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Heterocyclic Syntheses Utilizing Aryl Cyanates

Joseph Eugene Drumm

HETEROCYCLIC SYNTHESES UTILIZING ARYL CYANATES

by

Joseph Eugene Drumm III

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Also, to Dr. Harmon, thanks for all the chemistry and support you have given over the years.

Joseph Eugene Drumm III

DEDICATION

To my wife, Nancy, who made all of this possible -

Thanks, Sweetie.

DRUMM, JOSEPH EUGENE, III

HETEROCYCLIC SYNTHESES UTILIZING ARYL CYANATES

WESTERN MICHIGAN UNIVERSITY M.A. 1984

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CHAPTER I

INTRODUCTION

The goal of this research effort has been multi-faceted. Included are the syntheses of novel heterocyclic compounds of potential biological activity, providing sufficient characterization of these compounds, providing spectral evidence hitherto unpublished, and refining the laboratory skills needed by chemists. After discussing the chemistry of the cyanto group some of the interesting reaction pathways utilized in this work are discussed in detail. In particular, the syntheses of (a) 2-(5-aryloxy)-4,6-dimercapto-s-triazines, (b) 5-aryloxytetrazoles, (c) 5-aryloxy-1-aryltetrazoles, and their subsequent identification via mass spectral evidence, IR, and UV spectra will be presented.

CHAPTER II

ARYL CYANATES

Synthesis

The functionality known as the cyanato group 1 has been studied for a long time. Nef (1) is credited with their initial discovery, and

$$R\text{-}O\text{-}C{\equiv}N$$

1

R = Alkyl or Aryl

Figure 1. Cyanate Functionality

since that time others have also pursued their study. In 1960 Stroh and Gerber, and in 1961 Hoyer (2) prepared true cyanic esters, although in both cases, they assumed that sterically hindered phenols must be used. Grigat and Pütter (3) first discovered the method of choice for preparing cyanates in 1964, and it utilized the reactivity of cyanogen halides in the presence of base to carry out the reaction. Cyanogen chloride was used exclusively in their initial work (Figure 2).

$$Ar\text{-}OH + Cl\text{-}C{\equiv}N \xrightarrow[\text{Acetone}]{\text{Base}} \underset{2}{Ar\text{-}O\text{-}C{\equiv}N} + Base{\cdot}HCl$$

Figure 2. Original Synthesis of Aryl Cyanates

Dieter Martin (4,5), in 1964, discovered an alternate synthesis of cyanates, both aryl and alkyl. His reaction scheme was as follows (Figure 3). This pathway seemed less desirable due to the instability of some of the alkoxythiatriazoles, some of which decomposed violently.

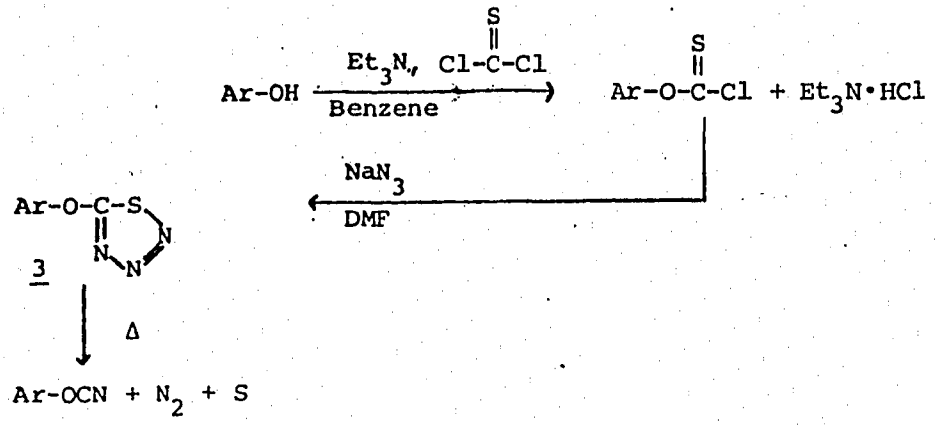


Figure 3. Alternate Synthesis of Cyanates (I)

In 1965 Jensen and Holm (6) were able to obtain alkyl cyanates by an analogous procedure to that of Martin (Figure 4).

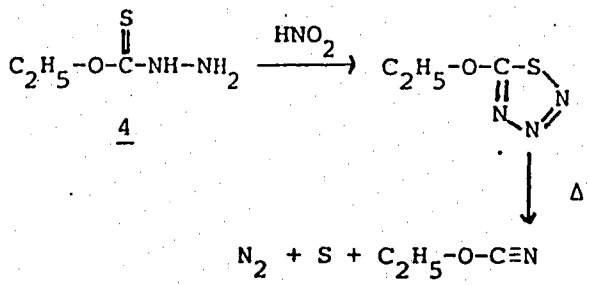


Figure 4. Alternate Route to Cyanate (II) Synthesis

The reaction utilizing 4 suffered from the same problems as that of Martin's, namely the decomposition of the alkoxythiatriazoles, thus leading to lower yields and hazardous reaction conditions.

One of the major problems facing chemists for the preparation of cyanic acid esters has been the tendency of the cyanato group 1 to undergo rearrangement to the isocyanato group (Figure 5).

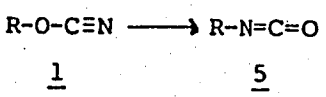


Figure 5. Cyanate Isomerization

To date, this reaction has been observed only with alkyl substituents, similar to the rearrangement of thiocyanates to isothiocyanates.

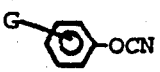
Aryl cyanates, on the other hand, do not exhibit this tendency. Grigat and Pütter (3), as well as Martin et al., have reported the aryl cyanates to be stable compounds possessing a moderate shelf life.

Experimental

All the cyanates listed in Table 1 were prepared according to

Table 1

Aryl Cyanates Prepared



G	G
H	4-S-CH_3
4-Cl	4-Cl; 3,5-CH_3
2,4-Cl	4-iPr
3,4-Cl	CH_3O
2,4,5-Cl	4-O-CH-C-O-CH_3
2,4-Br	2,6-t-Bu
4-Ar	2-F

General Procedure I, which follows.

General Procedure I: Synthesis of Aryl Cyanates

In a dry ice/2-propanol bath, 0.1 mol of the appropriate phenol and 0.1 mol (10.52 g) of cyanogen bromide were dissolved in 300 mL of dried (4Å molecular sieves) acetone. Over a 10 minute period, 0.1 mol (10.12 g, d^{25} 0.726, 13.94 mL) of dried triethylamine was added with constant hand stirring. The triethylamine had been previously dried

over potassium hydroxide pellets. After approximately two minutes, a white precipitate of triethylammonium bromide started forming. After ten minutes, the white solid was filtered, washed with cold acetone and discarded. The filtrate was then concentrated on a rotary evaporator and crystallized on cooling. The crystals were light yellow and waxy. Recrysrallization was performed using hexanes. Yields: 90-99%

Discussion

In a later work, Martin (7) suggested the possible use of cyanogen bromide as the nitrile source for the formation of cyanates. The compounds shown in Table 1 were thus prepared by this method (Figure 6).

$$Ar\text{-}OH + Br\text{-}C{\equiv}N \xrightarrow[\text{Acetone}\ /\ \text{Dry Ice}/\ 2\text{-Propanol}]{Et_3N} Ar\text{-}O\text{-}C{\equiv}N + Et_3N{\cdot}HBr$$

Figure 6. Synthesis of Aryl Cyanates

While at least one cyanate, 2,4-dichlorophenyl cyanate, had a shelf life of over six months, it was found that the subsequent reactions using the cyanates proceeded smoother and in greater yields if the appropriate cyanate was prepared fresh. In general, the most commonly encountered problem with cyanates that had been stored, was their tendency to trimerize to the triaryloxy-s-triazine (Figure 7).

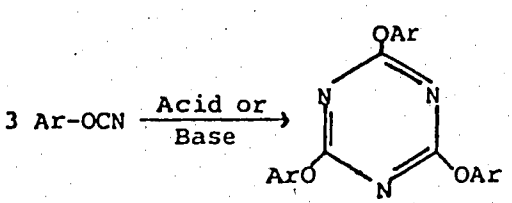


Figure 7. Cyanate Trimerization Product

This problem was also encountered on attempts to recrystallize the cyanate products. Recrystallizing attempts in acetone, the reaction solvent, while being successful, still led to some formation of the trimer. The crystals obtained still were quite waxy, as well. This problem was observed in hexanes as well, however, the yellow discoloration was removed.

Each of the cyanates listed in Table 1 was identified by its infrared absorption, namely the 2150-2250 cm^{-1} band, which was strong and sharp (2), plus the phenolic ether stretch, (Ar-O-C), at 1160 cm^{-1}. The aromatic C=C absorbances, 1550-1650 cm^{-1} were also used. The few melting points available for the cyanates were useful only in one instance, 2,4-dichlorophenyl cyanate, since all the products tended to be quite waxy.

The proposed mechanism for the formation of the aryl cyanates is in agreement with that proposed by Bacaloglu et al. (8) in their comprehensive study. Following the initial formation of the N-cyano-N,N,N-triethylammonium bromide salt via the von Braun reaction (9-11) (Figure 8), the nucleophilic attack by the phenol on the quaternary

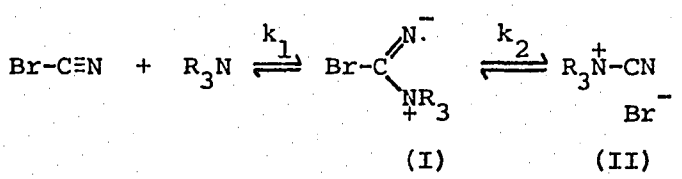


Figure 8. Von Braun Reaction.

ammonium salt was rapid (Figure 9).

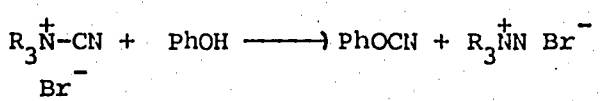


Figure 9. Proposed Mechanism for the Formation of Aryl Cyanates.

As a class, the aryl cyanates represent an interesting set of very reactive compounds. Many of the physical parameters for their formation have been previously studied, In particular, solvent effects (11), rate constants (12), and activity coefficients (13) for a variety of solvents have been investigated.

CHAPTER III

2-ARYLOXY-4,6-DIMERCAPTO-1,3,5-TRIAZINES

Synthesis

The tendency for aryl cyanates to trimerize to the corresponding s-triazines led Grigat and Pütter to investigate the possibility of reacting other similar nitrile bearing compounds with their aryl cyanates (14). Various molecules capable of 1,2-cycloadditions were used, thus altering the substituents on the triazine ring. Some, like the reaction of the aryl cyanates with anhydrous ammonia, did not lead to direct ring closure. In the presence of an acidic medium, however, the reaction proceeded to form the triazine ring.

In an acidic aqueous medium, ammonium thiocyanate dissociates to thiocyanic acid and the ammonium cation (Figure 10).

$$NH_4SCN + H_2O \overset{H^+}{\rightleftharpoons} HSCN + NH_3 + H_2O$$

Figure 10. Thicyanic Acid Formation.

The reaction to form s-triazines typically went as follows. One equivalent of the aryl cyanate dissolved in ether, reacts with two equivalents of thiocyanic acid in water. Thus, the reaction used for the formation of 2-aryloxy-4,6-dimercapto-s-triazines is shown in Figure 11.

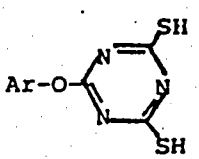
(1) $Ar\text{-}O\text{-}C{\equiv}N + 2NH_4SCN \xrightarrow[H_2O \\ Et_2O]{H_2SO_4}$ 

Figure 11. Synthesis of 2-Aryloxy-4,6-dimercapto-s-triazines.

In addition to the above reaction, many other studies have been done on the trimerization of cyanic acid (14) and other s-triazino systems (15).

Experimental

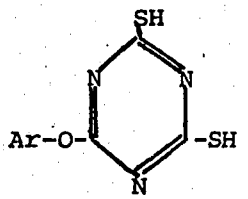
All the 2-aryloxy-4,6-dimercapto-s-triazines in Table 2 were prepared according to General Procedure II, which follows. Thin layer chromatography was performed using a hexanes/2-propanol (1:5) solution with the appropriate sample dissolved in acetone. Diethylacetoamidomalonate was used as the standard. Thin layer chromatography established that the samples consisted of only one component. All melting points were obtained using a Thomas-Hoover melting point apparatus. All NMR spectra were obtained from a Varian A-60 NMR. The mass spectra were obtained using both a DuPont 41-290B and Finnigan MAT GC/MS. A Beckman DU-6 UV/VIS spectrophotometer was used to collect the UV spectra. All IRs were obtained using a Beckman Acculab 8 spectrophotometer.

General Procedure II: Synthesis of 2-aryloxy-4,6-dimercapto-s-triazines

An aqueous solution of ammonium thiocyanate was prepared by dissolving 0.150 mol (11.42 g) of NH_4SCN in 50 mL of distilled water. To this was added 11 mL of concentrated H_2SO_4. After cooling, a solution of 0.075 mol of the aryl cyanate, dissolved in 50 mL of diethyl ether, was added. The heterogeneous reaction mixture was stirred using a magnetic stirrer. The reaction mixture was then stirred for thiry minutes whereupon the solid product formed at the interface of the two

Table 2

Reaction Data for 2-Aryloxy-4,6-dimercapto-s-triazines



Ar	Yield (%)	Elemental Analysis	Calculated	Found
4-Cl	82	C	39.79	39.49
		H	2.21	2.22
		N	15.46	15.81
		S	23.60	23.07
2,4-Cl	77	C	35.31	35.25
		H	1.64	1.83
		N	13.72	13.49
		S	20.95	20.69

layers. The solid was removed by filtration and washed with cold water. The products were recrystallized using hot diethyl ether followed by hexanes.

Discussion and Spectral Data for 2-Aryloxy-4,6-dimercapto-s-triazines

Mass Spectral Evidence

Each of the triazines analyzed showed a similar fragmentation pattern. In addition, molecular ions were also present. The fragments were readily indentifible with the pattern shown in Figure 12.

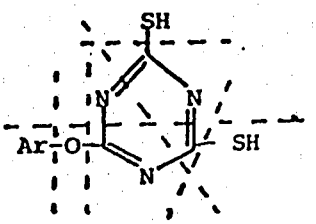
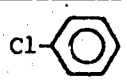
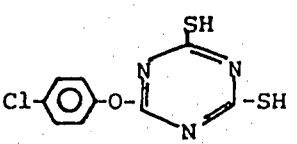
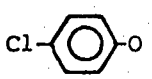
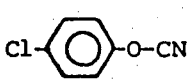
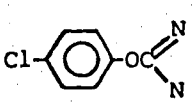


Figure 12. Fragmentation Pattern for 2-Aryloxy-4,6-dimercapto-s-triazine

Table 3 contains the specific fragments for one of the compounds examined.

Table 3

Fragmentation of 2-(4•-Chlorophenoxy)-4,6-dimercapto-s-triazine

Fragment	Mass	
	111	 = 271^{M+}
	127	M-33(SH) = 238
	153	
	167	M-59(HSCN) = 212

IR

Close examination of these compounds using infrared spectroscopy confirmed suspicions that the triazine system was capable of tautomerization (Figure 13). The absorbances for the mercapto groups, 2400-2600 and 900 cm^{-1}, were absent from the spectra. Instead, C=S absorbances, 1550-1600 cm^{-1}, were detected. The phenolic ether stretch

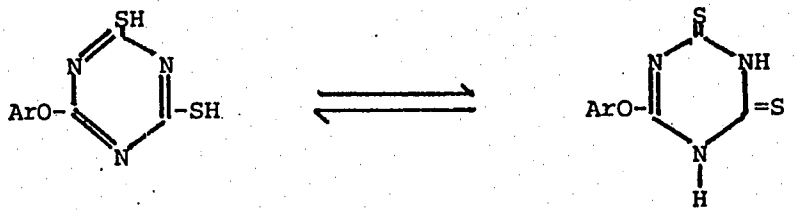


Figure 13. Dimercapto-s-triazine Tautomerization.

(Ar-O-C) was very strong and sharp, ν = 1180 cm^{-1}.

The absorbances between 3200-3600 cm^{-1} of the spectra could be assigned as N-H stretches associated with the dithionodiamido form.

The tautomerization was not observed in solution (NMR,UV), nor in the gas phase (MS). Since this was observed only in the solid phase, perhaps the cause for it lies in the crystalline lattice formation. Examination of this phenomena was not included in this paper. Table 4 contains a summary of the IR and UV data obtained.

UV

The ultraviolet spectra for two of the trizaines were recorded in p-dioxane. The λ_{max} were determined, as well as the molar absorptivity, to serve as a quick characterization method. The values were similar, as one would predict. A maximum of 324 nm was observed for both triazines.

Each solution was prepared by dissolving the appropriate number of grams in 25 mL of p-dioxane. The absorbance of p-dioxane (<242 nm) was sufficiently low as not to interfere with the value observed. A 1 cm quartz cell was used for all the UV spectra obtained pertinent to this paper. The spectrophotometer was equipped with an Epson MX-90

Table 4

Spectral Data for 2-Aryloxy-4,6-dimercapto-s-triazines

Ar	$\nu(cm^{-1})$	$g(\times 10^{-2})$	$M(\times 10^{-3})$	λ_{max}(nm)	ε*(l/mole·sec)
4-Cl	C=S 1560-1575 C=S 1580-1590 C-O-C 1180 N-H 3100-3600	3.51	5.168	324	445
2,4-Cl	C=S 1560 C=S 1570 C-O-C 1180 N-H 3050-3500	3.85	5.032	324	173

*Solutions in 25 mL of p-dioxane at 25°C

serial printer which served as the recorder. For each of the spectra, a background scan of the solvent was used for calibrating the instrument. The solvent spectrum was then automatically subtracted from the triazine's spectrum.

NMR

The NMR spectra of the two triazines discussed above were also obtained, albeit with great difficulty. The entire class of triazines proved to be insoluble in most solvents. The two spectra were obtained by repeatedly dissolving the triazines in deuterated dimethyl sulfoxide (DMSO-d_6). To facilitate solubilization, the samples required heating and concentration. After three concentrations, spectra were run. Table 5 contains the results of these determinations.

Table 5

NMR Proton Resonances for 2-Aryloxy-4,6-dimercapto-s-triazines

Ar	Assignment	Multiplicity	(ppm)
2,4-Cl	Aromatic	Multiplet	7.3-7.8
	S-H	Singlet	4.9-5.4
4-Cl	Aromatic	Multiplet	7.0-8.0
	S-H	Singlet	6.8-7.0

The mechanism for the triazine formation, as proposed in this paper, is summarized in Figure 14. Following the initial attack on the carbon

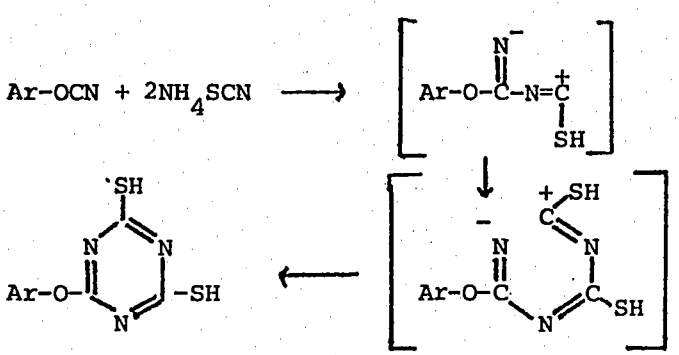


Figure 14. Proposed Mechanism for the Formation of 2-Aryloxy-4,6-dimercapto-s-triazines.

of the cyanato group by the nitrogen of one of the thiocyanato groups, the carbon of the attacking group thus develops a positive charge. Simultaneously to the initial attack, the nitrogen of the cyanato group develops a negative charge. The addition of a second molecule of thiocyanic acid proceeds, similar to the first addition.

The mercapto groups can be alkylated easily, or acylated to yield the thio ethers and thio esters respectively. Alkylated mercapto triazines can also be prepared by an analogous cyclization of the

corresponding alkylrhiocyanate with other 1,2-cycloaddition adducts.

It should be mentioned that some 2,4-diaryloxy-6-mercapto-s-triazines were formed during the reaction of the aryl cyanates with ammonium thiocyanate. The relative amounts of these contaminants was not ascertained, however, the very small fragment peaks in the mass spectra for these compounds implies that they were not formed in appreciable amounts.

CHAPTER IV

TETRAZOLES

Synthesis

The reaction of aryl cyanates with sodium azide belongs to a wide variety of reactions used in the formation of tetrazoles. The first available material regarding this reaction appeared in a paper by Grigat and Pütter (16). They used an acetone-water solvent system (Figure 15).

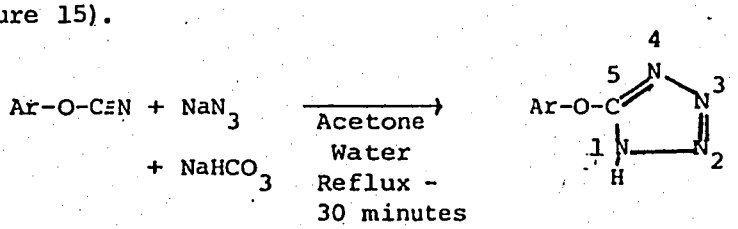


Figure 15. Synthesis of 5-Aryloxytetrazoles.

Other solvents have been suggested as the reaction medium. The most commonly mentioned solvent is N,N-dimethylformamide (DMF) (17). Other procedures have also been published. An alternate synthesis (18) called for the use of two equivalents of sodium azide, but no sodium bicarbonate in an acetone-water solvent system. The reaction of aryl cyanates, sodium azide, and ammonium chloride in DMF was also suggested (Figure 16).

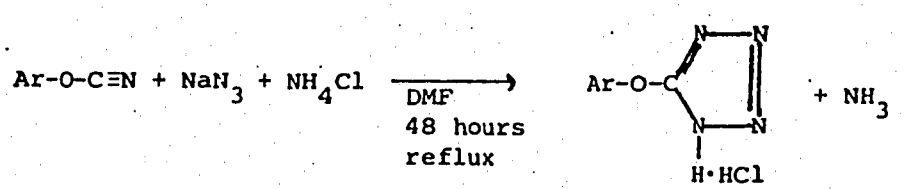


Figure 16. Alternate Synthesis of 5-Aryloxytetrazoles.

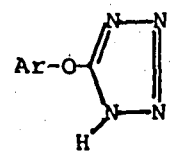
Two comprehensive review articles (19,20) concerning the various methods of preparing and reacting tetrazoles, specifically 5-aryloxy-tetrazoles, have been prepared.

Experimental

The equipment used to obtain the various spectra and melting points was the same as that described in the triazine experimental section. General Procedure III was used for all but one preparation. For the one exception, sodium bicarbonate was omitted, but the amount of sodium azide was double that used in General Procedure III. Table 6 contains the reaction data for the 5-aryloxytetrazoles prepared.

Table 6

Reaction Data for the Formation of 5-Aryloxytetrazoles

Ar	m.p.	Yield(%)	
4-Cl	157-158	58	
2,4-Cl	---	41	

General Procedure III: Synthesis of 5-Aryloxytetrazoles

An aqueous solution of 0.1 mol (6.5 g) of sodium azide in 100 mL of water was combined with a solution of 0.2 mol (8.4 g) of sodium bicarbonate in 100 mL of water. The resulting mixture was then added to an acetone solution of freshly prepared aryl cyanate (0.1 mol). The reaction mixture was then stirred with a magnetic stirrer and refluxed for 0.5-2.0 hours producing a red solution. After cooling to room temperature, the solution was poured onto a 200 mL ice-water slurry

to which one equivalent of 6M HCl has been added. The resulting white crystals were filtered and dried. The products were recrystallized from methanol. In the instances where oils were obtained rather than crystals, the following procedure was used. The oil was extracted several (three or more) times into diethyl ether, concentrated, and petroleum ether was added to initiate crystallization. In most cases, the first batch of crystals were dark red, whereas recrystallization from methanol yielded white-light brown crystals. These were subsequently collected by filtration and washed with cold water.

Spectral Data and Discussion

Mass Spectral Evidence

The most useful means of identifying 5-aryloxytetrazoles is through mass spectral means since in each case, molecular ions were present. In addition to this, the fragmentation pattern was readily discerned. In his review article, Butler (20) presents a thoroughly investigated section on the fragmentation patterns for mono- and disubstituted tetrazoles. Table 7 contains the results from the mass spectrum obtained through cooperation with The Upjohn Company, Kalamazoo, MI. While other spectra were obtained, and fragments identified, this particular spectrum was obtained using a high resolution MS and thus confirmed the pattern mentioned above.

IR

The infrared spectra for this class of tetrazoles were also useful

Table 7

Mass Spectral Data for 5-(4-chlorophenoxy)tetrazole

Fragment	Mass
M^+	196
$Cl-C_6H_4$	111
$Cl-C_6H_4-O$	127
$Cl-C_6H_4-OCN$	153
$Cl-C_6H_4-OCN_2H$	168
CN_4	68

for their identification. The N-H stretch (3500-3600) confirmed the presence of the amino proton. The phenolic C-O-C stretching was very intense and somewhat broad in some instances. Table 8 contains a summary of the spectrophotometric data obtained for these compounds.

Table 8

Spectral Data for 5-Aryloxytetrazoles

Ar	$\nu(cm^{-1})$	$g(x\ 10^{-2})$	$M(x\ 10^{-3})$	λ_{max}(nm)	ε(l/mole·cm)
4-Cl	N-H 3400 C-O-C 1200	2.43	4.944	274	555
2,4-Cl	N-H 3600 C-O-C 1180	2.93	5.072	267	594

UV

The ultraviolet spectra for the 5-aryloxytetrazoles provide a quick method for the characterization of these compounds. The λ_{max} for these

monosubstituted tetrazoles was 274 nm. The molar absorptivity was also calculated for these compounds (Table 8). This method also provides a means of ascertaining the purity of the sample examined. In one instance, the presence of 2,4-dichlorophenol was also detected.

NMR

The NMR spectra for two of the monosubstituted tetrazoles were obtained. These also confirmed the proposed structure. In both cases, the phenyl protons were evident, as well as the proton associated with the nitrogens of the tetrazole ring. DMSO-d_6 was used as the solvent for all determinations in this section. In one instance, 5-(2,4-dichlorophenoxy)tetrazole, the spectrum was difficult to obtain due to solubility problems. The spectrum was resolved enough, however, to assign the necessary resonances. Table 9 contains the data for these compounds.

Table 9

Proton NMR Data for 5-Aryloxytetrazoles

Ar	Assigment	Multiplicity	(ppm)
2,4-Cl	Aromatic	Multiplet	6.8-7.6
	N-H	Singlet	7.7-7.9
4-Cl	Aromatic	Multiplet	7.1-7.6
	N-H	Singlet	7.9-8.3

A look at the proposed mechanism for this reaction will assist in describing a controversy regarding the site of protonation, N1 versus

N2. It appears well documented (19,20) that, in the gas phase, 5-substituted tetrazoles have N2 as the proton location. This differs from liquid and solid state data which although somewhat inconsistent, is overall, convincing. In the solid state, it appears that the N1 nitrogen is the location of the hydrogen on the ring. Figure 17 contains the proposed mechanistic scheme.

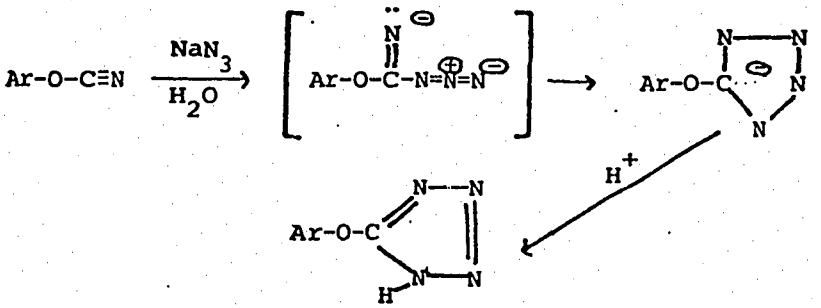


Figure 17. Proposed Mechanistic Pathway for the Formation of 5-Aryloxytetrazoles.

In terminating this section on 5-aryloxytetrazoles, it should be mentioned that these compounds present some danger in handling. During the work-up of the aqueous phase from the preparation of 5-(2,4-dichlorophenoxy)tetrazole, a violent explosion resulted when a small amount of residue was touched with a metal spatula. This explosion occurred after the compound had been prepared for the third time. During the first two preparations, metal spatulas were used too, with no detonations. It was assumed that some unreacted hydrazoic acid, HN_3, was present. The instability of this compound, as well as that of various metallic azides, creates situations requiring extra care. Thus, metal ions, other than sodium, should be avoided in routine preparations or handling of tetrazoles. A number of other tetrazoles have been shown to spontaneously decompose violently. These are thoroughly

described in the appropriate literature references listed in this section.

Aside from the hazards associated with the preparation of these tetrazoles, they present some interesting chemistry, in addition to various biological activities. It should be noted that, in contrast to the literature available, additional reflux times, sometimes up to four days, were required in order to obtain yields considered good (21). This concludes the section on a very interesting class of compounds which are worthy of additional study.

CHAPTER V

5-ARYLOXY-1-ARYLTETRAZOLES

Synthesis

While a wide variety of synthetic routes have been used for the formation of disubstituted tetrazoles, the reaction of phenyl azides and aryl cyanates has not yet appeared in the literature. Thus, this report represents a novel synthesis of 1,5-disubstituted tetrazoles. The reactivity of the cyanato group readily lends itself toward nucleophilic attack, and the azide functionality of substituted benzenes proved to be sufficient to promote this addition.

An alternate procedure for the synthesis of 5-aryloxy-1-aryltetrazoles has been developed producing good yields of these compounds (21, 22). The reaction involves the displacement of the chlorine of 5-chloro-1-phenyltetrazoles by phenols (Figure 18).

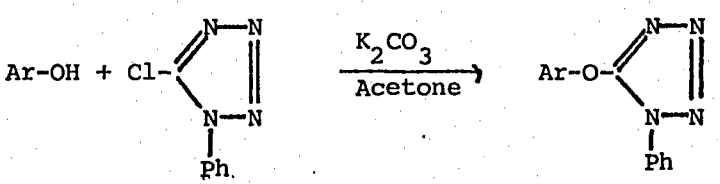


Figure 18. Alternate Synthesis of 5-Aryloxy-1-Aryltetrazoles.

Experimental

All spectra were obtained using the instruments mentioned in Chapter III. The formations of the aryldiazonium salts and phenyl azides will be included as well as the experimental procedures. All the

disubstituted tetrazoles were prepared according to General Procedure IV. All diazonium salts were prepared according to General Procedure V; all phenyl azides were prepared according to General Procedure VI.

General Procedure IV: Synthesis of 5-Aryloxy-1-aryltetrazoles

The preparation of 5-aryloxy-1-aryltetrazoles was similar to that of General Procedure III. Freshly prepared aryl cyanate (0.1 mol) was dissolved in 50 mL acetone. The appropriate aryl azide (0.1 mol) was also dissolved in 50 mL acetone. A sodium bicarbonate solution (optional) was prepared by dissolving 0.1 mol (8.4 g) in 100 mL of water. The solutions were then combined and refluxed 0.5-1.0 hour. The reaction mixture was then extracted three times into diethyl ether and the combined extracts were dried over $MgSO_4$. After concentration of the dried extracts, petroleum ether was added, with dark red crystals the result. Following collection of the filtered solids, the crystals were recrystallized using methanol. The recrystallized compounds were light pink-light orange in color.

General Procedure V: Synthesis of Aryldiazonium Chlorates

The following represents a procedure which was modified from that presented by Adams, Johnson and Wilcox (23).

After dissolving the appropriate aniline (0.2 mol) on a solution of 30 mL water and 15 mL hydrochloric acid, an additional 25 mL of HCl was added to precipitate the anilinium hydrochloride. The suspended salt was then cooled to 2-5^{o}C in an ice bath. A solution of sodium

nitrite was prepared by dissolving 0.2 mol (13.8 g) in 40 mL of water. The nitrite solution was then cooled to -5°C and placed in a 125 mL separatory funnel. Approximately 10-25 g of ice was then added to the anilinium hydrochloride suspension. The stem of the separatory containing the nitrite solution was placed slightly below the surface of the suspended salt. (This is to avoid loss of nitrous acid via air oxidation to nitrogen oxides). The nitrite solution was added over a period of ten minutes, the temperature being kept below 10°C. Approximately 0.1 g of sulfamic acid was then added slowly (foaming) to destroy any unreacted nitrous acid. After hand stirring for five minutes, approximately 0.5 g of Norit was added and the solution was stirred an additional thirty minutes in the ice bath. The decolorized solution was then filtered to remove the charcoal and was used within twenty minutes. Isolation of the diazonium salt was not attempted since this was not necessary. Dry diazonium salts tend to decompose violently; in solution, there is no problem in handling as long as the temperature is kept below 10°C. Keeping the solution cold prevents the hydrolysis to phenols.

General Procedure VI: Synthesis of Aryl Azides (24)

Assuming the reaction to form the aryldiazonium chloride went to 100% completion, the reaction to form the aryl azides was also carried out on a 0.2 mole scale. After formation of the diazonium salt, the acidic reaction mixture was brought to neutral pH by the addition of 6M sodium acetate. The sodium acetate solution was prepared by dissolving 3.0 mol (246.1 g) in 500 mL of water. After neutralization, the

diazonium salt solution was placed in a dry ice/ 2-propanol bath and cooled. Hydrazine hydrate was prepared from anhydrous hydrazine by mixing 6.4 g of the hydrazine in 10 mL of water. The hydrazine hydrate solution was then cooled. After cooling, the hydrazine solution was added to the diazonium salt solution in small portions over a twenty minute period, with continued cooling in the ice bath. The reaction was then stirred an additional ten minutes at which time a yellow solid formed. The solid was removed by filtration and washed with cold water. In one instance, the azide turned to a red oil which would not recrystallize from water, ethanol, or ether. In each preparation, the solvent was removed under vacuum on a rotary evaporator. The crude oil and crystals were then used without further purification. Yields: 66-95%

Discussion and Spectral Data

The reaction involving the 1,3-cycloaddition of aryl azides to aryl cyanates, as noted in Table 10 appears to be quite low yielding.

Table 10

Reaction Data for the Formation of 5-Aryloxy-1-Aryltetrazoles.

Ar	Ar'	mp(°C)	yield(%)
2,4-Cl	4-Cl	93-95	9
2,4-Cl	3,4-Cl	75-78	21
3,4-Cl	3-CF_3	187-190	27
3,4-Cl	4-Cl	216-219	2
3,5-Cl	4-Cl	174-175	8
3,5-Cl	3-CF_3	170-171	3

The reaction, however, was run for a maximum of one hour. It would seem that additional reaction times would increase the yields, since those which were refluxed for one hour compared to 0.5 hour showed a large increase in yield (21 and 27% compared to 2-9%) (Figure 19).

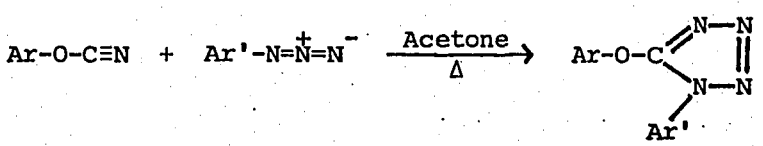


Figure 19. Novel Synthesis of 1,5-Disubstituted Tetrazoles.

The proposed mechanism for this reaction is analogous to that for the formation of monosubstituted tetrazoles. Following the attack on the cyanate carbon by the azide, cyclization was completed during the reflux period. Figure 20 shows our proposed mechanism.

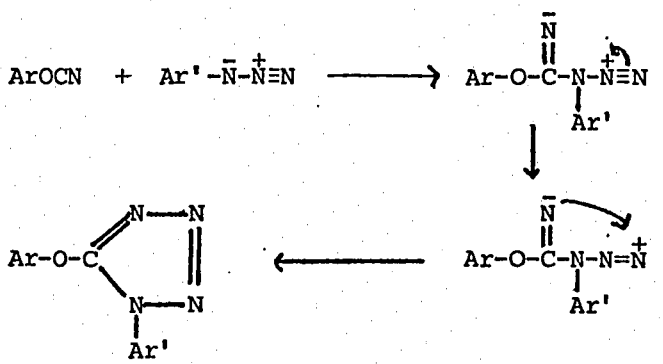


Figure 20. Proposed Mechanism for the Formation of 5-Aryloxy-1-aryltetrazoles.

As is obvious, the formation of 2,5-disubstituted tetrazoles is also possible. The amounts of this isomer was not ascertained. Mass spectral evidence, as well as, infrared data show that not much, if any, of the 2,5-disubstituted isomer was obtained.

Different solvents were used to carry out the reaction. Acetone was used in the highest yielding reactions. DMF, acetone-water, and

DMF-acetone combinations were also tried. The results were inconclusive, however, due to the short reflux times. In the Experimental section, aqueous sodium bicarbonate was called for, the role of the bicarbonate perhaps questionable. It was found that this was actually not necessary; better yields were obtained when water and bicarbonate were omitted. Again, however, the results of this were questionable due to the short reflux times used.

Mass Spectral Evidence

None of the compounds in this series exhibitied a molecular ion peak when subjected to mass spectral conditions, even with the use of "soft" ionization potential. This finding was consistent with other investigations on 1,5-disubstituted tetrazoles. Butler (20) has summarized these investigations, and also presented a fragmentation pattern (Figure 21) which is consistent with the results reported in this paper.

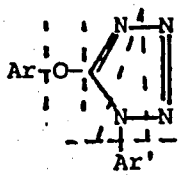


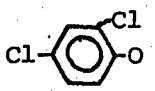
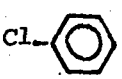
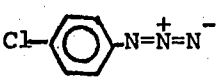
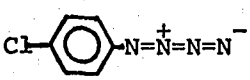
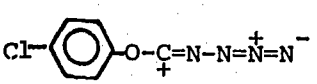
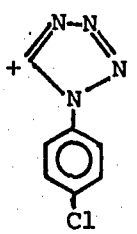
Figure 21. Fragmentation Scheme for 5-Aryloxy-1-aryltetrazoles.

As one would expect, the phenoxide fragment was lost easily, and was detected in great abundance. The most notable fragment seen was of the molecular formula; $C_7H_4ClN_4$. In this case, the Ar' group was the 4-chlorophenyl group. This fragment is consistent with the predicted M-161 peak corresponding to the product tetrazole minus the phenoxide residue. In the case of the 2,5-disubstituted tetrazoles (19,

20), molecular ion peaks were detected and different fragments were detected than those found in the 1,5-disubstituted molecules. Table 11 contains a summary of the mass spectral results obtained for one of the prepared tetrazoles.

Table 11

Mass Spectral Data for the Formation of
5-(2,4-Dichlorophenoxy)-1-(4-chlorophenyl)tetrazole

Fragment	Mass
	161
	111
	153
 (H)	167(168) $C_6H_4ClN_4$
	217
	179

IR

In their study of 5-chloro-1-phenyltetrazoles, Kauer and Sheppard

(25) observed four characteristic IR bands. These values were also consistently observed with other 1,5-disubstituted tetrazole systems. Surprisingly, these bands were absent from the 2,5-disubstituted tetrazoles they investigated. This information then, provides an easy method of differentiating between any 2,5- versus 1,5-disubstitution present on the tetrazole ring. The absorbances observed by Kauer and Sheppard were at approximately 960, 1000, 1090, and 1210 cm^{-1}. In this work, values close to these were also seen, but the phenolic ether stretch obscured the higher value in most instances. The absorbances around 1200 cm^{-1} in one example in this work appeared as shoulders on the broad C-O-C stretch mentioned above. The presence of the aromatic substituted chlorine atoms also made the other three absorbances difficult to assign. The presence of these bands did, however, assist in the structure confirmation. Table 12 contains a summary of the spectrophotometric data obtained.

Table 12

Spectral Data for 5-Aryloxy-1-aryltetrazoles

Ar	Ar'	$\nu(cm^{-1})$	$g(x10^{-2})$	$\underline{M}(x10^{-3})$	λ_{max}(nm)	ε(l/mole·cm)
3,4-Cl	3-CF_3	C-O-C 1240 C=C 1500-1650 1,5-tet 940,1020, 1110,1210	4.51	4.968	324	378
3,4-Cl	4-Cl	C-O-C 1250 C=C 1500-1650 1,5-tet 980,1030, 1120,1210	----	-----	339	---

Solution in 25 mL of p-dioxane at 25°C

The aryl azides were identified by the characteristic absorbances at 2040, 2060, and 2140 cm^{-1}.

UV

The ultraviolet spectra for these tetrazoles yielded maximum absorbances of 324 and 339 nm respectively for the two disubstituted tetrazoles. 1,4-dioxane (p-dioxane) was used as the solvent for the determinations. The original contention that UV absorbances would serve as a quick means of characterization, while being true, is not irrefutable. This is so, due to the similarity between the triazines and tetrazoles. Only one bit of UV spectral data is included in Table 12 because the IR spectra proved to be a more convenient means of structure confirmation.

NMR

The proton magnetic resonances for these disubstituted tetrazoles were indirectly useful in their identification. The absence of all resonances other than aromatic protons supported the contention that these compounds were cyclic in structure. Specifically, the absence of amino hydrogens, and also lack of methane proton resonances eliminated any acyclic product considerations, with the exception of a zwitterionic species, i.e. the proposed reaction intermediate.

The aromatic hydrogen resonances yielded complex multiplets between 6.8-7.9 (ppm) for each of the spectra obtained. Exact peak assignments were not attempted as the peaks were not well resolved. The NMR spectra were used only as an additional qualitative structure confirmation.

For the NMR spectra, both DMSO-d_6, and acetone-d_6 were employed as solvents for this series of tetrazoles. Resolution of the spectra in both solvents was poor at best.

In concluding this section, it should be mentioned that while other higher yielding methods are available for the preparation of 5-aryloxy-1-aryltetrazoles, the full potential of the method presented here has yet to be explored. The possibility for biological activity should also be investigated, since a myriad of tetrazolyl compounds have been prepared which have been shown to be active in various different biological systems. This fact should not be too surprising, considering that the tetrazole moiety has been shown to be a non-classical isotere for the carboxylic acid functionality (26).

CHAPTER VI

CONCLUSION

In concluding this effort, several points have been made regarding the reactivity of aryl cyanates. Different synthetic routes have been used to prepare aryl cyanates; the method provided in the Experimental Section of this paper gives quantitative yields. Elaborate apparatus was not necessary, and the reaction required only ten minutes to complete. The use of cyanogen bromide, rather than cyanogen chloride, has improved the safety of carrying out the reaction. In addition, the cyanogen bromide was much more convenient to work with.

Identification, via infrared spectroscopy, has been discussed, not only for aryl cyanates, but also for 2-aryloxy-4,6-dimercapto-s-triazines, mono- and especially disubstituted tetrazoles. Other spectroscopic methods, including MS, UV, and NMR provided additional data for elucidation of the various reaction structures. The syntheses of the products prepared have also been discussed.

The syntheses and elucidation of structures for the various heterocyclic compounds presented here have proven this project to be a valuable learning tool. Besides the educational aspects of this project, it has been interesting and lastly, fun.

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