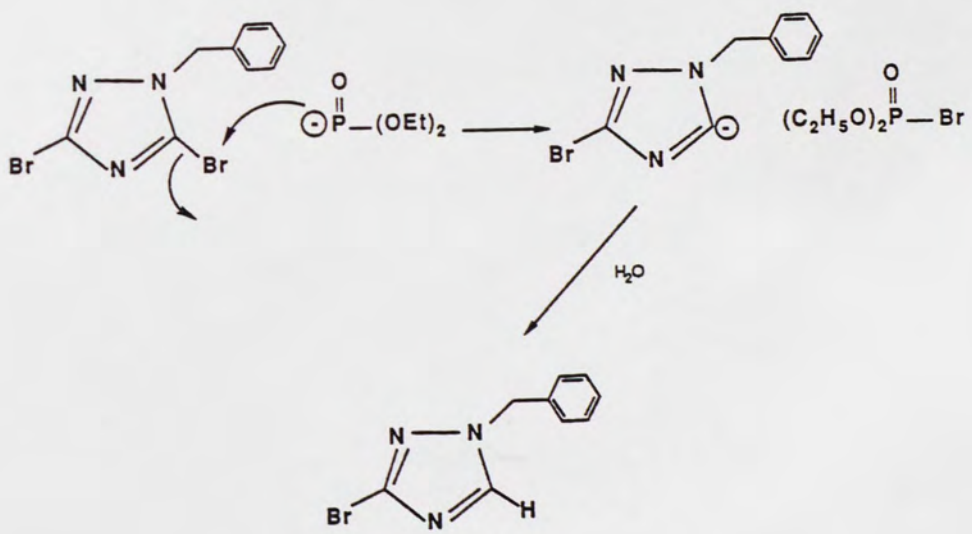


Figure 10. Proposed mechanism for the production of 1-benzyl-3-bromo-1H-1,2,4-triazole.

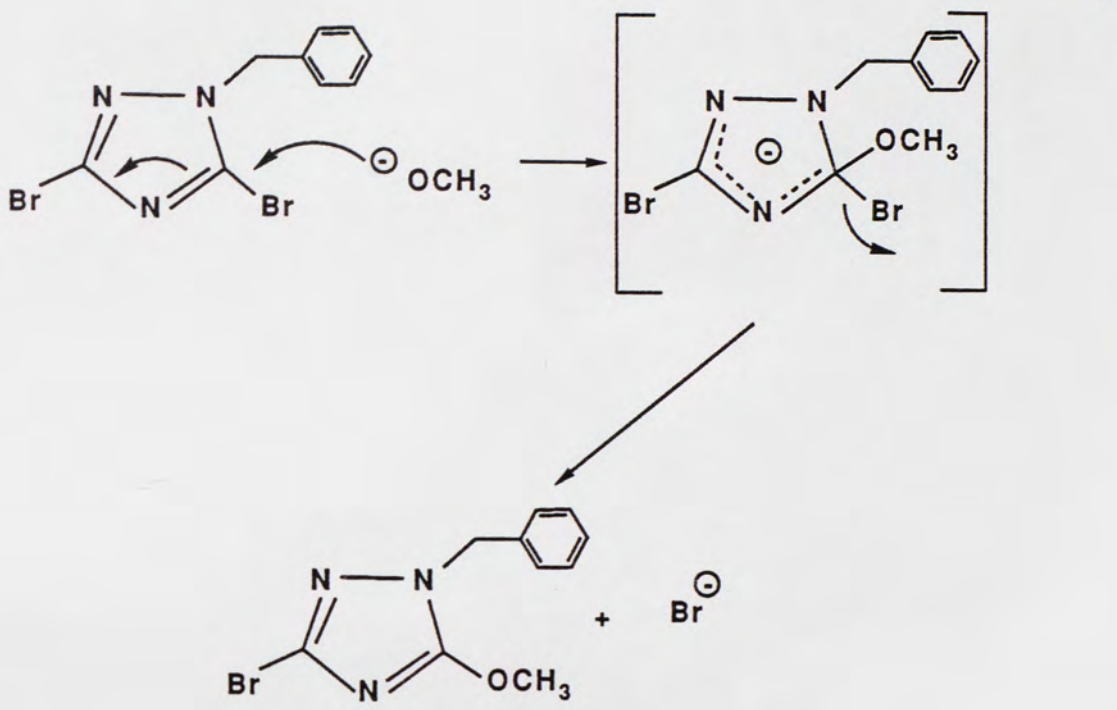


Figure 11. Proposed mechanism for the formation of 1-benzyl-3-bromo-5-methoxy-1H-1,2,4-triazole by an S_NAr process.

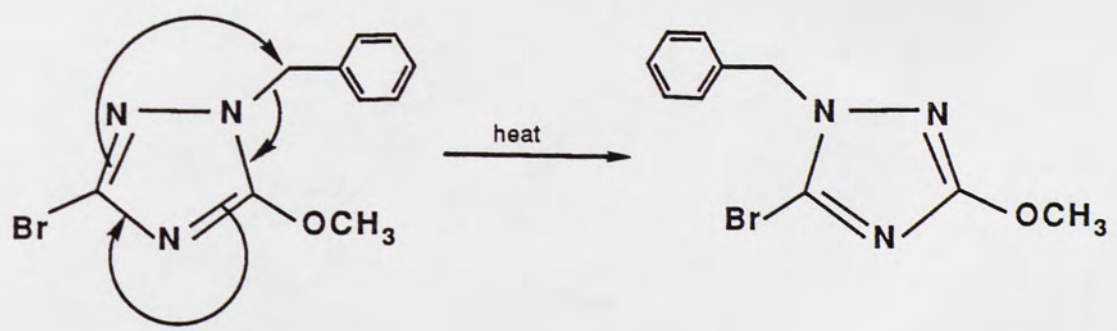


Figure 12. Proposed mechanism for production of 1-benzyl-3-methoxy-5-bromo-1H-1,2,4-triazole by a 1,5-sigmatropic rearrangement.

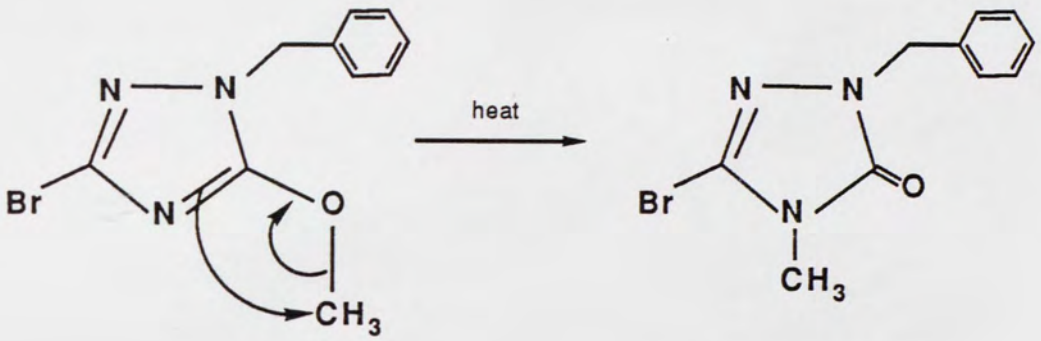


Figure 13. Proposed mechanism for the formation of 1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazol-5-one by a 1,3-sigmatropic shift.

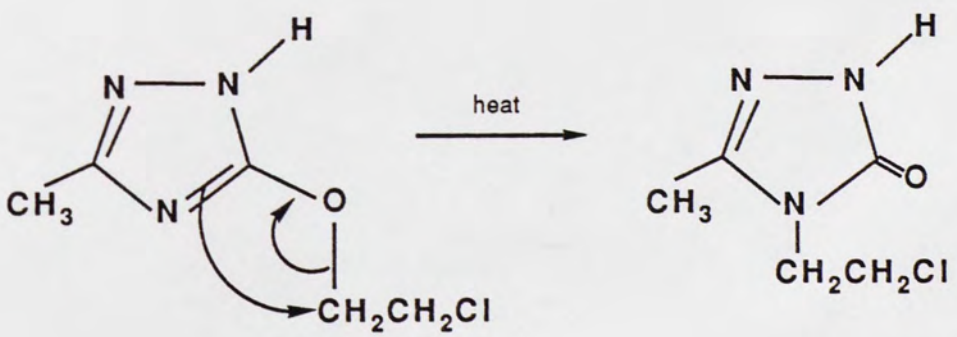
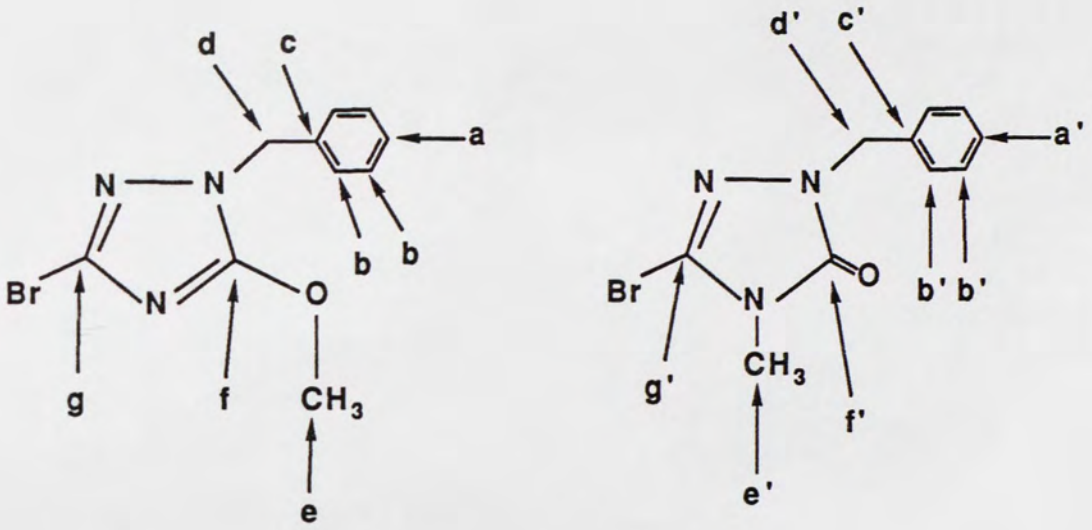


Figure 14. Rearrangement of 3-methyl-5-(2-chloroethoxy)-1H-1,2,4-triazole to 3-methyl-4-(2-chloroethyl)-1H-1,2,4-triazol-5-one.



Peak assignments
Chemical shifts

Carbons	ppm	Carbons	ppm
a	128.9	a'	128.7
b	128.5, 129.5	b'	129.0, 129.3
c	135.6	c'	136.4
d	50.7	d'	50.0
e	59.3	e'	29.6
f	159.9	f'	153.6
g	136.3	g'	122.7

Figure 15. Chemical shift assignments for the ^{13}C NMR spectra of 1-benzyl-3-bromo-5-methoxy-1H-1,2,4-triazole and 1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazol-5-one.

Peak assignments
Chemical shift

Carbons	ppm
a	128.2, 128.9
b	136.8
c	52.3
d	143.0
e	167.6

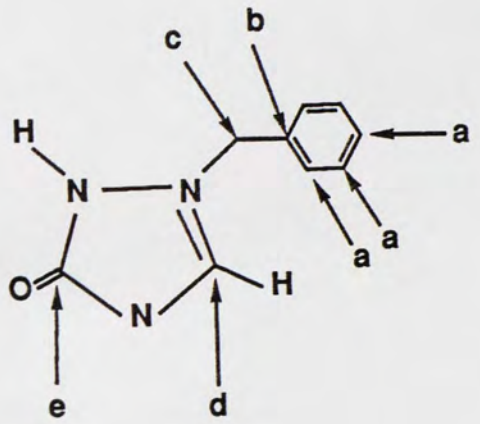


Figure 16. Chemical shift assignments for the ^{13}C NMR spectrum of 2,3-dihydro-1-benzyl-1H-1,2,4-triazol-3-one.

Peak assignments
Chemical shifts

Protons	ppm
a	7.35 (m,5H)
b	3.95 (s,3H)
c	7.73 (s,1H)
d	5.19 (s,2H)

Carbons	ppm
e	129.1
f	128.6, 129.5
g	135.1
h	54.0
i	142.9
j	170.1
k	57.1

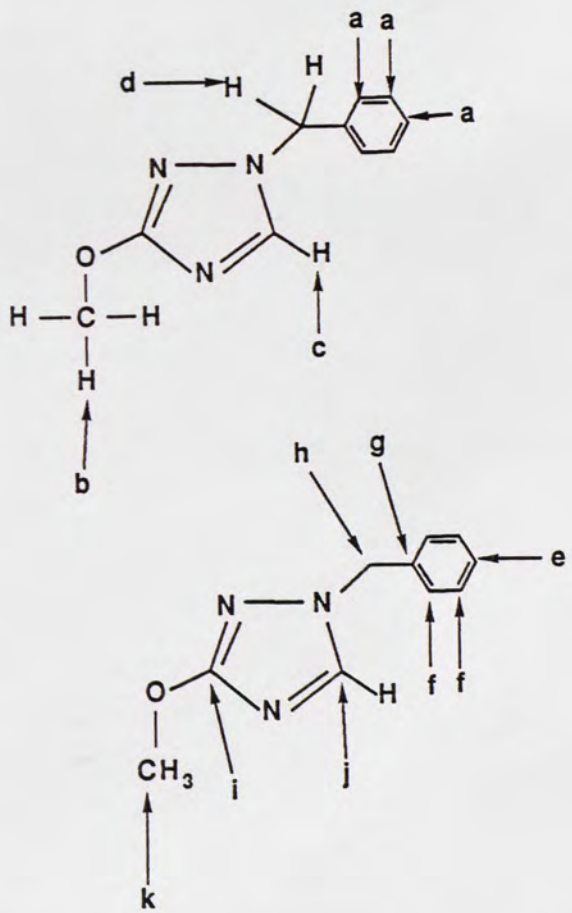
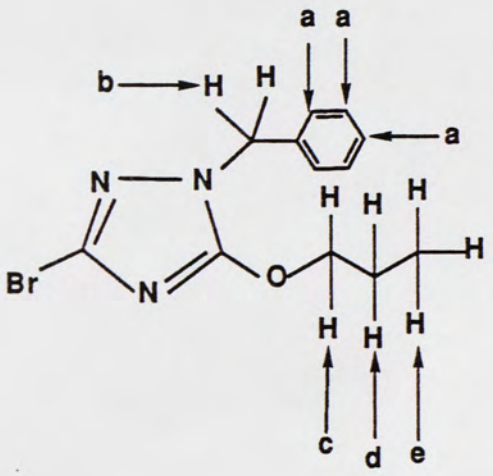


Figure 17. Chemical shift assignments for the ^{1}H NMR and ^{13}C NMR spectra of 1-benzyl-3-methoxy-1H-1,2,4-triazole.



Peak assignments
Chemical shifts

Protons	ppm
a	7.3 (m,5H)
b	5.0 (s,2H)
c	4.35 (t,J=7.9,2H)
d	1.8 (m,J=7.9,2H)
e	.93 (t,J=7.9,3H)

Carbons	ppm
f	128.6, 129.4
g	128.9
h	135.6
i	50.7
j	159.4
k	136.2
l	74.3
m	22.5
n	10.3

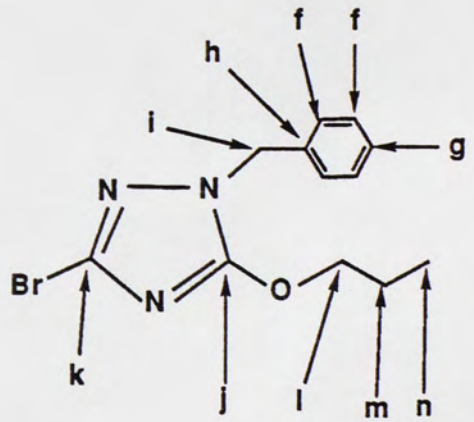
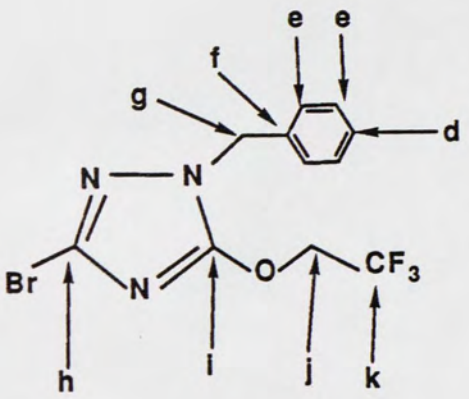


Figure 18. Chemical shift assignments for the ^{1}H NMR and ^{13}C NMR spectra of 1-benzyl-3-bromo-5-(n-propoxy)-1H-1,2,4-triazole.



Peak assignments
Chemical shifts

Protons	ppm
a	7.35 (m,5H)
b	5.1 (s,2H)
c	4.75 (q,J=9,2H)

Carbons	ppm
d	129.2
e	129.5, 128.7
f	134.7
g	51.2
h	136.0
i	157.5
j	67.7 (q,J=1.7)
k	122.7 (q,J=14.1)

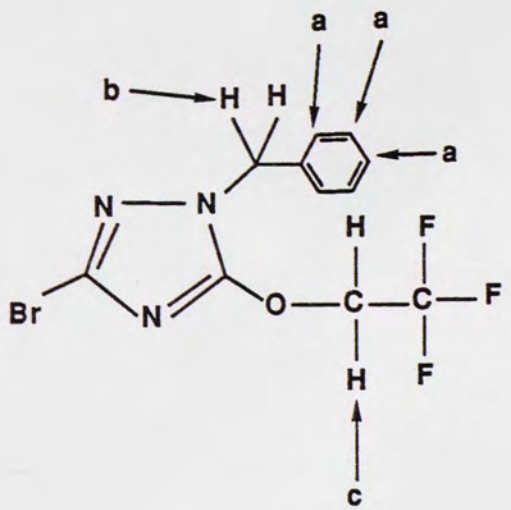


Figure 19. Chemical shift assignments for the ^{1}H NMR and ^{13}C NMR spectra for 1-benzyl-3-bromo-5-(2,2,2-trifluoroethoxy)- 1H-1,2,4-triazole.

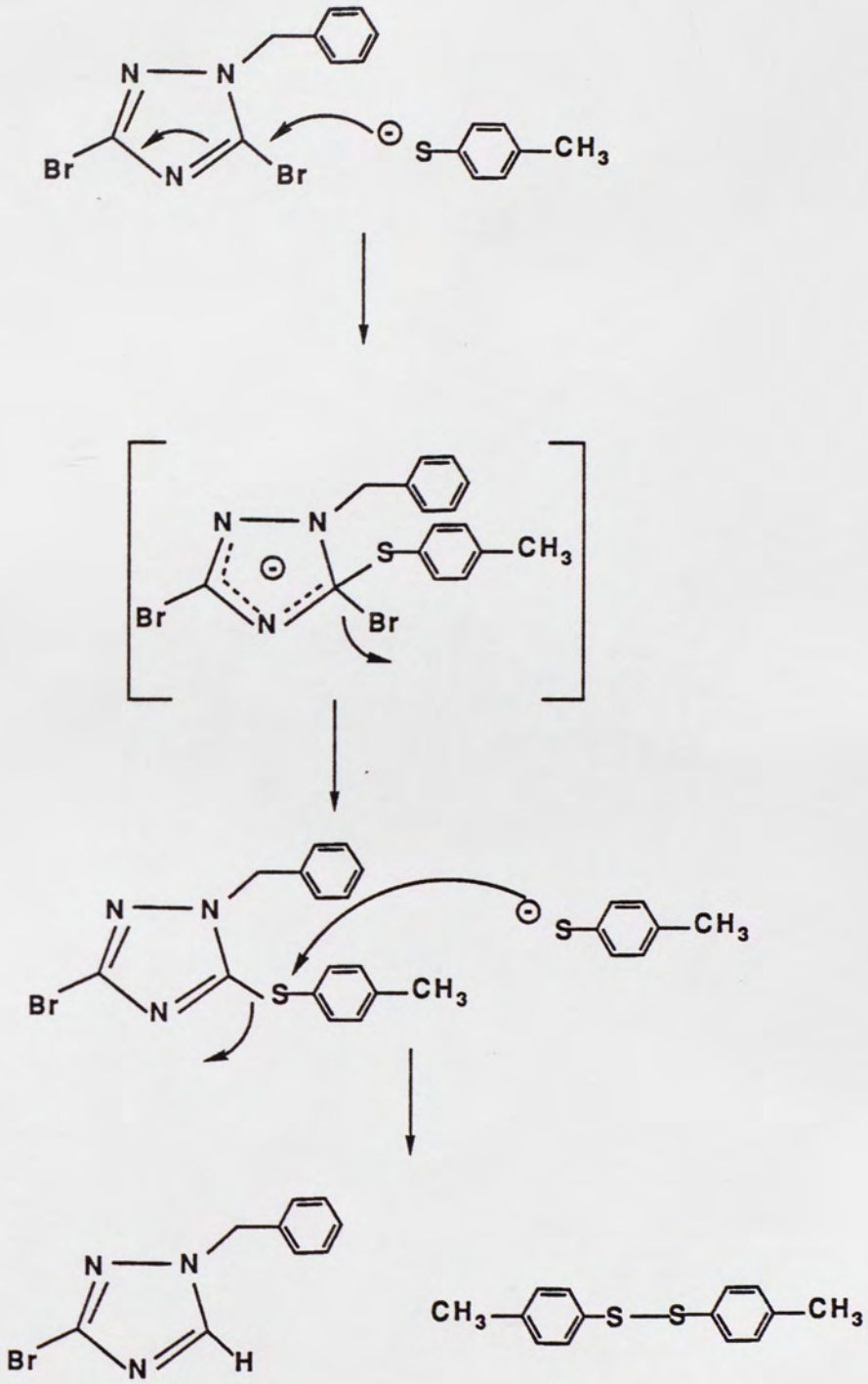
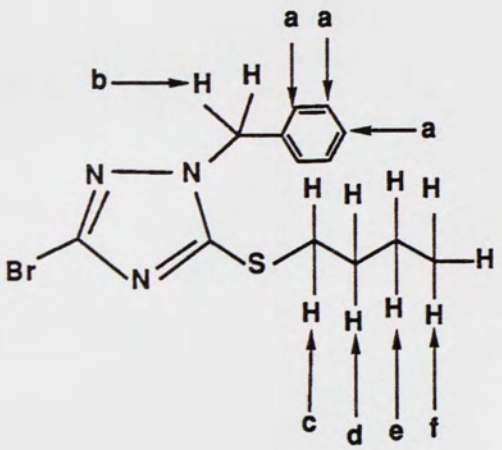


Figure 20. The mechanism for the formation of p-tolyl disulfide.



Peak assignments
Chemical shifts

Protons	ppm
a	7.30 (m,5H)
b	5.18 (s,2H)
c	3.18 (t,2H)
d	1.65 (m,J=7.4,2H)
e	1.38 (m,J=7.4,2H)
f	.88 (t,J=7.4,3H)

Carbons	ppm
g	129.1
h	128.6, 129.5
i	135.0
j	53.1
k	139.8
l	155.1
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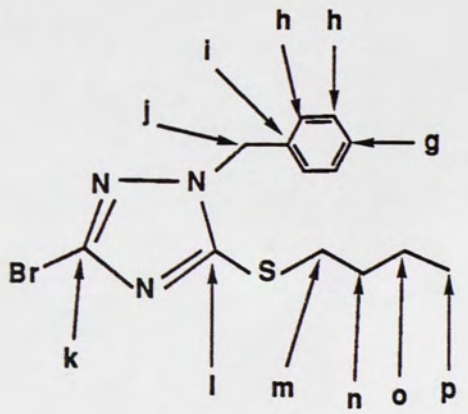


Figure 21. Chemical shift assignments for the ^{1}H NMR and ^{13}C NMR spectra for 1-benzyl-3-bromo-5-(n-butylthio)-1H-1,2,4-triazole.

CONCLUSIONS

The reactions of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with either triethyl phosphite or the sodium salt of diethyl phosphite have been shown not to produce the desired 1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl phosphonic acid ethyl ester. However, under several conditions, these reactions have produced the dehalogenated product 1-benzyl-3-bromo- 1H-1,2,4-triazole in good yields.

The preparation of 1-benzyl-3-bromo-5-alkoxy, 1H-1,2,4-triazoles from the corresponding alcohols and 1-benzyl-3,5-dibromo-1H-1,2,4-triazole, has been shown to proceed smoothly under mild conditions in excellent yields if the primary alcohol is used. These reactions are believed to have involved an S_NAr process. Secondary and tertiary alcohols do not undergo substitution onto the triazole ring.

The 5-substituted fluoroalkoxy compounds proceed in much the same way as the 5-substituted alkoxy compounds. The primary fluoroalcohol: 2,2,2-trifluoroethanol proceeded under mild conditions in excellent yields. However, the branched fluoroalcohol: 2-trifluoromethylpropan-2-ol, did not react. In addition, 1H, 1H-heptafluorobutan-1-ol did

not react either, because it is much less nucleophilic than the analogous 1-butanol.

The preparation of 1-benzyl-3-bromo-5-alkyl or arylthio-1H-1,2,4-triazole from the corresponding substituted thiols were shown to proceed smoothly under mild conditions except for the p-thiocresol. The p-thiocresol reacted to produce the p-tolyl disulfide in good yields.

In summation, this thesis has presented evidence that nucleophilic substitution of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole proceeds regioselectively at the C-5 position. Nine unique substituted triazoles have been prepared which have possible biological, herbicidal and insecticidal activity. Furthermore, the 1,3-shift of 3-methyl-5-(2-chloroethoxy)-1H-1,2,4-triazole to 3-methyl-4-(2-chloroethyl)-1H-1,2,4-triazol-5-one indicated by Gehlen and Stein[16] has been expanded to include the shift of 1-benzyl-3-bromo-5-methoxy-1H-1,2,4-triazole to 1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazol-5-one. Other 1,3-shifts are expected. These 1,3-shifts may be useful in activating the C-3 position for nucleophilic substitution. If the 1,3-shift does in fact activate the C-3 position, the original objective of this research has been achieved: the activation of both the C-3 and C-5 positions of 1-substituted-1H-1,2,4-triazole.

RECOMMENDATIONS

The following recommendations are suggested in order to direct future research involving 1-benzyl-3,5-dibromo-1H-1,2,4-triazole.

1. The 1,3-sigmatropic rearrangement seen in the reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with sodium methoxide in N,N-dimethylformamide at reflux is a potentially useful synthetic reaction. In order to widen the scope of the reaction, all of the 5-substituted alkoxides, fluoroalkoxides,and alkylthio compounds discussed in this report should be heated at high temperatures in an appropriate solvent, to discover whether they will undergo the rearrangement.

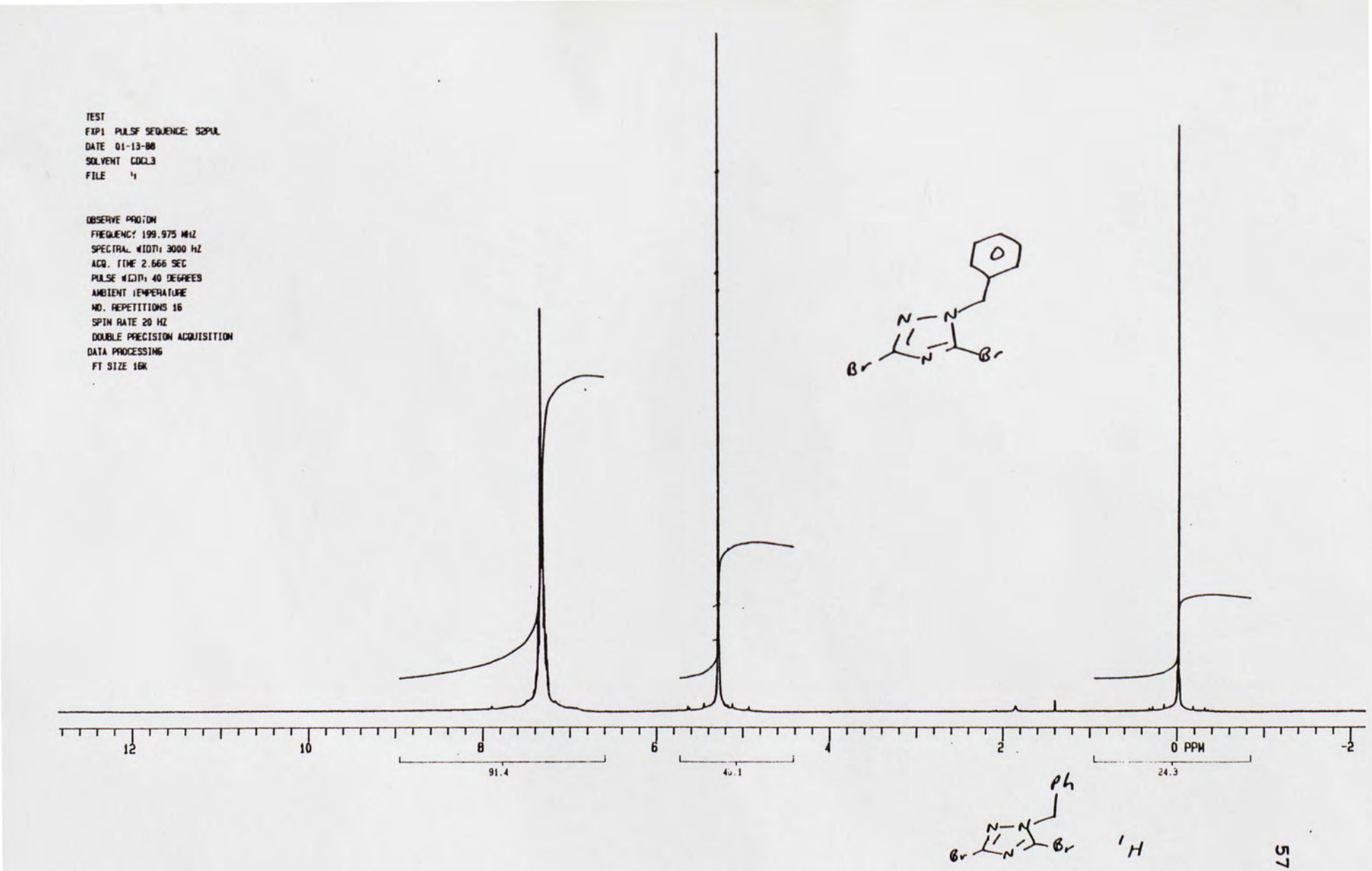
2. The formation of the p-tolyl disulfide during the reaction of 1-benzyl-3,5-dibromo-1H-1,2,4-triazole with the sodium salt of p-thiocresol should be explored more deeply. Other para-substituted thiophenols should be reacted in similar fashion to determine whether this is a general reaction. It also may be interesting to perform the reaction with ortho- or meta-substituted thiophenols.

3. The study of the substitution of amines at the C-5 position should be explored. The formation of quaternary ammonium salts at C-5 might lead to some interesting chemistry.

4. The 1,3-shift may activate the C-3 position for nucleophilic substitution. Thus, it will be extremely important to try nucleophilic substitution of the 1-benzyl-3-bromo-4-methyl-1H-1,2,4-triazol-5-one and any other rearrangement product that will subsequently be discovered.

APPENDIX A

Examples Of ^{1}HNMR, ^{13}CNMR, and Mass Spectra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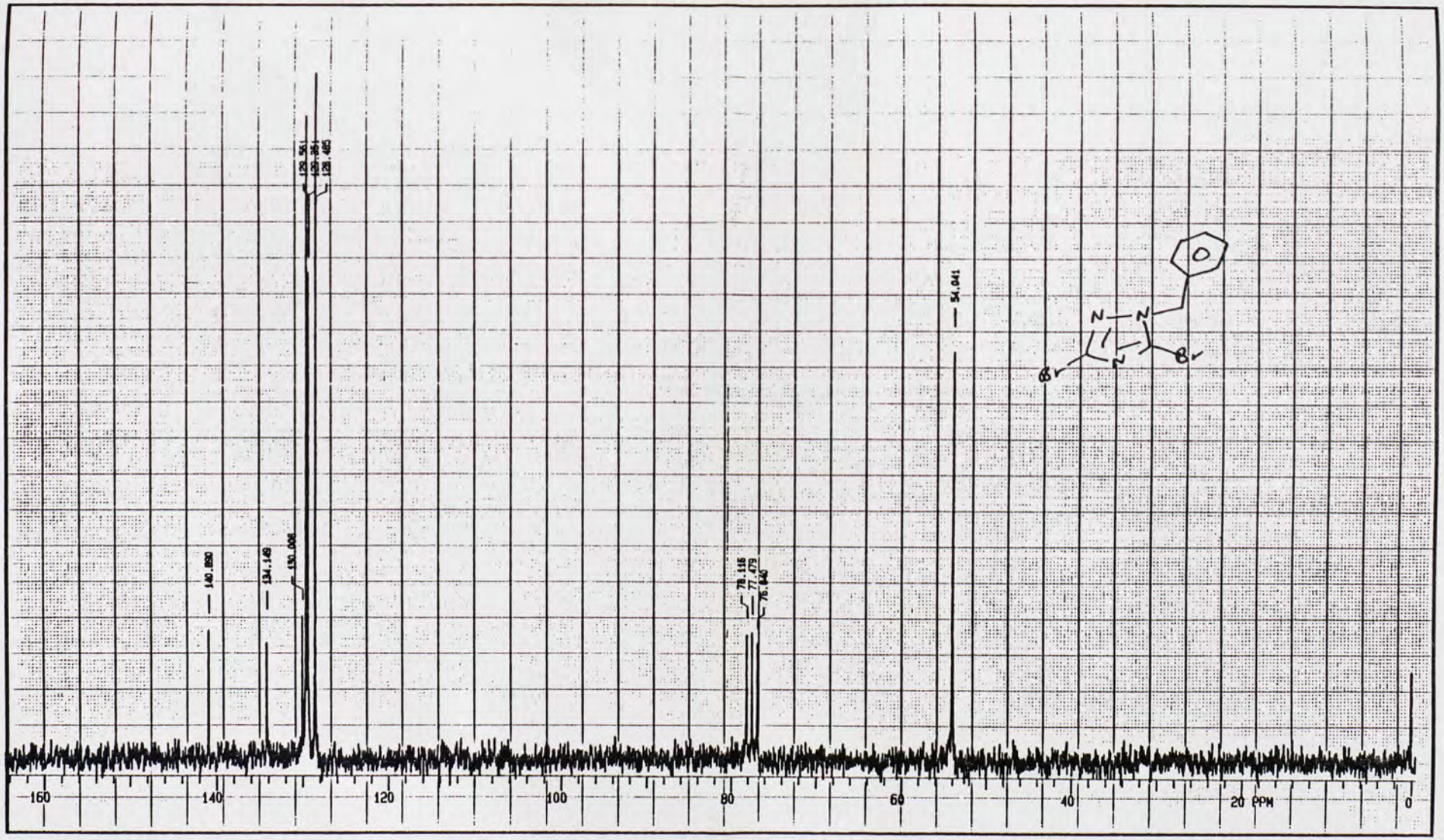

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PLOT/PROCESSING: FN ____ K RE ____ sec CD ____ sec; LB ____ Hz AF ____ sec CCD ____; Width ____ Hz/ppm Start ____ Hz/ppm; Reference ____

EXPERIMENT: Pulse Sequence ____; Tube O.D. ____ mm; Temp. ____ °C; Solvent ____

SAMPLE ^{13}C

Number ____

File ____

58

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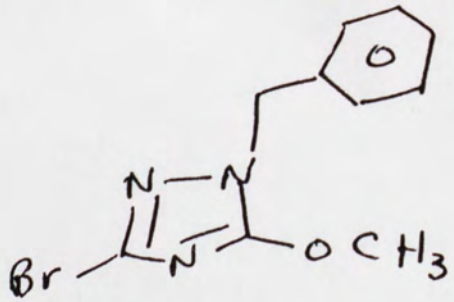
PART NO 807259

CHART XL SERIES



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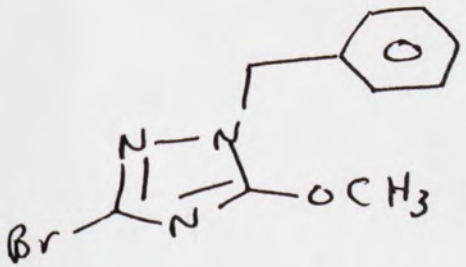

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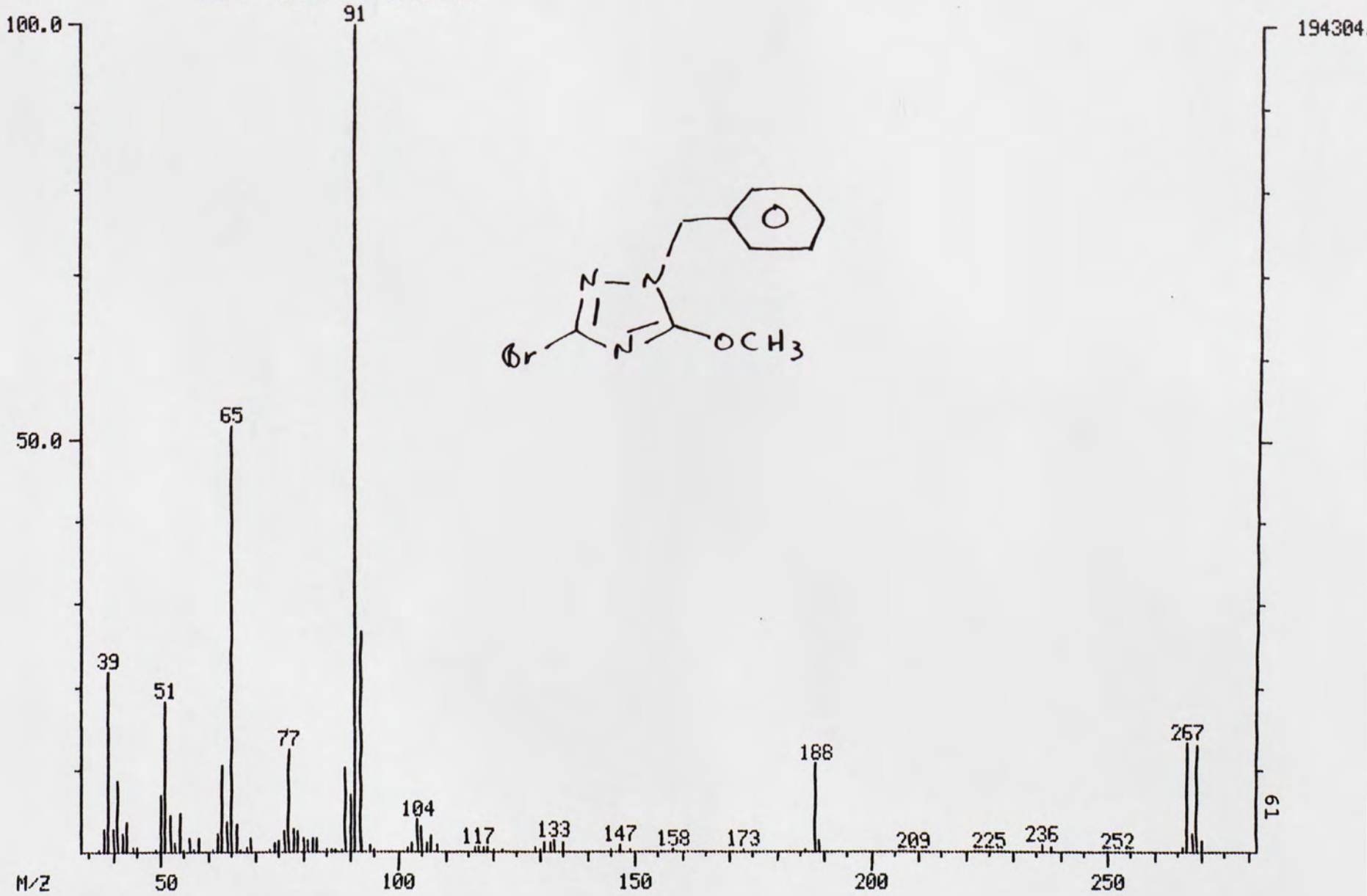
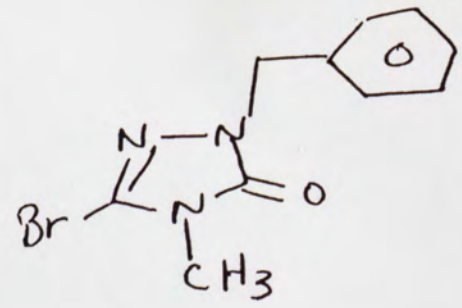
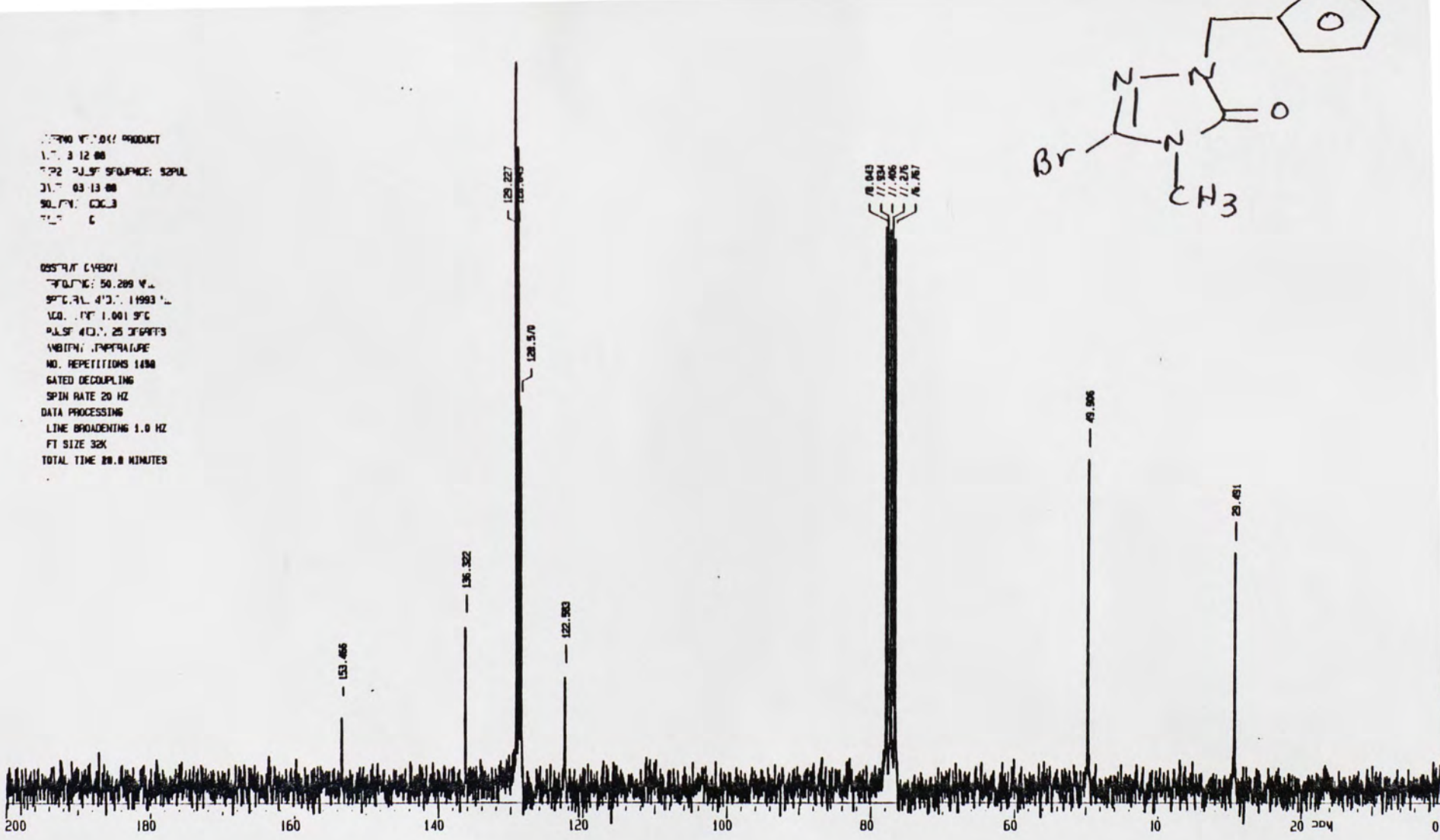
GC TEMP: 264 DEG. C
#695 - #689 - #701 X1.00



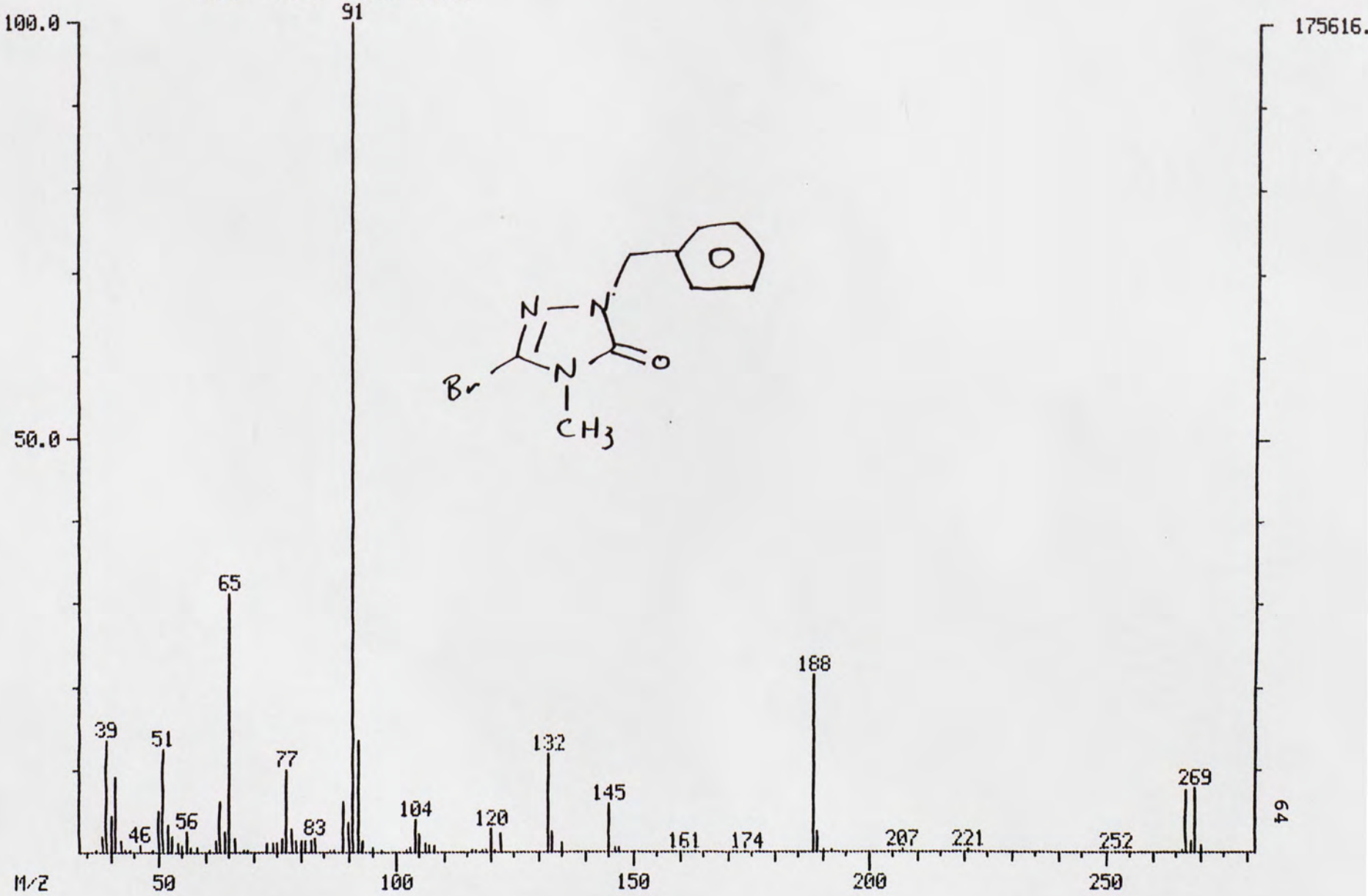


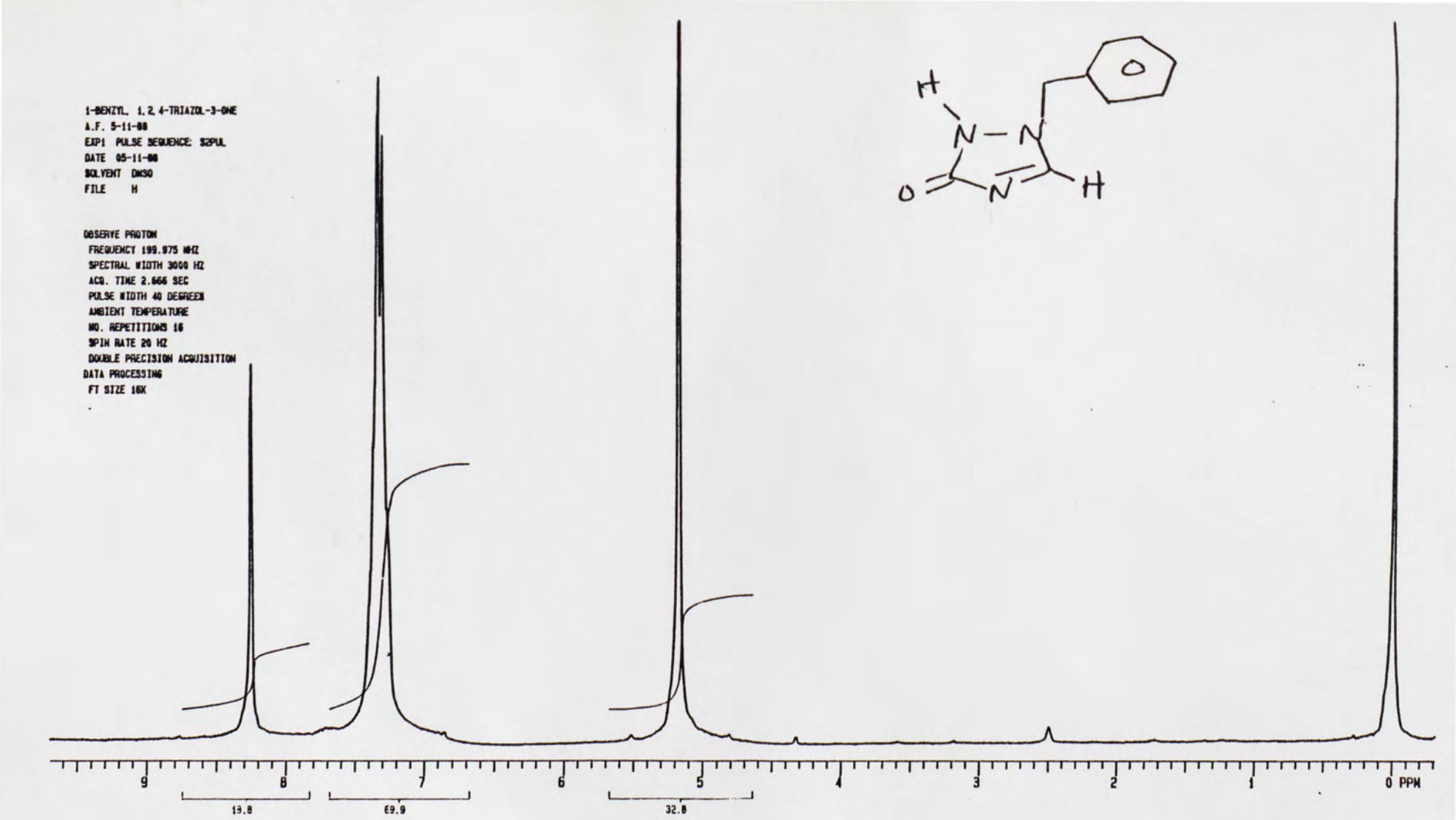
1.000	200	1.000	300.0	16	---	---	92PUL
3000.3	0	NNN	20.0	---	---	---	
2.666	0	C	200	2099.8	100.0		
12.9	16		1.0				CDCL3

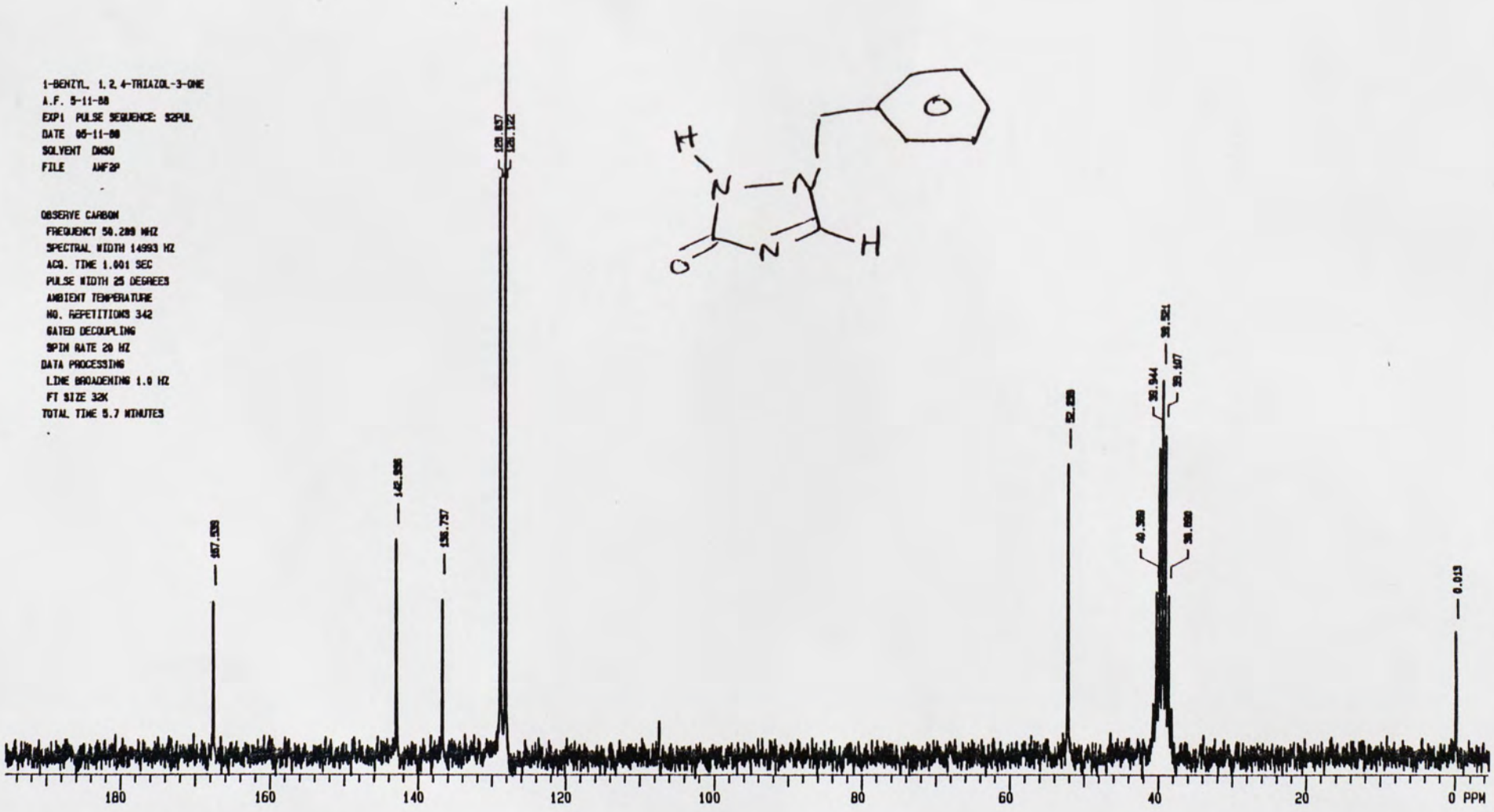
THERMO METHODAY PRODUCT
1.". 3-12 88


Br
N
N
N
O
O
CH3
153.466
136.322
129.227
128.570
122.583
78.843
77.534
77.406
77.276
76.767
49.906
29.491
200
180
160
140
120
100
80
60
10
20
0

08/10/87 9:44:AM + 12:09 CAL1: CHM2887A #2 RIC: 593920.
SAMPLE: #1
CONDS.: DB-5 30M 0.25MM 0.25UM FILM 50(1)-20-290(5)
GC TEMP: 271 DEG. C
#729 - #723 - #735 X1.00

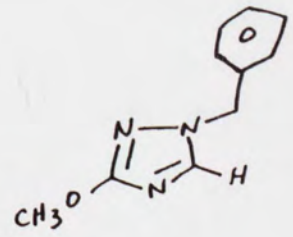



1-BENZYL 1,2,4-TRIAZOL-3-ONE
A.F. 5-11-88
EXP1 PULSE SEQUENCE: S2PUL
DATE 05-11-88
SOLVENT DMSO
FILE H
OBSERVE PROTON
FREQUENCY 199.975 MHZ
SPECTRAL WIDTH 3000 HZ
ACQ. TIME 2.666 SEC
PULSE WIDTH 40 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 16
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 16K
H
N
N
O
N
H
O
9
8
7
6
5
4
3
2
1
0 PPM
19.8
69.9
32.8


1-BENZYL, 1,2,4-TRIAZOL-3-ONE
A.F. 5-11-88
EXP1 PULSE SEQUENCE: S2PUL
DATE 05-11-88
SOLVENT DMSO
FILE AMF2P
OBSERVE CARBON
FREQUENCY 50.289 MHZ
SPECTRAL WIDTH 14993 HZ
ACQ. TIME 1.001 SEC
PULSE WIDTH 25 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 342
GATED DECOUPLING
SPIN RATE 20 HZ
DATA PROCESSING
LINE BROADENING 1.0 HZ
FT SIZE 32K
TOTAL TIME 5.7 MINUTES
157.539
142.936
136.757
128.857
128.122
52.239
39.524
39.197
0.013
180
160
140
120
100
80
60
40
20
0 PPM

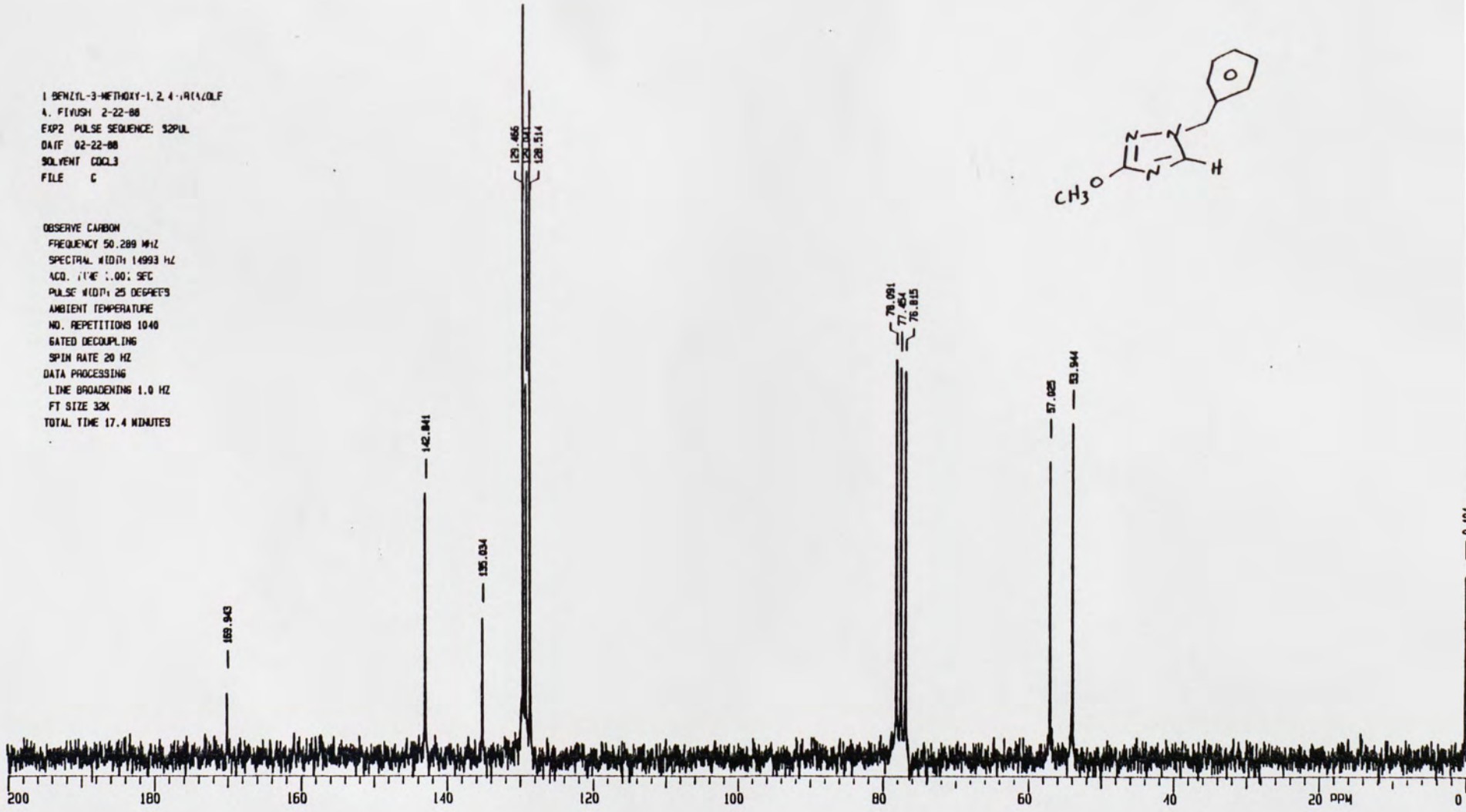
1-BENZYL-3-METHOXY-1, 2, 4-TRIAZOLE
A. FIVUSH 2-22-88
EXP1 PULSE SEQUENCE: S2PUL
DATE 02-22-88
SOLVENT CDCL3
FILE H

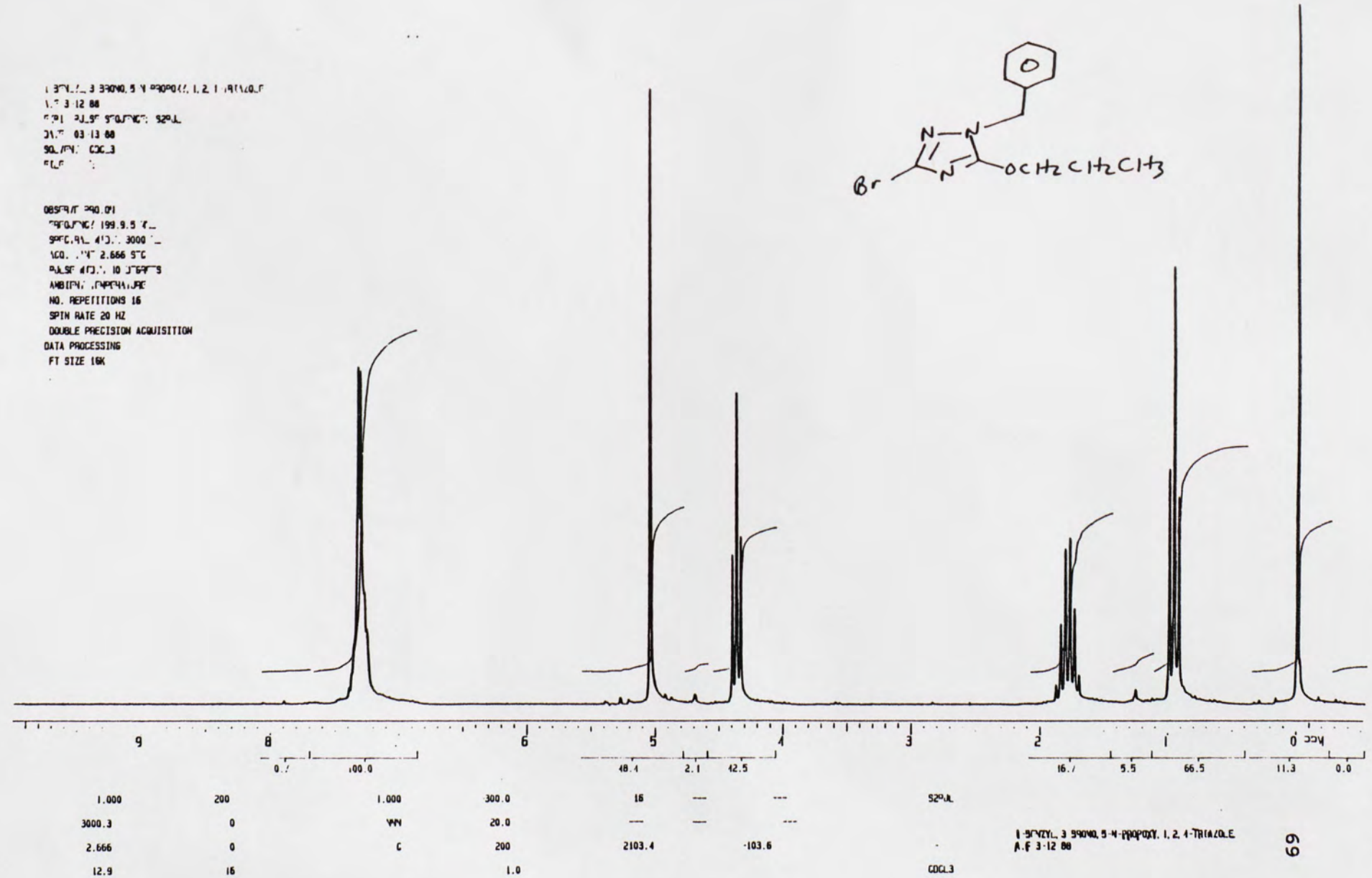
OBSERVE PROTON
FREQUENCY 199.975 MHZ
SPECTRAL WIDTH 3000 HZ
ACQ. TIME 2.666 SEC
PULSE WIDTH 40 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 16
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 16K

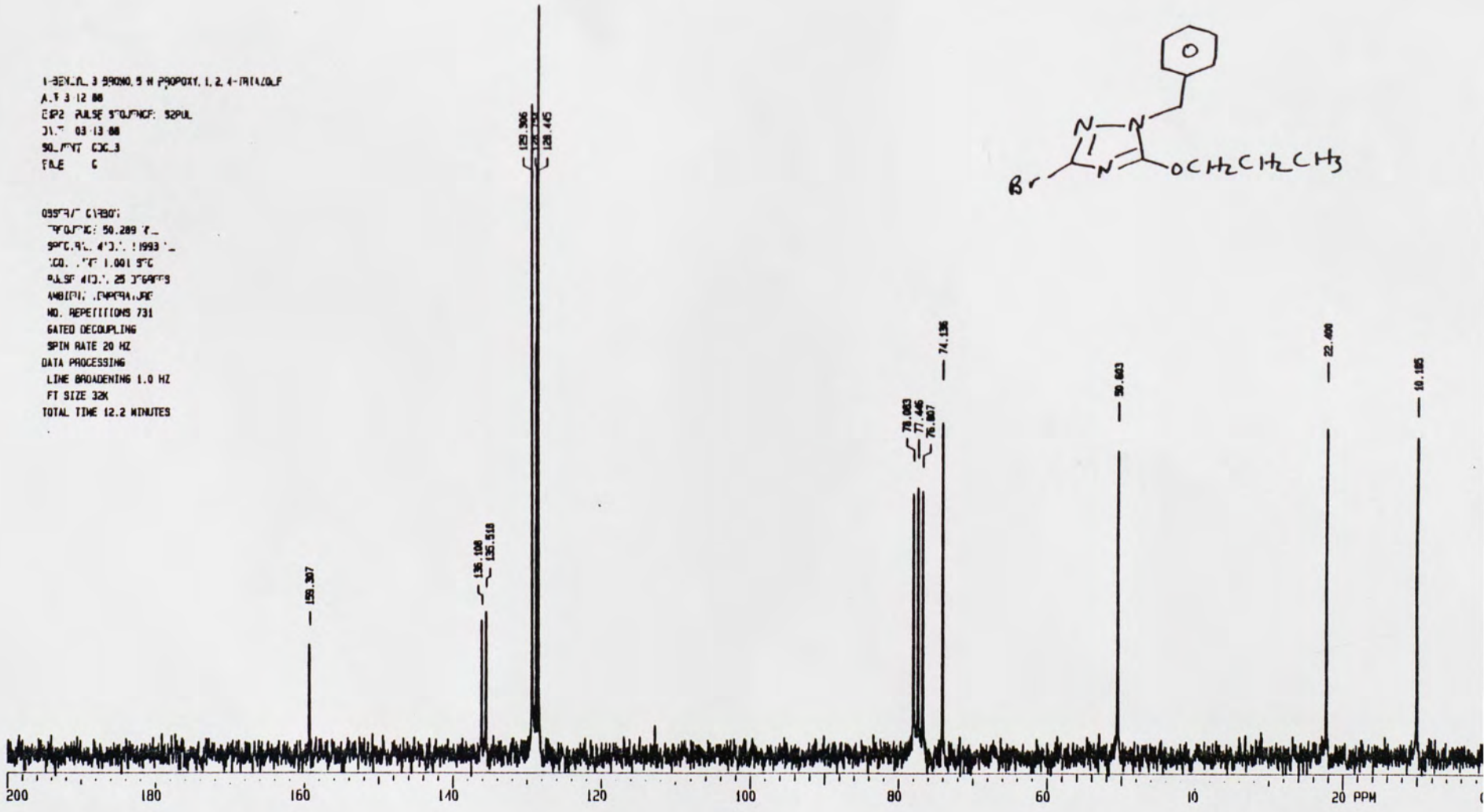


1.000	200	1.000	300.0	16	S2PUL	
3000.3	0	YYY	20.0			
2.666	0	C	200	2099.8	-100.0	
12.9	16		1.0		CDCL3	

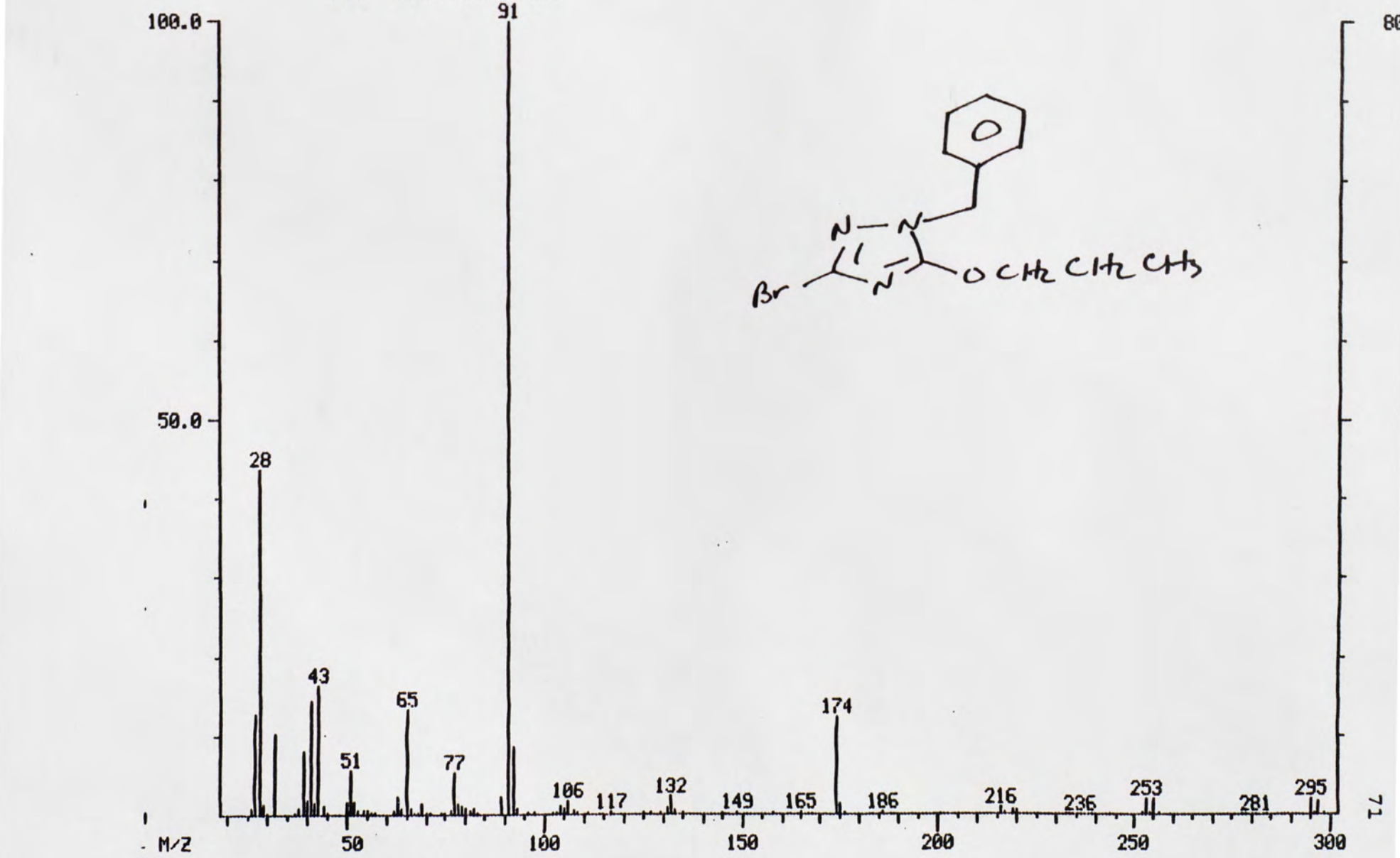
1-BENZYL-3-METHOXY-1, 2, 4-TRIAZOLE
A. FIVUSH 2-22-88

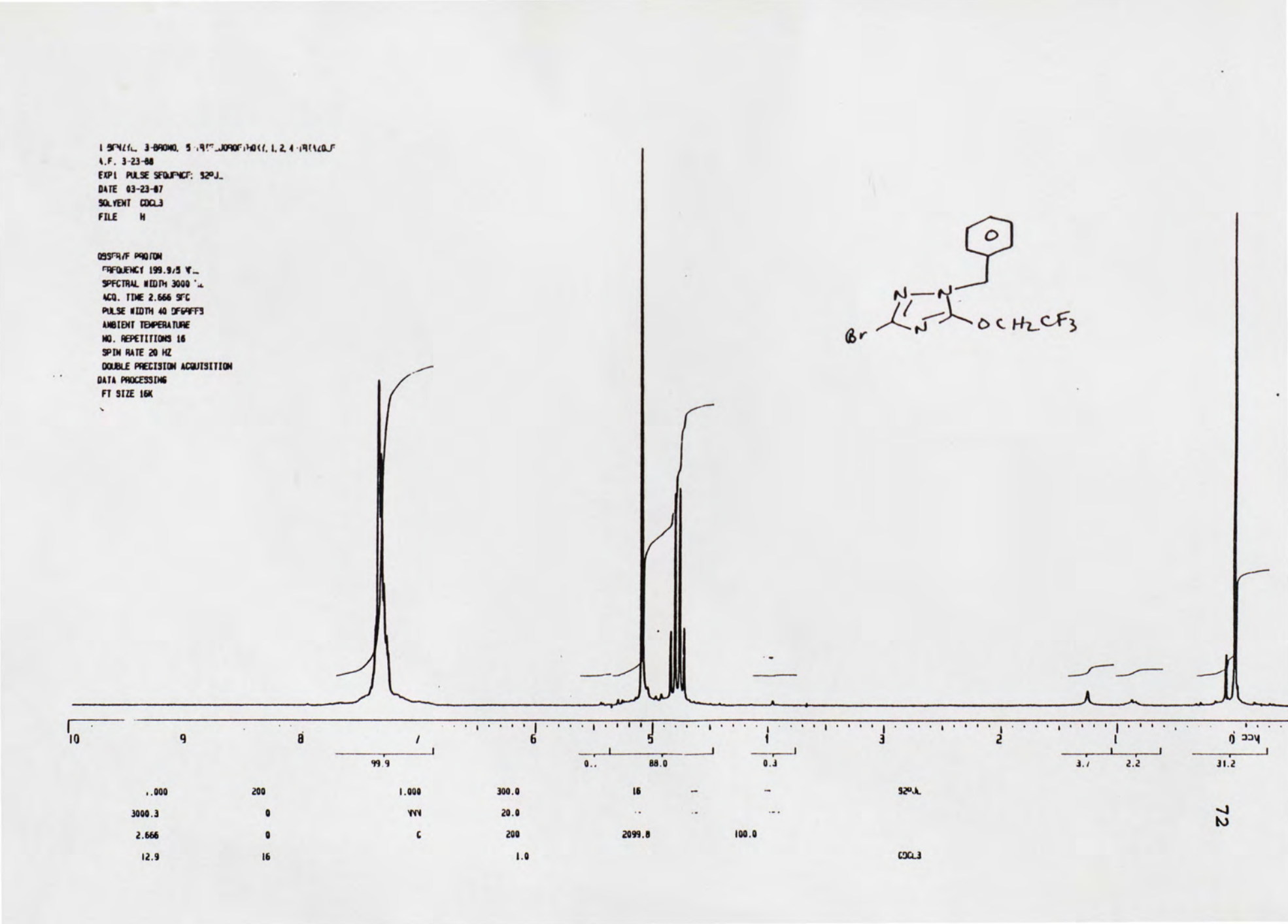

1-BENZYL-3-METHOXY-1,2,4-TRIAZOLE
A. FIVUSH 2-22-88
EXP2 PULSE SEQUENCE: S2PUL
DATE 02-22-88
SOLVENT CDCL3
FILE C
OBSERVE CARBON
FREQUENCY 50.289 MHZ
SPECTRAL WIDTH 14993 HZ
ACQ. TIME 1.00 SEC
PULSE WIDTH 25 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 1040
GATED DECOUPLING
SPIN RATE 20 HZ
DATA PROCESSING
LINE BROADENING 1.0 HZ
FT SIZE 32K
TOTAL TIME 17.4 MINUTES
169.943
142.841
135.034
129.466
129.041
128.514
78.091
77.454
76.815
57.025
53.944
200
180
160
140
120
100
80
60
40
20 PPM
0
CH3O
N
N
N
H
O


Br
N
N
N
OCH2CH2CH3
DATA PROCESSING
FT SIZE 16K
NO. REPETITIONS 16
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
9
8
6
5
4
3
2
1
0
0.0
16.7
5.5
66.5
11.3
0.0
48.4
2.1
42.5
1.000
200
1.000
300.0
16
52°.JL
3000.3
0
20.0
2.666
0
C
200
2103.4
-103.6
12.9
16
1.0
CDCL3
A.F 3-12 88
69


DEPT PULSE SEQUENCE: S2PUL
GATED DECOUPLING
SPIN RATE 20 HZ
DATA PROCESSING
LINE BROADENING 1.0 HZ
FT SIZE 32K
TOTAL TIME 12.2 MINUTES
159.307
136.108
135.518
129.306
128.445
78.083
77.446
76.807
74.136
50.803
22.490
10.185
200
180
160
140
120
100
80
60
40
20 PPM
Br
OCH2CH2CH3

03/17/88 17:12:00 + 0:34
CALI: CHM2088A #2 RIC: 246272.
SAMPLE: 1-BENZYL-3-BROMO-5-PROPOXY-1,2,4-TRIAZOLE
CONDS.: SOLID PROBE 30-350 BALLISTIC
GC TEMP: 343 DEG. C
#34 - #11 - #45 X1.00

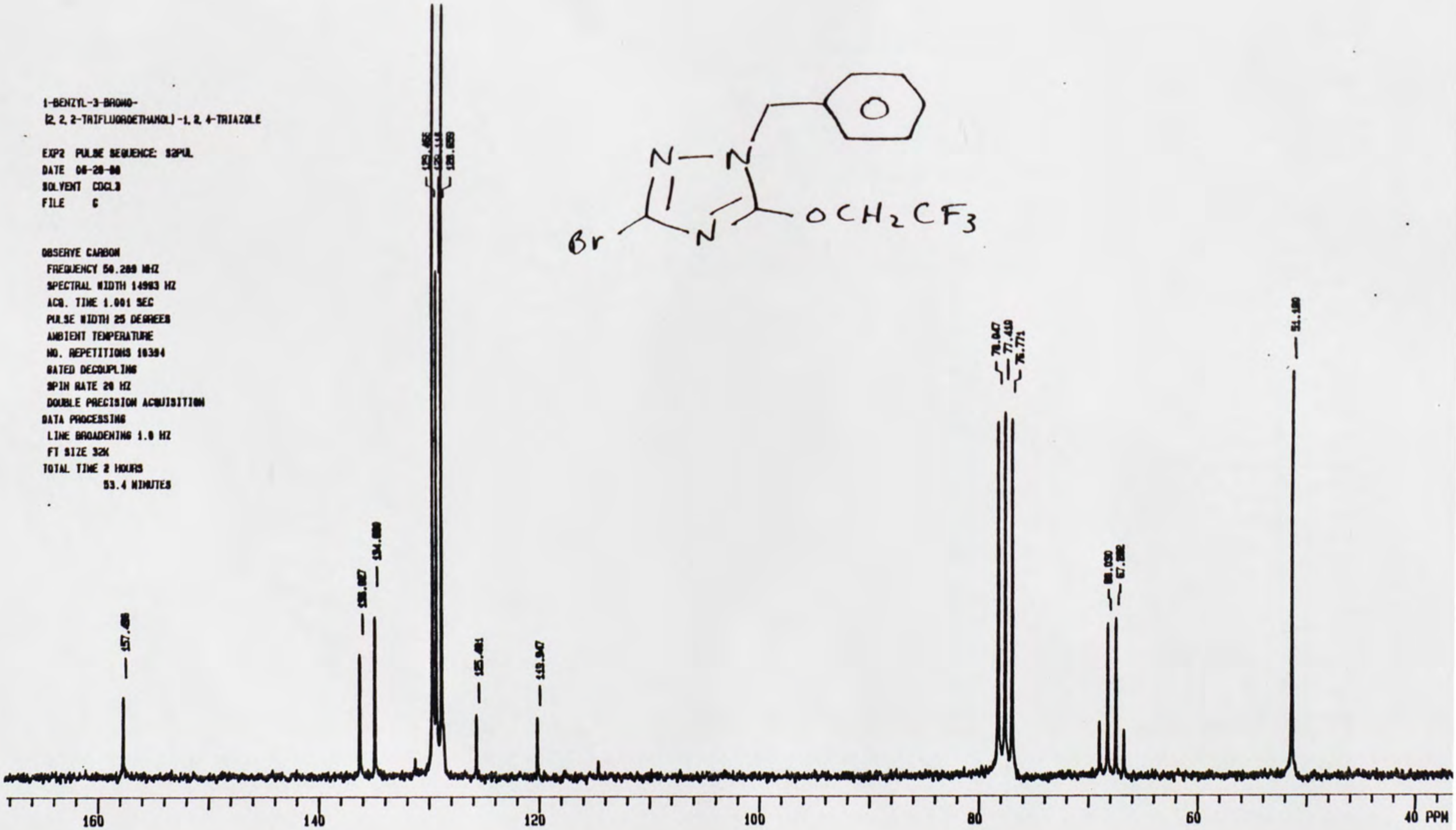



A.F. 3-23-88
EXPL PULSE SEQUENCE: 52°J_
DATE 03-23-87
SOLVENT CDCL3
FILE H
OBSERVE PROTON
FREQUENCY 199.975 MHz
SPECTRAL WIDTH 3000 Hz
ACQ. TIME 2.666 SEC
PULSE WIDTH 40 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 16
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 16K
Br
OCH2CF3
10
9
8
7
6
5
4
3
2
1
0
99.9
88.0
0.3
3.7
2.2
31.2
.000 200 1.000 300.0 16 52°
3000.3 0 20.0
2.666 0 200 2099.8 100.0
12.9 16 1.0 CDCL3

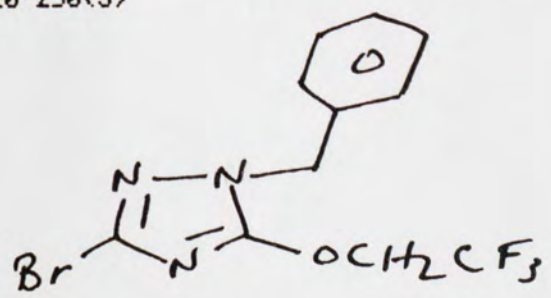
1-BENZYL-3-BROMO-
(2, 2, 2-TRIFLUOROETHANOL) -1, 2, 4-TRIAZOLE

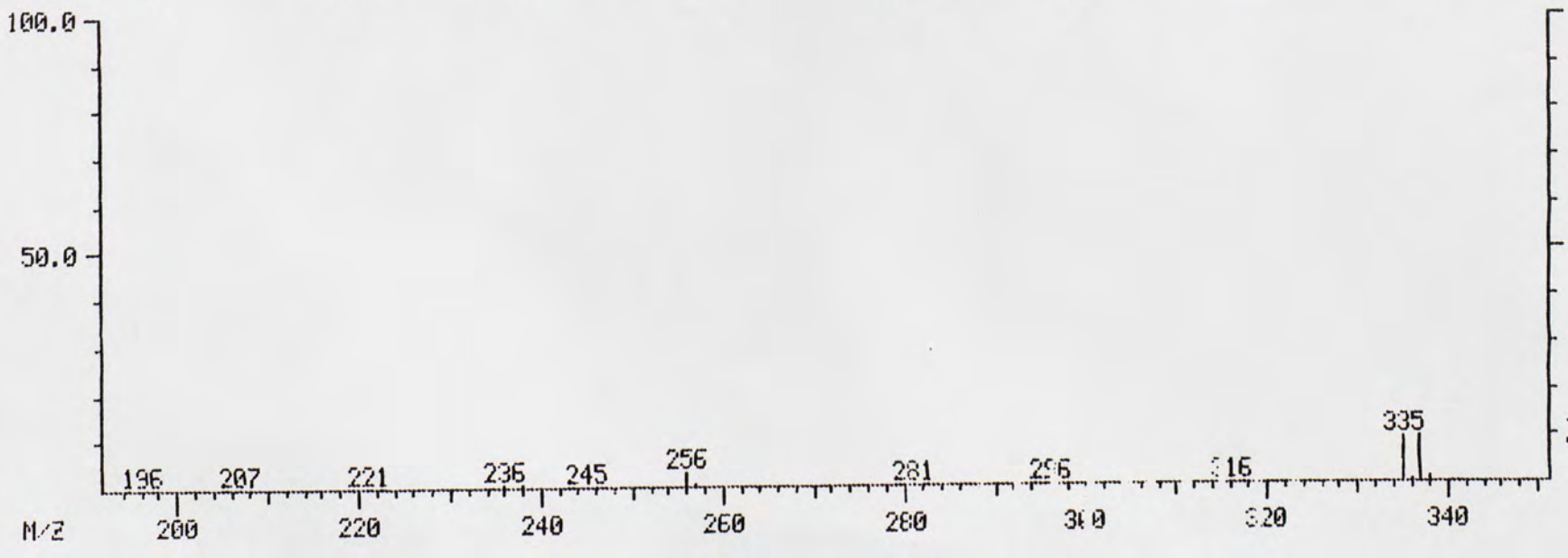
EXP2 PULSE SEQUENCE: S2PUL
DATE 06-20-88
SOLVENT CDCL3
FILE C

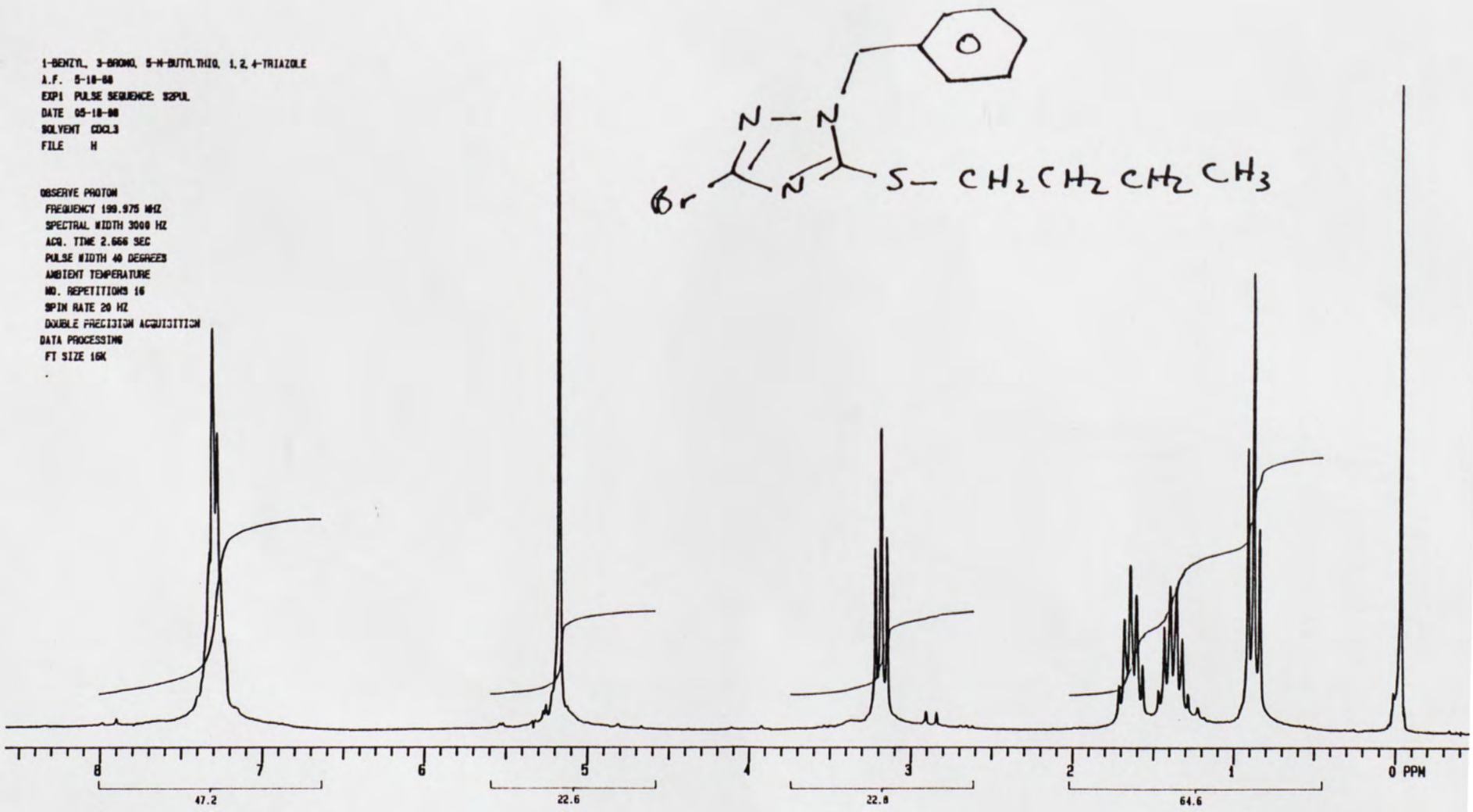
OBSERVE CARBON
FREQUENCY 50.289 MHZ
SPECTRAL WIDTH 14993 HZ
ACQ. TIME 1.001 SEC
PULSE WIDTH 25 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 10394
GATED DECOUPLING
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 HZ
FT SIZE 32K
TOTAL TIME 2 HOURS
53.4 MINUTES

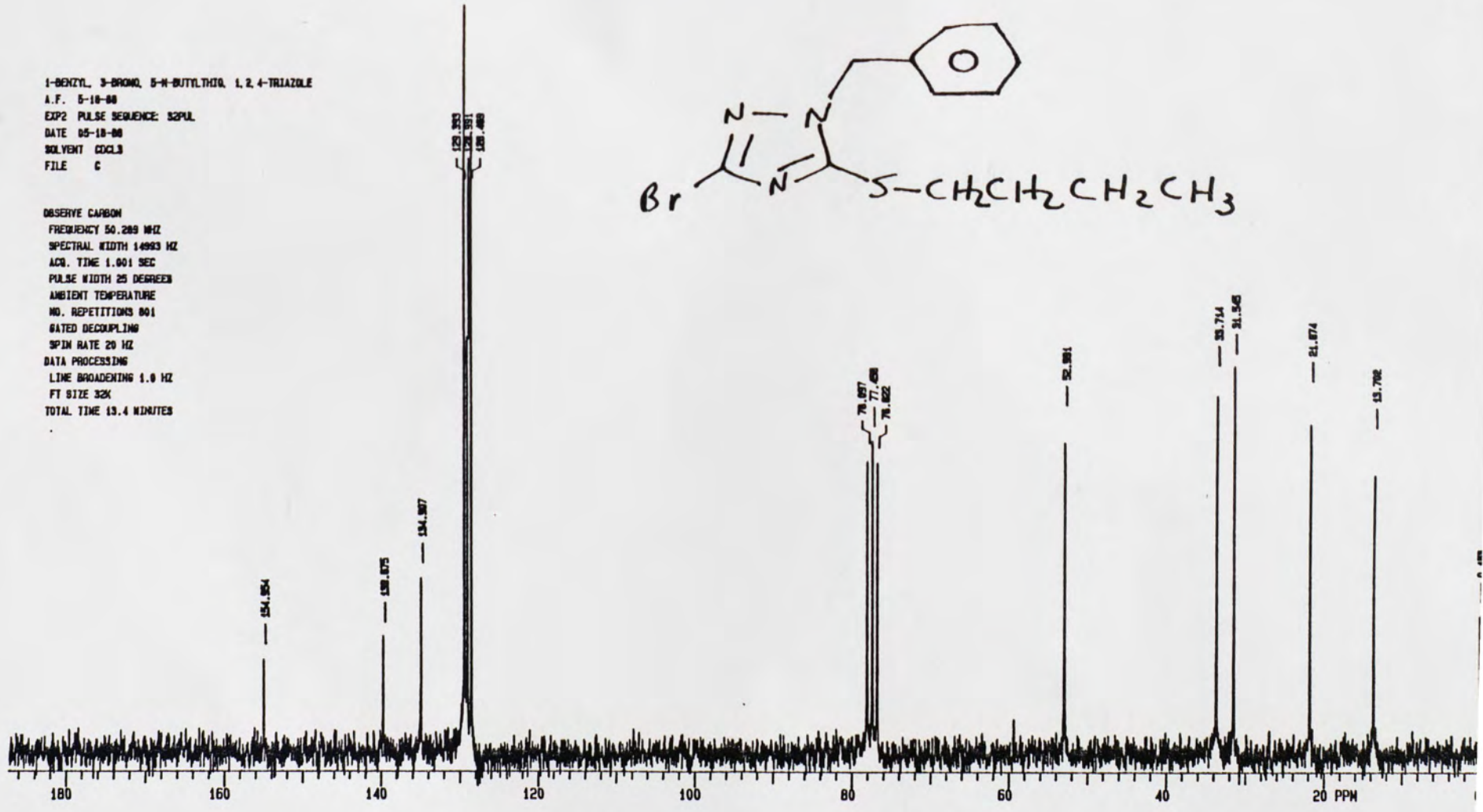


MID MASS SPECTRUM
08/10/87 16:01:00 + 10:38
DATA: CHM3287A #638
CALI: CHM3287A #2
BASE M/Z: 91
RIC: 3665910.
SAMPLE: 1-BENZYL-3-BROMO-5-(2,2,2-TRIFLUOROETHOXY)-1,2,4-TRIAZOLE
CONDS.: DB-5 30M 0.25MM 0.25UM FILM 50(1)-20-290(5)
GC TEMP: 247 DEG. C
#636 TO #641 SUMMED





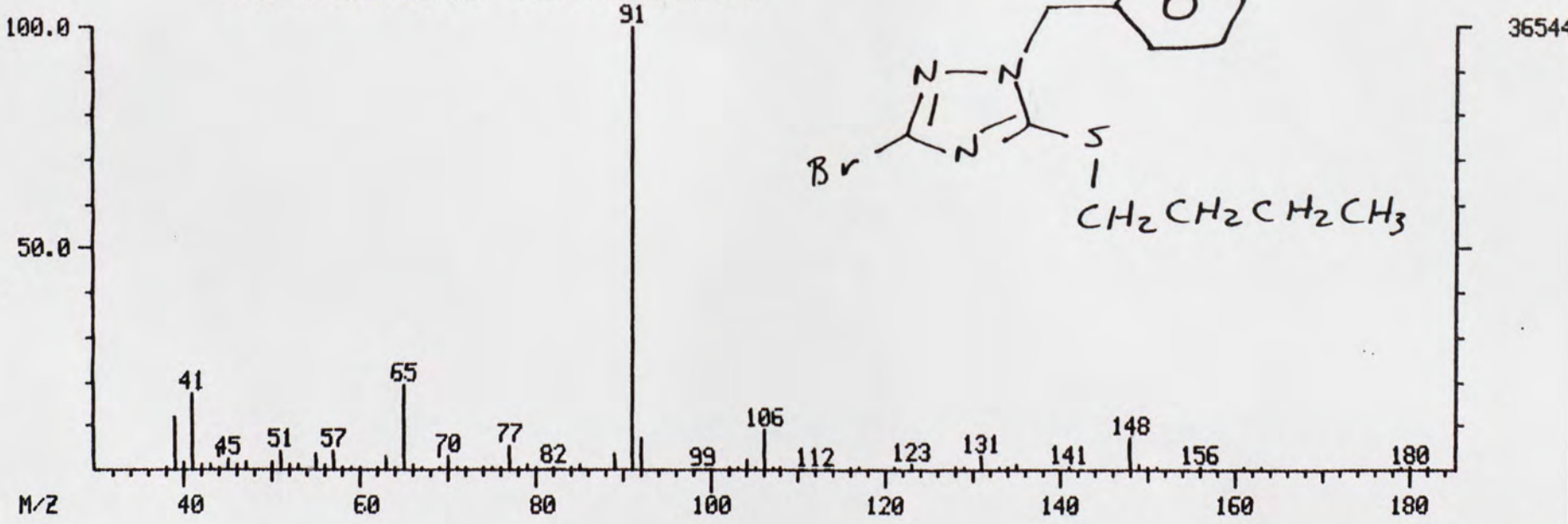

1-BENZYL, 3-BROMO, 5-N-BUTYLTHIO, 1,2,4-TRIAZOLE
A.F. 5-18-88
EXP1 PULSE SEQUENCE: S2PUL
DATE 05-18-88
SOLVENT CDCL3
FILE H
OBSERVE PROTON
FREQUENCY 199.975 MHZ
SPECTRAL WIDTH 3000 HZ
ACQ. TIME 2.666 SEC
PULSE WIDTH 40 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 16
SPIN RATE 20 HZ
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 16K
Br
S— CH2CH2CH2CH3
8
7
6
5
4
3
2
1
0 PPM
47.2
22.6
22.8
64.6

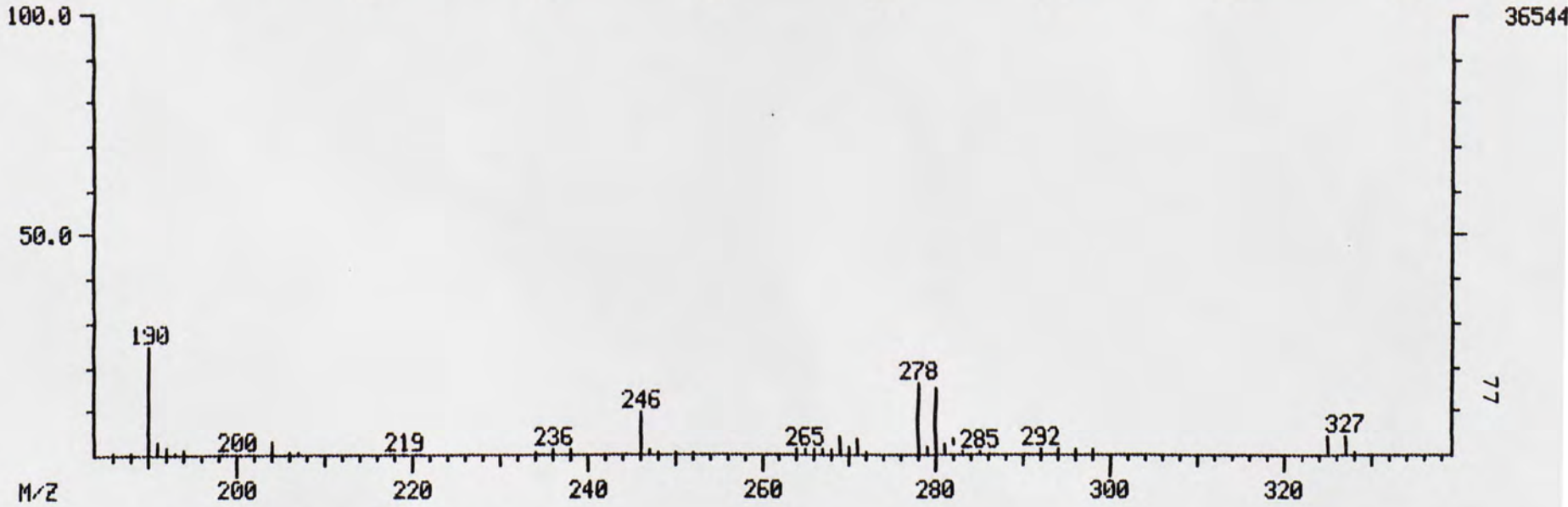

1-BENZYL, 3-BROMO, 5-N-BUTYLTHIO, 1,2,4-TRIAZOLE
A.F. 5-18-88
EXP2 PULSE SEQUENCE: S2PUL
DATE 05-18-88
SOLVENT CDCL3
FILE C
OBSERVE CARBON
FREQUENCY 50.289 MHZ
SPECTRAL WIDTH 14993 HZ
ACQ. TIME 1.001 SEC
PULSE WIDTH 25 DEGREES
AMBIENT TEMPERATURE
NO. REPETITIONS 801
GATED DECOUPLING
SPIN RATE 20 HZ
DATA PROCESSING
LINE BROADENING 1.0 HZ
FT SIZE 32K
TOTAL TIME 13.4 MINUTES
Br
S—CH2CH2CH2CH3
154.354
139.875
134.307
129.393
128.391
128.089
78.657
77.458
76.822
52.591
33.714
31.545
21.674
13.762
180
160
140
120
100
80
60
40
20 PPM

MID MASS SPECTRUM
04/22/88 14:52:00 + 14:23
SAMPLE: 1-BENZYL-3-BROMO-5-THIOBUTYL-1,2,4-TRIAZOLE
CONDS.: DB-5 30M 0.25MM ID 0.25UM FILM 50(2)-20-290(10)
GC TEMP: 280 DEG. C
#861 TO #865 SUMMED - #849 TO #854 X1.00

DATA: CHM3088A #863
CALI: CHM3088A #2

BASE M/Z: 91
RIC: 135936.





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