

Ahmad S. Shawali (1) and Cyril Párkányi

Department of Chemistry, The University of Texas at El Paso, El Paso, Texas 79968

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Introduction

- I. Types of Reactions
- II. Monocyclic Systems
 - A. Nitrogen-Containing Rings
 1. Pyrazoles and Pyrazolines
 2. 1,2,4-Triazoles and 1,2,4-Triazolines
 3. Tetrazoles
 4. Tetrazines
 - B. Nitrogen- and Oxygen-Containing Rings
 1. 1,3,4-Oxadiazoles and 1,3,4-Oxadiazolines
 - C. Nitrogen- and Sulfur-Containing Rings
 1. Thiazoles, Thiazolines and Thiazolidines
 2. 1,3,4-Thiadiazoles and 1,3,4-Thiadiazolines
 3. 1,2,3,5-Thiatriazoles
 - D. Nitrogen- and Selenium-Containing Rings
 1. 1,3,4-Selenodiazolines
 - E. Nitrogen- and Phosphorus-Containing Rings
 1. 1,3,4-Phosphadiazoles
- III. Bicyclic Systems
 - A. Nitrogen-Containing Rings
 1. Benz[*d*]imidazoles
 2. Cycloalka[1,2-*d*]pyrazoles
 3. Quinazolines
 4. 1*H*-1,2-Benzodiazepines
 5. Benzo-1,2,3-triazoles
 6. Pyrrolo[3,4-*c*]pyrazoles
 7. *s*-Triazolo[4,3-*a*]pyridines
 8. Imidazo[1,2-*a*]pyridines
 9. 1*H*-Pyrazolo[1,5-*b*]imidazoles
 10. Imidazotriazoles
 11. Pyrazolo[1,5-*c*]-*s*-triazoles
 12. *s*-Triazolo[4,3-*b*]pyridazines
 13. Pyrazolo[4,5-*e*]triazines
 14. 2*H*-Pyrazolo[3,4-*d*]pyridazines
 15. *s*-Triazolo[1,5-*c*]-*s*-triazoles
 16. *s*-Triazolo[4,3-*d*]tetrazoles
 - B. Nitrogen- and Oxygen-Containing Rings
 1. Benz[*c*]isoxazoles and Benz[*d*]oxazoles
 2. Furo[3,4-*c*]pyrazoles and Furo[2,3-*d*]pyrazoles
 3. *s*-Triazolo[3,4-*b*]oxadiazoles
 4. Pyrano[3,4-*c*]pyrazoles
 5. 4*H*-1,3,4-benzoxadiazines
 - C. Nitrogen- and Sulfur-Containing Rings
 1. Benzo[*d*]thiazoles
 2. Imidazo[1,5-*b*]thiazoles
 3. 4*H*-1,3,4-Benzothiadiazines

IV. Tricyclic Systems

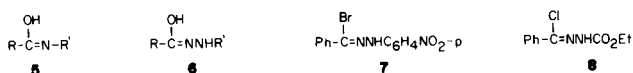
- A. Nitrogen-Containing Rings
 1. Indeno[1,2-*c*]pyrazoles and Indazoles
 2. Naphtho[1,2-*c*]pyrazoles
 3. Cyclopropa[*c*]cinnolines
 4. Pyrazolo[3,4-*b*]indoles
 5. Triazino[4,5-*a*]quinolines
 6. 1*H*-Pyrrolo[2,3-*c*:4,5-*c'*]dipyrazoles and Pyrazolo[3',4'-4,5]pyrrolo[2,1-*c*]-*s*-triazoles
 7. Imidazo[1,2-*b*]-*s*-triazolo[4,3-*f*]pyridazines
 8. Pyrido[3,2-*d*]-*s*-triazolo[4,3-*b*]pyridazines
 9. Bis-*s*-triazolo[4,3-*b*:3',4'-*f*]pyridazines
- B. Nitrogen- and Oxygen-Containing Rings
 1. Octahydrofuro[4,3,2-*c*,*d*]indazoles
 2. Benzofuro[2,3-*d*]pyrazolines
 3. 4*H*-Pyrazolo[5,1-*c*][1,4]-benzoxazines
 4. Benzopyrano[4,3-*c*]pyrazoles
- C. Nitrogen- and Sulfur-Containing Rings
 1. Triazolo[4,5-*b*]benzothiazoles
 2. Naphtho[1,2-*e*]1,3,4-thiadiazines
- V. Miscellaneous Polycyclic Systems

Introduction.

Hydrazidoyl halides are a group of compounds with the general formula **1**, where X represents a chlorine or bromine atom. These compounds are structurally related to aldehyde hydrazones **2** in the same way as imidoyl chlorides **3** are related to aldomethines **4**.



Various names have been used for compounds of the type **1**. For example, compound **1** (R = R' = Ph; X = Cl) was reported in the literature under the following names: ω -chlorobenzylidene phenylhydrazone, α -chlorobenzaldehyde phenylhydrazone, and *N*-phenylbenzhydrazonoyl chloride. In this review, by analogy to imidoyl chlorides **3** which are considered to be the derivatives of the corresponding imidoic acid **5**, compounds of the type **1** are named as halides of the corresponding hydrazidoic acids, **6**. Thus, compounds **7** and **8** are called *N-p*-nitrophenylbenzhydrazidoyl bromide and *N*-ethoxycarbonylbenzhydrazidoyl chloride, respectively.



Within the last few years, an increased interest in the chemistry of this class of compounds has developed. The results reported so far show that hydrazidoyl halides undergo a wide variety of reactions that lead to new chemical systems. Most of the work reported in the literature deals with hydrazidoyl chlorides and bromides.

Hydrazidoyl fluorides and iodides have not yet been reported. There seems to be no comprehensive review on the chemistry of hydrazidoyl halides, although several summaries (2-4) have been published. The present review is devoted exclusively to the use of such compounds in the synthesis of heterocyclic compounds. Two limitations are being placed on the scope of this review. First, it is considered appropriate to emphasize the synthetic routes to heterocyclic compounds *via* hydrazidoyl halides rather than to discuss the mechanisms of the reactions involved. However, the mechanisms of reactions that lead to different products under various experimental conditions will be outlined wherever appropriate. Secondly, no attempt is made here to document the literature concerning the synthesis of hydrazidoyl halides whose reactions are discussed.

In this review, the heterocyclic systems prepared from hydrazidoyl halides are presented in order of their increasing ring size and in order of the increasing number of heteroatoms. The heteroatoms have been arranged in the following sequence: nitrogen, oxygen, sulfur, and other elements. The heterocycles are grouped according to the number of rings and in order of increasing number of heteroatoms. The literature has been covered up to the end of 1978.

I. Types of Reactions.

The reactions of hydrazidoyl halides leading to heterocycles may be generally divided into two classes:

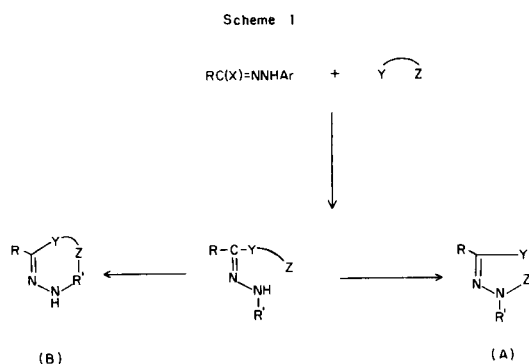
A. Displacement reactions.

1. Nucleophilic substitutions followed by cyclization.
2. Intramolecular nucleophilic substitutions.

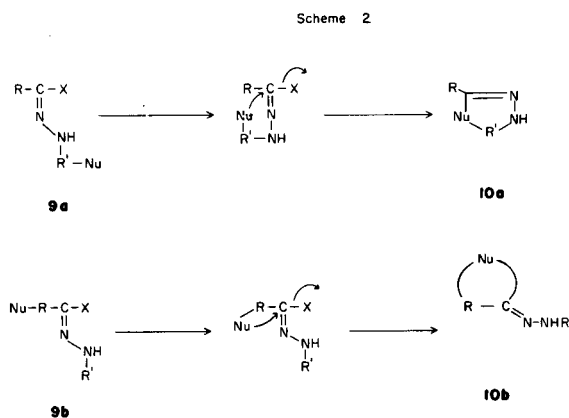
B. Cycloaddition reactions.

1. Intermolecular 1,3-dipolar cycloadditions.
2. Intramolecular dipolar cycloadditions.

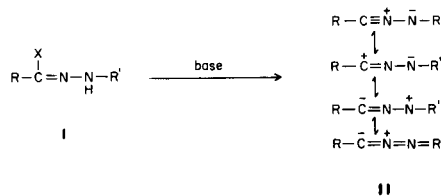
Hydrazidoyl halides react with various reagents *via* nucleophilic substitution of the halogen atom, followed by a cyclization reaction at either the nitrogen (A) or an *N*-substituent (B). These reactions have been used in the synthesis of many five- and six-membered heterocyclic systems.



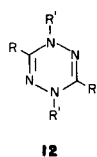
Intramolecular nucleophilic substitution reactions are exhibited by hydrazidoyl halides of type **9a,b**, in which Nu represents a basic group or atom (Scheme 2). In such compounds, the internal nucleophilic attack by the neighboring Nu group yields cyclic products **10a,b**.



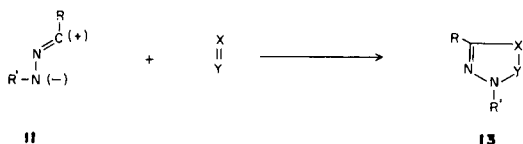
Hydrazidoyl halides **1**, when treated with a base such as triethylamine, are converted into the corresponding nitrile imines **11**. The elimination of HX from **1** is now the



preferred method for the generation of **11 in situ**. Attempts to isolate **11** have failed, however, since **11** were found to be relatively reactive intermediates. In the absence of a dipolarophile in the reaction mixture, such intermediates exhibit a facile head-to-tail dimerization and give the corresponding tetrazines **12**. When the nitrile imine intermediate is generated *in situ* in presence of a dipolarophile, X=Y or X≡Y, the latter will add to it and form the cycloadduct **13**. Such types of reactions are referred to as 1,3-dipolar cycloaddition reactions.

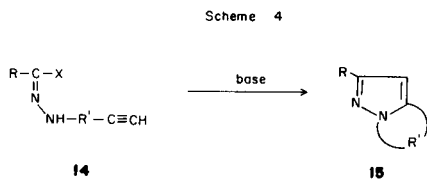


Scheme 3



In recent years, 1,3-dipolar cycloaddition reactions have received considerable attention because they have been shown to be an efficient synthetic tool for the preparation of a wide variety of heterocyclic compounds (5). The mechanism of cycloaddition reactions has been reviewed by several authors (5-7). It is surprising that there is no single mechanism that would account for all cycloaddition reactions, even though they are of the same type. This is probably due to the fact that a large variety of reactions have been used.

Intramolecular cycloaddition reactions are exhibited by hydrazidoyl halides containing carbon-carbon double or triple bonds that are able to behave as potential dipolarophiles in the *N*-residue or the *C*-moiety of the hydrazidoyl halide molecule. Such compounds, *e.g.*, **14**, when treated with a base, give a nitrile imine intermediate which adds intramolecularly to the unsaturated dipolarophile group and forms a fused cyclic product **15**. This method has opened new possibilities for the synthesis of several fused heterocyclic compounds.



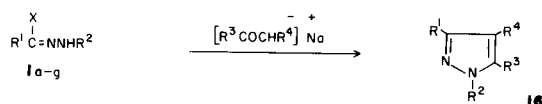
Scheme 4

II. Monocyclic Systems.

A. Nitrogen-Containing Rings.

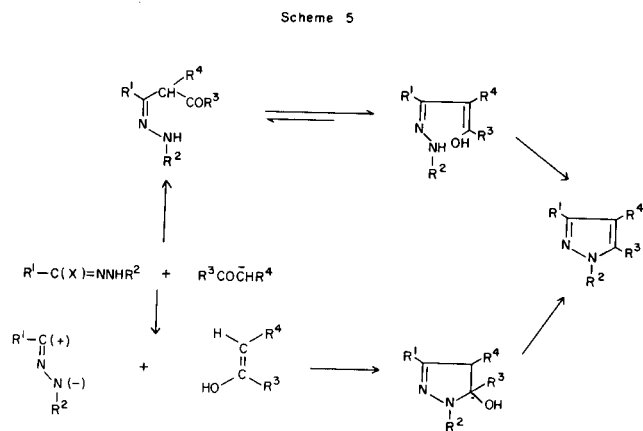
1. Pyrazoles and Pyrazolines.

In a series of papers, Fusco and co-workers (8-13) showed that hydrazidoyl chlorides **1a-c** react with sodium salts of β -keto esters and β -diketones and give the corresponding 4-ethoxycarbonyl- and 4-acylpyrazole derivatives **16a-c**, respectively. This reaction was extended by Shawali and coworkers (14-19) to other hydrazidoyl halides **1d-g** and other compounds with an active methylene group, such as β -ketosulfones, β -ketoanilides, and β -cyanoketones. Numerous pyrazole derivatives **16a-k** have been prepared in this manner (Table 1).



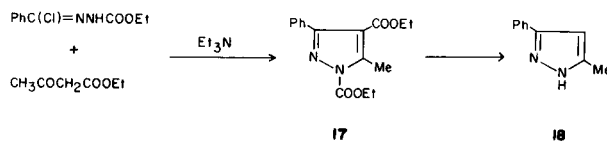
$\text{R}^1/\text{X}/\text{R}^2$:	a) Ar/Cl/Ar	R^3/R^4 :	a) Me/COOEt	
	b) COOEt/Cl/Ar		b) Me/Ac	
	c) PhN=N/Cl/Ar		c) Ph/Bz	
	d) ArCO/Br/Ar		d) Ph/COOEt	h) Ph/CN
	e) Ar/Br/Ar		e) Me/CONHPh	i) NH_2/COOEt
	f) PhNHCO/Cl/Ar		f) Ph/CONHPh	j) $\text{NH}_2/\text{CONHPh}$
	g) alkyl/Br/Ar		g) Ph/SO ₂ Ph	k) Ph/Ar

The reaction can be considered to proceed *via* a primary nucleophilic attack by the carbanion, followed by cyclization and loss of water giving the pyrazole product. Also, it is reasonable to assume that the hydrazidoyl halide is first converted into the corresponding nitrile imine that adds to the double bond of the enol form of the active CH compound used. Loss of water leads to the pyrazole derivative (Scheme 5).



Scheme 5

Bacchetti (20) used this reaction to prepare 1,4-dicarboethoxypyrazoles **17** by treating *N*-ethoxycarbonylbenzhydrazidoyl chloride with ethyl acetoacetate in benzene in the presence of triethylamine. Acid hydrolysis and decarboxylation of **17** gave 3-phenyl-5-methylpyrazole (**18**).



Hydrazidoyl halides react with alkenes in benzene in the presence of triethylamine and give the corresponding pyrazolines **19** in good yield (21-25). In this reaction, compounds such as acrylonitrile, styrene, stilbene, ethyl acrylate, diethyl fumarate, chalcones, *etc.*, have been used with a variety of hydrazidoyl halides (Table 2). Dehydrogenation of the resulting pyrazoline products affords the corresponding pyrazole derivatives **20**.

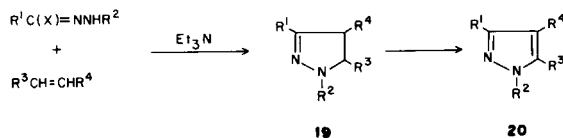
Table I

Series No.	Substituents	References
1	R ¹ = EtCOO; R ² = <i>p</i> -NO ₂ C ₆ H ₄ R ³ /R ⁴ : Me/Ac; Ph/Bz; H/Bz; Me/Bz; COOMe/Bz; COOMe/Ac; Me/EtCO; Me/ <i>n</i> -PrCO; <i>n</i> -Pr/COOH; Et/EtCO; CH ₂ OPh/Ac; Me/COOEt; Ph/COOEt; COOEt/COOEt	9,10,12
2	R ¹ = R ² = Ph R ³ /R ⁴ : Me/Ac; Ph/Bz; Me/COOEt; Ph/COOEt; vinyl/H; C ₂ H ₅ /H; COOH/H; OEt/H; Ph/Ph; COOEt/H; CN/H; COOMe/COOMe; Ph/H; COOMe/H	9,12
3	R ¹ = PhN=N; R ² = Ph R ³ /R ⁴ : Me/CN; Ph/CN; CH ₂ OPh/Ac; Me/Ac	25
4	R ¹ = R ⁴ = Bz; R ³ = Ph R ² : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -MeOC ₆ H ₄	15
5	R ¹ = Bz; R ⁴ = CONHPh R ² /R ³ : Ph/Me; <i>p</i> -ClC ₆ H ₄ /Me; <i>p</i> -MeOC ₆ H ₄ /Me; <i>p</i> -MeC ₆ H ₄ /Me; Ph/Ph; <i>p</i> -ClC ₆ H ₄ /Ph; <i>p</i> -MeOC ₆ H ₄ /Ph	
6	R ³ = Ph; R ⁴ = COOEt R ¹ /R ² : Bz/ <i>p</i> -NO ₂ C ₆ H ₄ ; Bz/ <i>p</i> -MeOC ₆ H ₄ ; <i>p</i> -NO ₂ Bz/ Ph; <i>p</i> -MeOBz/Ph	15
7	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = NH ₂ ; R ⁴ = COOEt R ¹ : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄ ; <i>o</i> -ClC ₆ H ₄ ; COOEt; Me; <i>i</i> -Pr	16
8	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Me; R ⁴ = Ac R ¹ : Ph; 2-ClC ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -NO ₂ C ₆ H ₄ ; 2,6- Cl ₂ C ₆ H ₃	14
9	R ³ = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Ph; R ⁴ = Bz R ¹ : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄ ; <i>m</i> -NO ₂ C ₆ H ₄ ; 2,6-Cl ₂ C ₆ H ₃	14
10	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Me; R ⁴ = COOEt R ¹ : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄ ; <i>m</i> -NO ₂ C ₆ H ₄ ; 2,6-Cl ₂ C ₆ H ₃	14
11	R ⁴ = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Ph; R ⁴ = COOEt RR ¹ : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>o</i> -ClC ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄ ; <i>m</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -BrC ₆ H ₄ ; 2,6-Cl ₂ C ₆ H ₃	14
12	R ³ = Me; R ⁴ = Ac R ¹ /R ² : Bz/Ph; Bz/ <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -NO ₂ Bz/Ph; <i>p</i> -MeBz/ Ph	15
13	R ³ = Ph; R ⁴ = Bz; R ¹ = Bz R ² : Ph; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -MeOC ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄	15
14	R ³ = NH ₂ ; R ⁴ = CONHPh R ¹ /R ² : Ph/ <i>p</i> -NO ₂ C ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄ / <i>p</i> -NO ₂ C ₆ H ₄ ; COOEt/Ph; COOEt/ <i>p</i> -MeOC ₆ H ₄	16
15	R ¹ = COOEt; R ³ = Me; R ⁴ = Ac R ² : Ph; <i>p</i> -MeC ₆ H ₄ ; <i>p</i> -MeOC ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄	17
16	R ¹ = COOEt; R ³ = Ph; R ⁴ = Bz R ² : Ph; <i>p</i> -MeC ₆ H ₄ ; <i>p</i> -MeOC ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄	17
17	R ¹ = COOEt; R ³ = Ph R ² /R ⁴ : Ph/COOEt; <i>p</i> -ClC ₆ H ₄ ; COOEt; Ph/CN; <i>p</i> -MeOC ₆ H ₄ /CN; <i>p</i> -ClC ₆ H ₄ /CN	17
18	R ² = R ³ = Ph; R ⁴ = CN R ¹ : Bz; <i>p</i> -MeOBz; <i>p</i> -ClBz	17

Table I continued

Series No.	Substituents	References
19	R ¹ = PhNHCO; R ² = Me R ³ /R ⁴ : Ph/Ac; <i>p</i> -MeC ₆ H ₄ /Ac; <i>p</i> -ClC ₆ H ₄ /Ac; <i>o</i> -ClC ₆ H ₄ /Ac; <i>p</i> -BrC ₆ H ₄ /Ac; Ph/COOEt; <i>o</i> -MeC ₆ H ₄ /COOEt; <i>p</i> -MeC ₆ H ₄ /COOEt; <i>o</i> -ClC ₆ H ₄ /COOEt; <i>p</i> -ClC ₆ H ₄ /COOEt	18
20	R ¹ = PhNHCO; R ³ = Ph; R ⁴ = Bz R ² : Ph; <i>m</i> -MeC ₆ H ₄ ; <i>p</i> -MeC ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄ ; <i>p</i> -BrC ₆ H ₄	18
21	R ¹ = PhNHCO; R ³ = Ph; R ² = Ac R ² : Ph; <i>p</i> -MeC ₆ H ₄ ; <i>o</i> -ClC ₆ H ₄ ; <i>p</i> -ClC ₆ H ₄	18
22	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Me R ¹ /R ⁴ : Me/Ac; Et/Ac; <i>n</i> -Pr/Ac; <i>i</i> -Pr/Ac; Me/COOEt	
23	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Ph R ¹ /R ⁴ : Me/Bz; <i>i</i> -Pr/Bz; Me/COOEt; <i>n</i> -Pr/COOEt; <i>i</i> -Pr/COOEt	19
24	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ⁴ = CONHPh R ¹ /R ³ : Me/Me; Et/Me; <i>i</i> -Pr/Me; Me/Ph; <i>n</i> -Pr/Ph; <i>i</i> -Pr/Ph	19
25	R ² = <i>p</i> -NO ₂ C ₆ H ₄ ; R ³ = Ph; R ⁴ = PhSO R ¹ : Me; Et; <i>n</i> -Pr; <i>i</i> -Pr	19
26	R ¹ = PhN=N; R ² = Ph R ³ /R ⁴ : Me/CN; Ph/CN; CH ₂ OPh/Ac; Me/Ac	13
27	R ¹ /R ² /R ³ /R ⁴ : Ph/COOEt/Me/COOEt Ph/H/Me/H <i>p</i> -MeBz/ <i>p</i> -MeOC ₆ H ₄ /Ph/Bz <i>p</i> -BrBz/Ph/Ph/PhNHCO Bz/ <i>p</i> -ClC ₆ H ₄ /Ph/ <i>p</i> -MeC ₆ H ₄ NHCO Bz/Ph/Ph/ <i>p</i> -MeC ₆ H ₄ NHCO Ac/Ph/vinyl/H COOEt/Ph/vinyl/H <i>p</i> -NO ₂ C ₆ H ₄ /Ph/vinyl/H Ph/ <i>p</i> -MeC ₆ H ₄ /vinyl/H <i>p</i> -MeBz/Ph/Ph/Ac Ph/Ph/Bz/H COOMe/Ph/Bz/H Ph/Ph/CN/H Ph/Ph/COOMe/H Ph/Ph/Ph/-CH(OAc)COPH <i>p</i> -MeC ₆ H ₄ /Ph/Ph/-CH(OAc)COPH Ph/Ph/ <i>p</i> -MeC ₆ H ₄ / <i>p</i> -MeC ₆ H ₄ Ph/Ph/OMe/H Ac/Ph/OEt/H	20 20 15 15 15 15 23 23 23 15 78 78 78 78 95 95 95 98 98

(a) To save space the following abbreviations were used for the organic groups: Ac = COCH₃; Bs = C₆H₅SO₂; Bz = C₆H₅CO; RBz = RC₆H₄CO; Me = CH₃; Et = CH₂CH₃; *n*-Pr = CH₂CH₂CH₃; *i*-Pr = (CH₃)₂CH; Ph = C₆H₅.



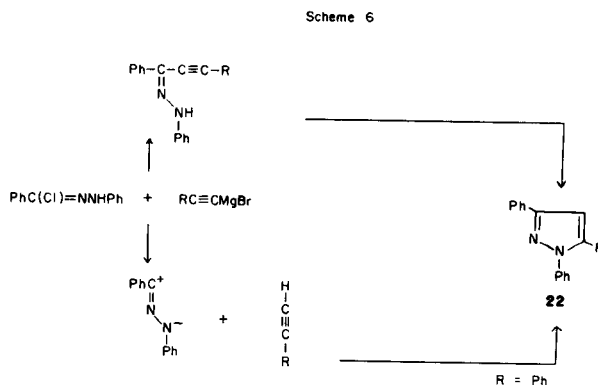
Phenylacetylene and other acetylene derivatives also react with hydrazidoyl halides in aprotic media in the presence of a basic catalyst and give the corresponding pyrazole derivatives **21** directly (25).

Table II

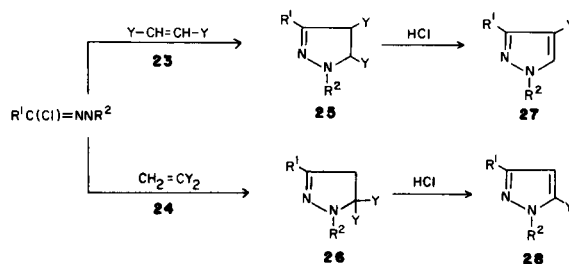
Series No.	Substituents	References
1	$R^3 = \text{CN}; R^4 = \text{H}$ R^1/R^2 : <i>Me/p-NO₂C₆H₄</i> ; <i>Bz/Ph</i> ; <i>Bz/p-MeC₆H₄</i> ; <i>Bz/p-ClC₆H₄</i> ; <i>Bz/p-MeC₆H₄</i> ; <i>p-BrBz/Ph</i> ; <i>Ph/Ph</i>	14,21,22,25
2	$R^3 = \text{COOEt}; R^4 = \text{H}$ R^1/R^2 : <i>Bz/Ph</i> ; <i>Bz/p-MeC₆H₄</i> ; <i>Bz/p-ClC₆H₄</i> ; <i>p-MeBz/Ph</i> ; <i>p-BrBz/Ph</i> ; <i>Ph/Ph</i>	22,25
3	$R^3 = \text{Ph}; R^4 = \text{H}$ R^1/R^2 : <i>COOEt/Ac</i> ; <i>p-NO₂C₆H₄/Ac</i> ; <i>Ph/COOH</i> ; <i>Ph/Ac</i> ; <i>Ph/n-C₃H₇</i> ; <i>Ph/(CH₂)₆COOEt</i> ; <i>Ph/Ph</i>	23,25
4	$R^3 = \text{Ph}; R^4 = \text{Ac}; R^5 = \text{H}$ R^1 : <i>Ph</i> ; <i>Ac</i> ; <i>COOEt</i> ; <i>p-NO₂C₆H₄</i>	23
5	$R^1/R^2/R^3/R^4$ <i>Ph/Ph/Ph/Ph</i> 25 <i>Ph/Ph/Ph/COOEt</i> 25 <i>Ph/Ph/COOMe/COOMe</i> 25 <i>Me/p-NO₂C₆H₄/Ph/Bz</i> 14,21 <i>Ph/Ph/H/H</i> 97 <i>Ph/p-NO₂C₆H₄/COOEt/COOEt</i> 96	25 25 25 14,21 97 96
6	$R^3 = \text{Ph}; R^4 = \text{SO}_2\text{C}_6\text{H}_5$ R^1/R^2 : <i>Ph/Bz</i> ; <i>COOMe/Bz</i> ; <i>Ph/CN</i> ; <i>Ph/COOMe</i>	87
6	$R^3 = \text{Me}$ R^1/R^2 : <i>Ac/Ph</i> ; <i>Ac/p-MeC₆H₄</i> ; <i>COOEt/p-BrC₆H₄</i> ;	24
7	$R^3 = t\text{-Bu}$ R^1/R^2 : <i>Ac/Ph</i> ; <i>COOEt/Ph</i> ; <i>COOEt/p-MeC₆H₄</i>	23
8	$R^3 = \text{Me}$ R^1/R^2 : <i>Ph/Ph</i> ; <i>Ac/Ph</i> ; <i>COOEt/p-BrC₆H₄</i> ; <i>Ac/p-</i> <i>MeC₆H₄</i> ; <i>p-NO₂C₆H₄/p-NO₂C₆H₄</i>	24
9	$R^3 = i\text{-Pr}$ R^1/R^2 : <i>Ac/Ph</i> ; <i>COOEt/Ph</i> ; <i>Ph/Ph</i> ; <i>p-NO₂C₆H₄/Ph</i>	23
10	$R/\text{Ar}/\text{Ar}'$: <i>COOEt/Ph/Ph</i> 94 <i>COOMe/Ph/Ph</i> 94 <i>COO-t-Bu/Ph/Ph</i> 94 <i>Ac/Ph/Ph</i> 94 <i>Ph/Ph/Ph</i> 94 <i>COOMe/p-IC₆H₄/Ph</i> 94 <i>COOEt/o-NO₂C₆H₄/Ph</i> 94 <i>COOEt/Ph/p-MeOC₆H₄</i> 94 <i>COOEt/Ph/3,4-(MeO)₂C₆H₃</i> 94 <i>COOEt/Ph/p-MeOC₆H₄</i> 94 <i>COOEt/Ph/3,4-(MeO)₂C₆H₃</i> 94 <i>COOEt/Ph/p-ClC₆H₄</i> 94	94 94 94 94 94 94 94 94 94 94

(a) See footnote a in Table I.

Gruenanger and Langella (26) have described the reaction of *N*-phenylbenzhydrazidoyl chloride with phenylethynylmagnesium bromide, which gives 1,3,5-triphenylpyrazole (22), perhaps *via* the phenylhydrazone of an ethynyl ketone or *via* a diphenyl nitrile imine (Scheme 6).

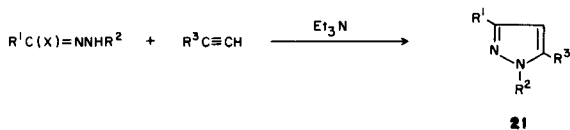


The reaction of hydrazidoyl halides with the diaminoethanes **23** and **24** in benzene in the presence of triethylamine was reported to give the pyrazoline derivatives **25** and **26**, respectively (27). The acid-catalyzed amine elimination from **25** and **26** affords a convenient method of preparation of the 4- and 5-amino derivatives of pyrazoles, **27** and **28**, respectively (27).

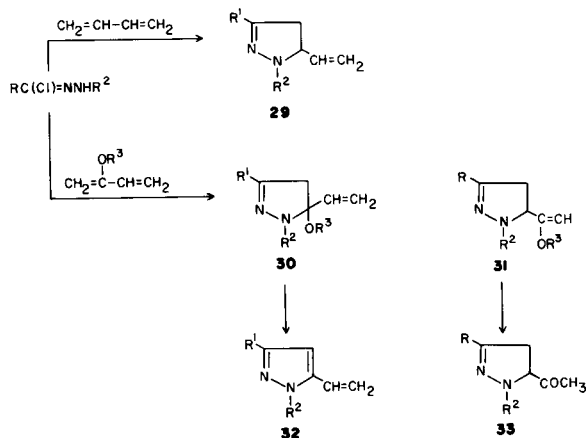


- $R^1/R^2/Y$:
- COOEt/Ph/1-morpholinyl*
 - Ac/p-MeOC₆H₄/1-morpholinyl*
 - Ac/m-F₃CC₆H₄/1-morpholinyl*
 - COOMe/Ph/1-piperidinyl*
 - COOEt/Ph/1-morpholinyl*
 - Ac/p-MeOC₆H₄/1-morpholinyl*
 - Ac/p-F₃CC₆H₄/1-morpholinyl*
 - COOMe/Ph/1-piperidinyl*

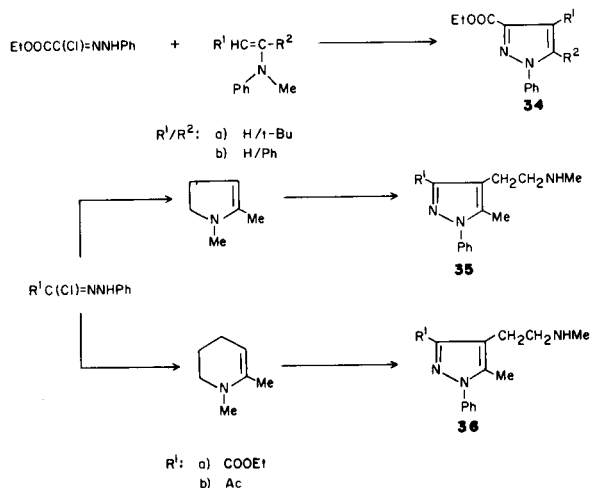
Butadiene was reported to react with hydrazidoyl halides in the presence of triethylamine and give 1,3-disubstituted-5-vinyl- Δ^2 -pyrazolines **29** (25). Recently, the reaction of hydrazidoyl halides with 2-alkoxybutadienes under similar conditions was reported to give a mixture of the products **30** and **31** (23,24). The amount of each of the products **30** and **31** was found to depend on the structure of the hydrazidoyl halide and the 2-alkoxy group in the butadiene derivative used. Thus, in the reaction of *C*-arylhydrazidoyl halides with 2-methoxy-, 2-isopropoxy-, and 2-*t*-butoxybutadienes, the major products



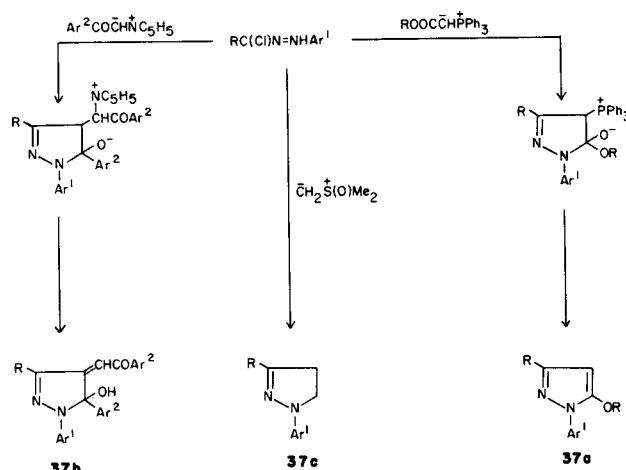
were the corresponding 1,3-diaryl-5-(α -alkoxyvinyl)- Δ^2 -pyrazolines, **31**. On the other hand, reactions of *C*-acetyl- and *C*-ethoxycarbonyl hydrazidoyl halides with 2-methoxy- and 2-isopropoxybutadienes lead to mixtures of **30** and **31** in yields of 30-60 and 70-40%, respectively. In the reaction of 2-*t*-butoxybutadiene with *C*-ethoxycarbonyl hydrazidoyl halides, products of the type **31** are obtained in 44-58% yields, accompanied by the formation of a considerable amount of the corresponding tetrazine products. These results were assumed (23,24) to indicate that in the case of 2-alkoxy-1,3-butadienes the regioselectivity of the addition of nitrile imine intermediate involved in the base-catalyzed reaction of hydrazidoyl halides is largely determined by the electronic effects of the substituents in the dipolarophile and dipole. Steric effects have a considerably smaller influence.



Pyrazole derivatives were also prepared by interaction of hydrazidoyl halides with enamines derived from acyclic ketones (28). Thus, *C*-ethoxycarbonyl-*N*-phenylhydrazidoyl chloride reacts with enamines and forms the pyrazole derivatives **34a-b** in good yield. Hydrazidoyl chlorides also react with 2,*N*-dimethyl- Δ^2 -pyrroline and 2,*N*-dimethyl-1,4,5,6-tetrahydropyridine and give the pyrazole derivatives **35** and **36**, respectively (28).

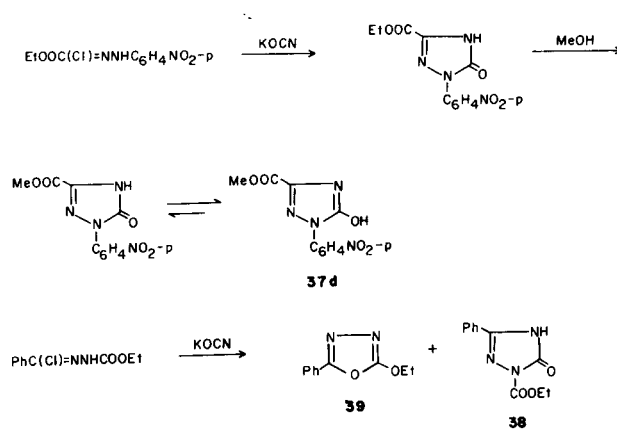


Reactions of hydrazidoyl halides with carbalkoxy-methylene triphenylphosphonium ylide (98) and pyridinium phenacylide (94) were reported to give the pyrazole and pyrazoline derivatives **37a** and **37b**, respectively. 1,3-Diarylpyrazolines **37c** (R = an aryl) were also obtained by the reaction of hydrazidoyl chlorides with dimethylxosulfonium methylide (97) in good yields.

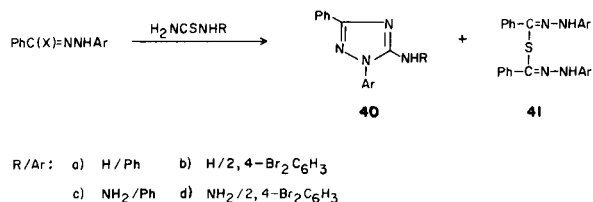


2. 1,2,4-Triazoles and 1,2,4-Triazolines.

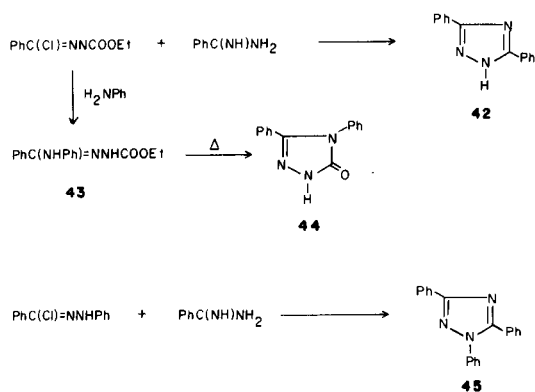
Treatment of *C*-ethoxycarbonyl-*N*-*p*-nitrophenylhydrazidoyl chloride with potassium cyanate in methanol was reported (29) to give 1-*p*-nitrophenyl-3-methoxycarbonyl-5-hydroxy-1,2,4-triazole (**37d**), probably *via* an ester exchange. However, a poor yield of 1-ethoxycarbonyl-3-phenyl-1,2,4-triazolin-5-one (**38**) was obtained from the reaction between *N*-ethoxycarbonyl benzhydrazidoyl chloride and sodium cyanate in ethanol. The major product was reported (20) to be 5-ethoxy-2-phenyl-1,3,4-oxadiazole (**39**), from an intramolecular reaction.



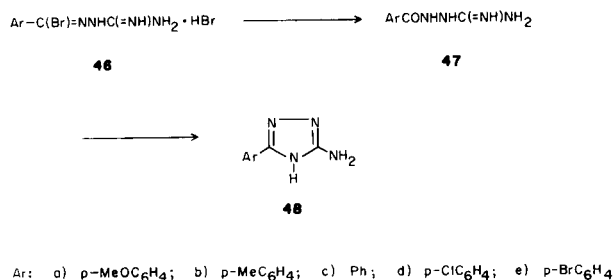
Thiourea and thiosemicarbazide react with *N*-arylbenzhydrazidoyl halides in the presence of triethylamine and give the corresponding 1,2,4-triazole derivatives **40a-b** and **40c-d**, respectively, in 59-65% yield together with the hydrazidoyl sulfide **41** (30).



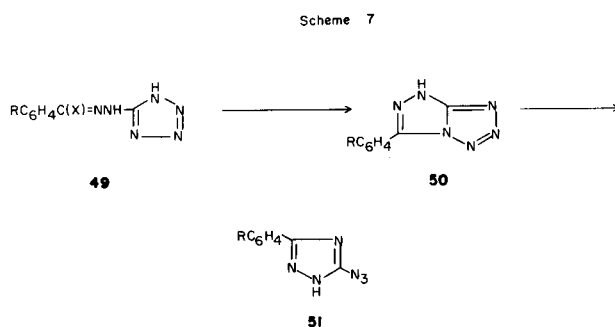
Reaction of *N*-ethoxycarbonylbenzhydrazidoyl chloride with benzamidine hydrochloride in the presence of sodium hydroxide was reported to give an almost quantitative yield of 3,5-diphenyl-1,2,4-triazole (**42**) (20). Also, a quantitative yield of 3,4-diphenyl-1,2,4- Δ^2 -triazolin-5-one (**44**) was obtained from *N*-ethoxycarbonylhydrazidoyl chloride by treatment with aniline followed by heating the resulting amidrazone **43** (20). 1,3,5-Triphenyl-1,2,4-triazole (**45**) was isolated from the reaction of *N*-phenylbenzhydrazidoyl chloride with benzamidine (31).



Scott and O'Halloran (32) prepared a series of 2-aryl-5-amino-1,3,4-triazoles **48** indirectly from the hydrazidoyl bromides **46** by solvolysis of the latter compound in an acid or alkaline medium and refluxing the resulting hydrazides **47** in an aqueous medium.

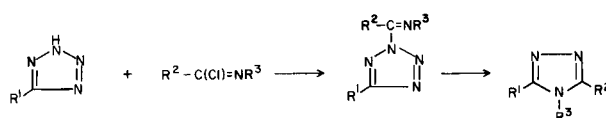


When the hydrazidoyl halides **49** are dissolved in 95% aqueous ethanol, they undergo several reactions to give 3-azido-5-substituted-1,2,4-triazoles **51** as the final products (33). It was argued that the reaction gives first the triazolotetrazole **50** as an intermediate that isomerizes into its valence isomer **51**. This change is similar to the reaction of imidoyl chloride with 5-substituted tetrazoles (Scheme 7) (33).

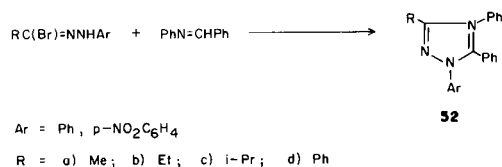


X = Cl or Br

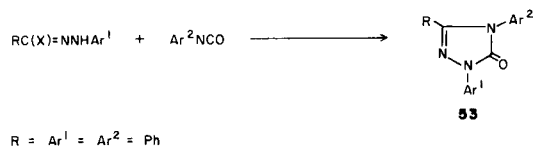
R: a) H; b) *p*-Br; c) *p*-i-Pr; d) *p*-Me; e) *p*-Cl; f) *p*-NO₂



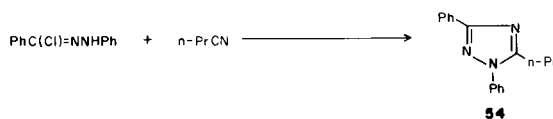
Reaction of *C*-alkyl-*N*-arylhydrazidoyl bromide with benzalaniline in benzene in presence of triethylamine was reported recently (21) to give triazoline derivatives **52a-d**. This reaction is considered to be the easiest route to the 1,2,4- Δ^2 -triazoline derivatives.



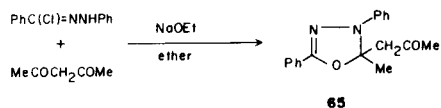
Aryl isocyanates react with hydrazidoyl halides in the presence of a base to give 1,3,4-trisubstituted 1,2,4- Δ^2 -triazolin-5-ones **53** (34).



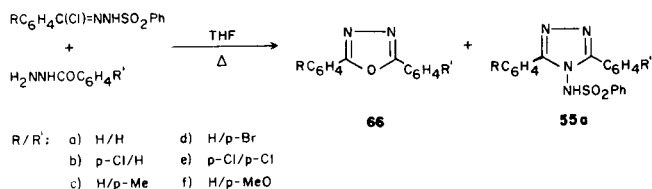
1,3-Diphenyl-5-*n*-propyl-1*H*-1,2,4-triazole (**54**) was also prepared from *N*-phenylbenzhydrazidoyl chloride and *n*-butyronitrile in dry *o*-dichlorobenzene in the presence of aluminum chloride (35).



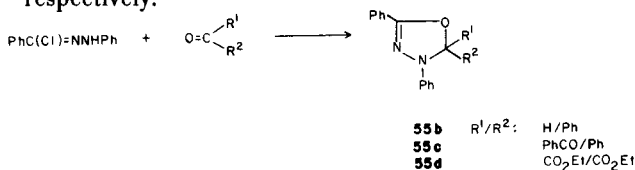
When *N*-phenylsulfonylbenzhydrazidoyl chloride was treated with an equivalent amount of benzoylhydrazine in ethanol, 4-phenylsulfonylamino-3,5-diphenyl-4*H*-1,2,4-triazoles **55** were obtained in an 80-90% yield (36).



Shawali and Fahmi (36) described the synthesis of 2,5-diaryl-1,3,4-oxadiazoles **66** in 35-45% yield from *N*-phenylsulfonylbenzhydrazidoyl chlorides by treating the latter with two equivalents of aroyl hydrazides in tetrahydrofuran. This reaction leads to a mixture of **66** and 4-phenylsulfonylamino-4*H*-1,2,4-triazoles **55a**.



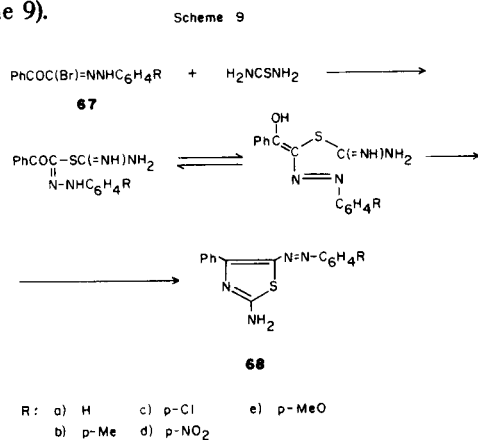
Nitrile imines generated from hydrazidoyl halides undergo addition to the C=O group in carbonyl compounds and give the corresponding 1,3,4-oxadiazole derivatives. Thus, 1,3,5-triphenyl-2,3-dihydro-1,3,4-oxadiazole (**55b**) was obtained in a 77% yield by treatment of *N*-phenylbenzhydrazidoyl chloride with benzaldehyde in the presence of triethylamine (89). A similar treatment of *N*-phenylbenzhydrazidoyl chloride with benzil and diethyl mesoxalate was reported (89) to give **55c** and **55d**, respectively.



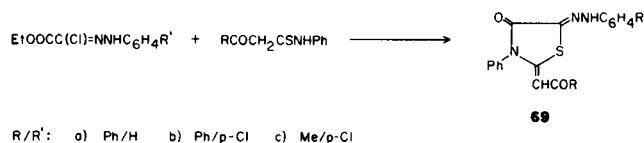
C. Nitrogen- and Sulfur-Containing Rings.

1. Thiazole and Thiazolidines.

According to Shawali and Abdelhamid (43,44), *C*-aroyl-*N*-arylhydrazidoyl bromides **67**, when heated with thiourea in ethanol, give 2-amino-4-aryl-5-arylazothiazoles **68** (Scheme 9).

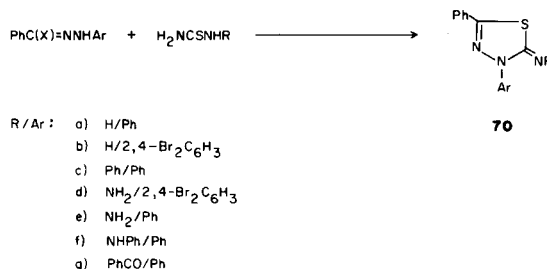


Reaction of *C*-ethoxycarbonyl-*N*-arylhydrazidoyl chlorides with β -keto thioanilides in the presence of sodium ethoxide was reported (45) to give the thiadiazolines **69a-c**.

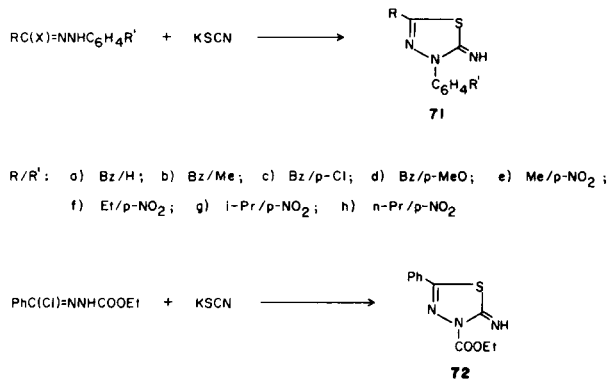


2. 1,3,4-Thiadiazoles and 1,3,4-Thiadiazolines.

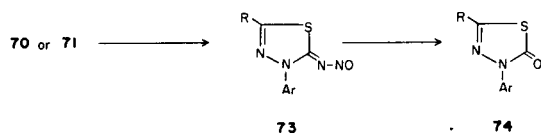
Wolkoff and co-workers (30) reported that hydrazidoyl halides refluxed with thiourea in ethanol in the absence of triethylamine as a base catalyst gave 5-imino-1,3,4-thiadiazolines **70a-b**. A similar treatment of hydrazidoyl halides with thiosemicarbazide, 1-phenylthiosemicarbazide, and phenylthiourea afforded the corresponding 1,3,4-thiadiazoline derivatives **70c-g**, respectively (30,90).



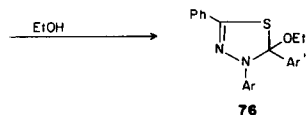
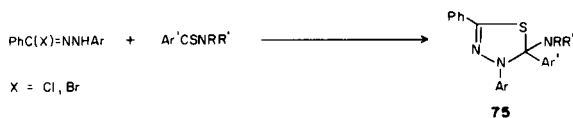
Compounds of the type of **70a-b** were also obtained from treatment of hydrazidoyl halides with potassium thiocyanate (27). The same route was used by Shawali and co-workers (43,44,46) to prepare the 5-alkyl- and 5-aryloxy derivatives of Δ^2 -1,3,4-thiadiazoline derivatives **71a-h**. *N*-Ethoxycarbonylbenzhydrazidoyl chloride reacts similarly with potassium thiocyanate and gives the thiadiazoline derivative **72** (20).



Compounds of the type **70a-b** and **71a-g** were converted into 1,3,4-thiadiazolin-5-ones **74** by nitrosation followed by thermal decomposition of the *N*-nitroso intermediates **73**.

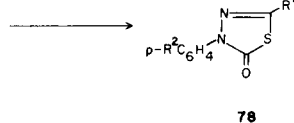
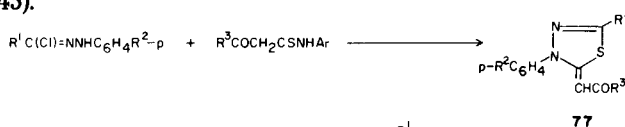


Thiobenzanilide and tertiary thioamides react with hydrazidoyl halides and give 5-amino-2,4,5-triaryl-1,3,4-thiadiazolines **75** in 80% yield (47). Upon alcoholysis, **75** leads to 5-alkoxy-1,3,4-thiadiazolines **76** in 90-95% yield.



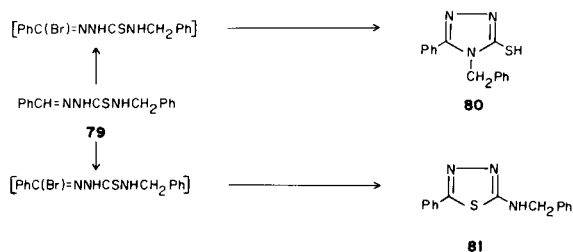
- Ar/Ar'/R/R':
- | | |
|---|---|
| a) Ph / Ph / H / Me | e) 2,4-Br ₂ C ₆ H ₃ / Ph / Me / Me |
| b) 2,4-Br ₂ C ₆ H ₃ / Ph | f) Ph / p-MeOC ₆ H ₄ / Me / Me |
| c) 2-Br-4-ClC ₆ H ₃ / Ph | g) Ph / Ph / -(CH ₂) ₅ - |
| d) Ph / Ph / Me / Me | h) Ph / p-MeOC ₆ H ₄ / -(CH ₂) ₅ - |

β -Ketothioanilides react with hydrazidoyl chlorides in the presence of triethylamine or sodium acetate and yield the 1,3,4-thiadiazoline derivatives **77** (45). Ozonolysis or oxidation of the latter products with hydrogen peroxide in acetic acid affords 2-oxo- Δ^2 -1,3,4-thiadiazolin-5-ones **78** (45).

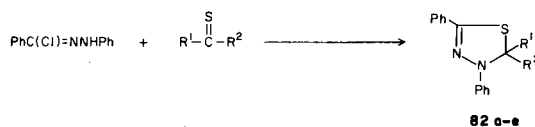


- R'/R²/R³:
- | | |
|---|--|
| a) COOEt / H / Ph | f) COOEt / H / p-MeC ₆ H ₄ |
| b) COOEt / Cl / Ph | g) Ac / Me / p-MeC ₆ H ₄ |
| c) Ac / MeO / Me | h) Ac / H / Ph |
| d) COOEt / Me / p-MeC ₆ H ₄ | i) Ac / H / p-MeC ₆ H ₄ |
| e) Ph / H / p-MeC ₆ H ₄ | |

Bromination of aldehyde 4-benzylthiosemicarbazones **79** was reported to give 1-benzyl-2-aryl-5-mercapto-1,3,4-triazoles **80** and 2-aryl-5-benzylamino-1,3,4-thiadiazoles **81**. The yields of the reaction products depend on the reaction conditions. Thus, treatment of **79** with bromine in chloroform gave **80** and **81** in 50-80 and 10-30% yield, respectively, whereas in the case of bromination in carbon tetrachloride the yield of **80** decreases (1-30%) and that of **81** increases (55-80%). Bromination of **79** with bromine in acetic acid or *N*-bromosuccinimide in carbon tetrachloride afforded only **81** in 65-85% and 60-90% yield, respectively. The reactions presumably proceed through the hydrazidoyl bromide intermediates (47,48).

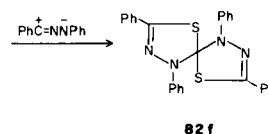


Huisgen and co-workers (89) reported that *N*-phenylbenzhydrazidoyl chloride reacts with thiobenzophenone in benzene in the presence of triethylamine to yield 2,2,3,5-tetraphenyl-2,3-dihydro-1,3,4-thiadiazole (**82a**) in a 72% yield. Similarly, *O*-ethyl-*N,N*-dimethylthiocarbamate, *N,N*-dimethylthiobenzamide, ethyl thiobenzoate, and ethyl dithiobenzoate react with *N*-phenylbenzhydrazidoyl chloride and give the corresponding 1,3,4-thiadiazole derivatives **82b-e**, respectively, in good yields (89).



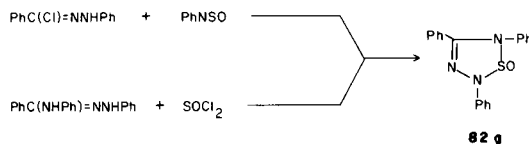
- R¹/R²:
- | | | | |
|-----------------------------|----------------------------|--------------|--------------|
| a) OEt / NMe ₂ ; | b) Ph / NMe ₂ ; | c) Ph / MeO; | d) Ph / OEt; |
| e) Ph / SPh | | | |

Reaction of *N*-phenylbenzhydrazidoyl chloride with carbon disulfide in the presence of triethylamine yields 2,2'-spiro-bis[3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole] (**82f**) in a 91% yield (89).



3. 1,2,3,5-Thiadiazoles.

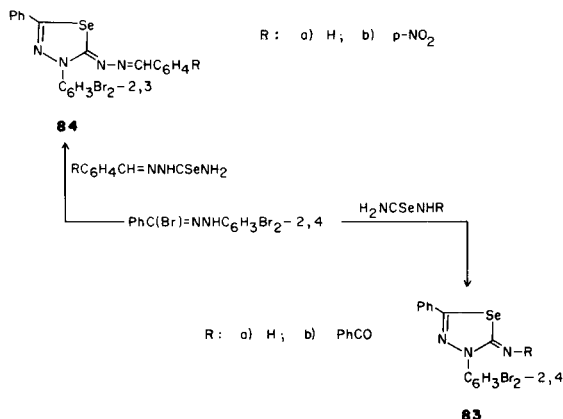
The reaction of *N*-phenylbenzhydrazidoyl chloride with thionyl aniline in benzene in the presence of triethylamine was reported (89) to give the corresponding cycloadduct, 2,4,5-triphenyl-2,5-dihydro-1,2,3,5-thiadiazole 1-oxide (**82g**). The structure of the latter compound was confirmed by its alternate synthesis from 1,4-diphenylbenzamidrazone and thionyl chloride (90).



D. Nitrogen- and Selenium-Containing Rings.

1. 1,3,4-Selenadiazolines.

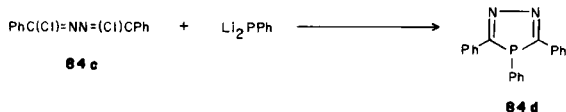
Reactions of *N*-(2,4-dibromophenyl)benzhydrazidoyl bromide with selenourea derivatives were reported (49) to give the selenadiazoline derivatives **83a-b**. The product **83b** forms **83a** upon hydrolysis. Similar treatment of *N*-(2,4-dibromophenyl)benzhydrazidoyl bromide with selenosemicarbazones yielded the products **84a-b**.



E. Nitrogen- and Phosphorus-Containing Rings.

1. 1,3,4-Phosphadiazoles.

The bis-hydrazidoyl chloride **84c** upon treatment with dilithium phosphide yields 1,2,5-triphenyl-1,3,4-phosphadiazole (**84d**) (92).

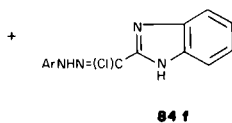
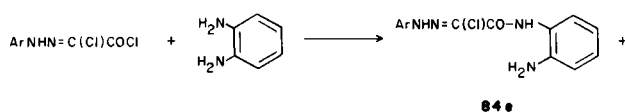


III. Bicyclic Systems.

A. Nitrogen-Containing Rings.

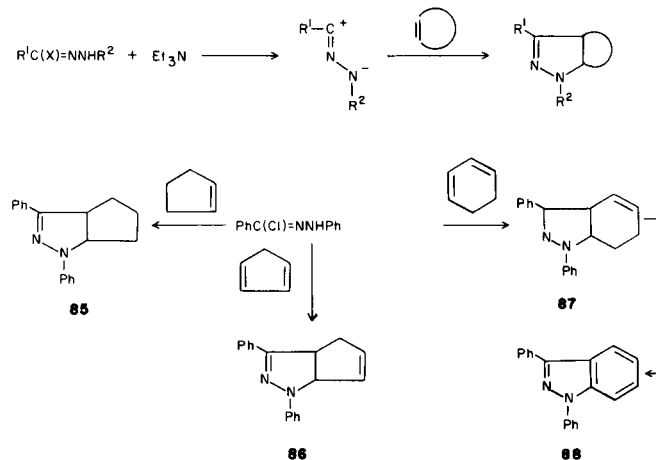
1. Benz[*d*]imidazoles.

Reaction of *N*-aryl-*C*-chlorocarbonylhydrazidoyl chlorides with *o*-phenylenediamine was reported to give benz[*d*]imidazoles **84e** together with the substitution products **84f** (90,91).

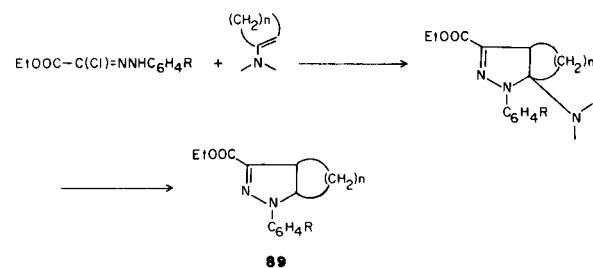
2. Cycloalka[1,2-*d*]pyrazoles.

Two methods were adopted for the synthesis of cycloalka[1,2-*d*]pyrazoles from hydrazidoyl halides. The

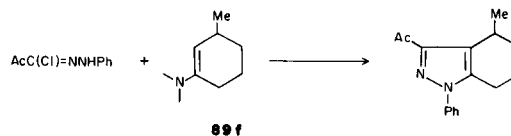
first method involves the interaction of hydrazidoyl halide with a cycloalkene or a cycloalkadiene (**25**) in the presence of triethylamine. Using this method, Huisgen and co-workers (25) prepared the cycloalka[1,2-*d*]pyrazoles **85-87**. Dehydrogenation of **87** gives 1,3-diphenylindazole **88**.



The second method involves the treatment of hydrazidoyl halides with the appropriate enamine derived from a cycloketone and secondary amine. Thus, *C*-ethoxycarbonyl-*N*-arylhazidoyl chlorides react with various enamines (**28**) giving cycloalka[1,2-*d*]pyrazoles **89a-e**. *C*-Acetyl-*N*-phenylhydrazidoyl chloride reacts similarly with *N*-methyl-*N*-phenyl-3-methyl-1-aminocyclohexane and gives 1-phenyl-3-acetyl-4-methyl-4,5,6,7-tetrahydroindazole (**89f**) (**28**).



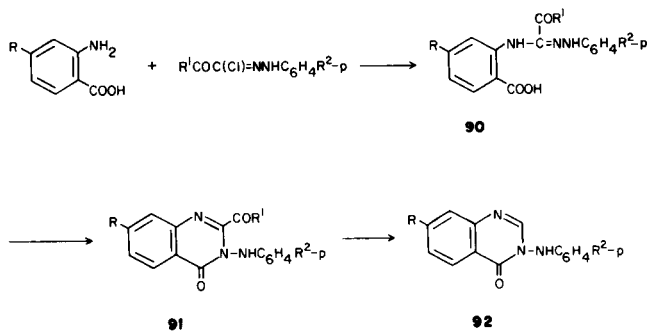
R/n: a) H/3; b) p-Cl/3; c) p-Cl/4; d) H/5; e) p-Cl/5



3. Quinazolines.

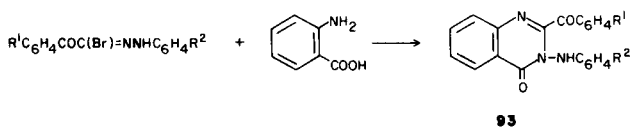
Trimarco and Lastrucci (50) have reported the synthesis of 2-ethoxycarbonyl- and 2-acetyl-3-arylamino-4(3*H*)quinazolinones **91a-b** and **91c-d**, respectively. Reaction of hydrazidoyl chlorides with anthranilic acids in ethanol in the presence of triethylamine yields the amidrazones **90**. A brief heating of **90** in acetic anhydride quickly results in the formation of **91a-d**. The 2-ethoxycarbonyl substituted

quinazolones **91a-b** easily undergo basic hydrolysis with concurrent decarboxylation affording the corresponding 2-unsubstituted quinazolones **92a-b**.



R/R¹/R²: a) H/EtO/H; b) H/EtO/MeO; c) NO₂/Me/H; d) H/Me/H

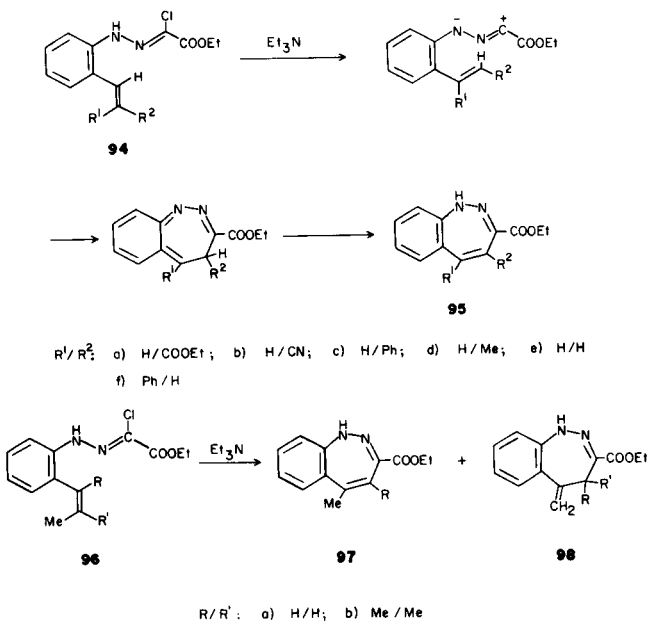
Condensation of *C*-royl-*N*-arylhyaizidoyl bromides with anthranilic acid in ethanol in the presence of triethylamine gives directly 2-royl-3-arylamino-4(3*H*)quinazolones **93a-c** (51).



R¹/R²: a) H/H; b) *p*-Me/H; c) H/*p*-Me

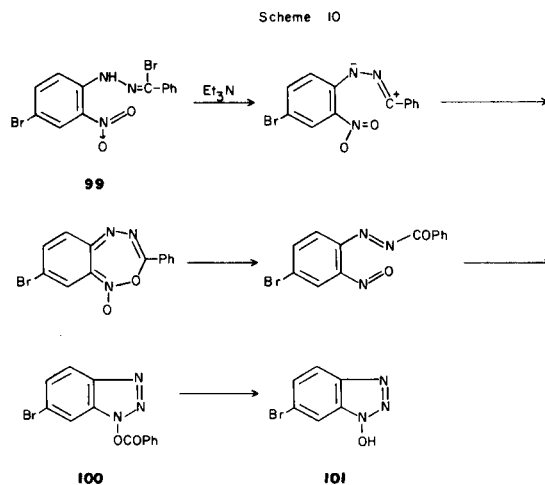
4. 1*H*-1,2-Benzodiazepines.

Reaction of hydrazidoyl halides of type **94** with triethylamine was reported (52-53) to give 54-75% yield of the corresponding 1*H*-1,2-benzodiazepines **95a-f**. A similar treatment of hydrazidoyl chlorides **96** with triethylamine leads to a mixture of the isomeric diazepine derivatives **97** and **98**. The yields of **98** do not exceed 25%.



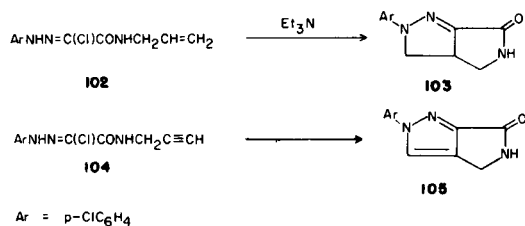
5. Benzo-1,2,3-triazoles.

6-Bromo-1-hydrobenzotriazolyl benzoate (**100**) was obtained in 20% yield by treatment of hydrazidoyl bromide **99** with triethylamine in benzene under anhydrous conditions. The formation of **100** was assumed to follow the sequence shown in Scheme 10. The reaction involves oxygen transfer from the *o*-nitro group to the α -carbon atom. Hydrolysis of **100** in an alkaline medium gave 6-bromo-1-hydroxybenzotriazole (**101**) (54).



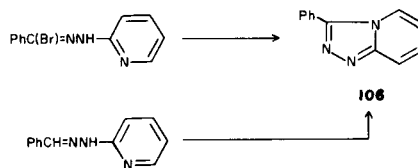
6. Pyrrolo[3,4-*c*]pyrazoles.

2-*p*-Chlorophenylpyrrolo[3,4-*c*]pyrazolin-6-one **103** was obtained by treatment of the hydrazidoyl chloride **102** with triethylamine in benzene for several hours at reflux temperature of the reaction mixture (55). A similar treatment of the hydrazidoyl chloride **104** gives 2-*p*-chlorophenylpyrrolo[3,4-*c*]pyrazolin-6-one (**105**).



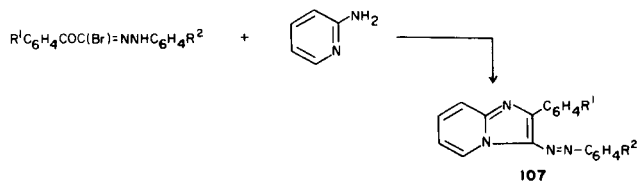
7. *s*-Triazolo[4,3-*a*]pyridines.

Treatment of *N*-(2-pyridyl)benzhydrazidoyl bromide with a base yields 3-phenyl-*s*-triazolo[4,3-*a*]pyridine (**106**) (57). The triazolopyridine **106** was also prepared directly from benzylidene 2-pyridylhydrazine by bromination in acetic acid in the presence of sodium acetate, without isolating the intermediate hydrazidoyl bromide (57).



8. Imidazo[1,2-*a*]pyridines.

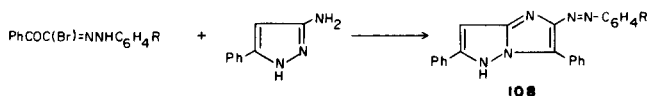
Shawali and co-workers (51) found that *C*-aryl-*N*-arylhyaazidoyl bromides condense with 2-aminopyridine in ethanol to give almost quantitative yields of the corresponding 2-aryl-3-aryazo-imidazo[1,2-*a*]pyridines **107**. The structure of the latter was elucidated on the basis of their identity with the coupling products of 2-arylimidazo[1,2-*a*]pyridines with diazotized anilines (51).



R/R²: a) H/H; b) H/*p*-MeO; c) H/*p*-Me; d) *p*-Me/H; e) *p*-Br/H
f) *p*-Cl/H; g) *p*-NO₂/H

9. 1*H*-Pyrazolo[1,5-*b*]imidazoles.

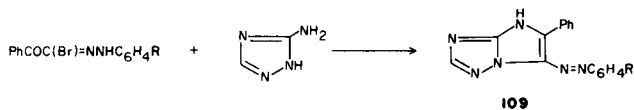
When *C*-benzoyl-*N*-arylhyaazidoyl bromides were refluxed with 3(5)-phenyl-5(3)-aminopyrazole in ethanol, 2,6-diphenyl-5-aryazo-1*H*-pyrazolo[1,5-*b*]imidazoles **108** were obtained in 60-90% yields (56).



R: a) H; b) *p*-Me; c) *p*-MeO; d) *p*-Cl; e) *p*-Br; f) *p*-NO₂

10. Imidazotriazoles.

Reaction of *C*-benzoyl-*N*-arylhyaazidoyl bromides with 3-amino-1,2,4-triazole in ethanol was found to give 2-phenyl-3-aryazoimidazo[1,2-*b*]-*s*-triazoles **109** in good yield (56). Scott and co-workers (58) reported that solvolysis of hydrazidoyl chlorides of the type **110** in aqueous dioxane produced readily 3-arylimidazo[2,3-*d*]-*s*-triazolines **111** in a high yield (90%). Similar treatment of *N*-imidazolidin-2-yl-benzhydrazidoyl bromides in aqueous dioxane gave 6,7-dihydro-3-aryl-5*H*-imidazo[2,1-*c*]-*s*-triazoles **113** (59).



R: a) H; b) *p*-Me

11. Pyrazolo[1,5-*c*]-*s*-triazoles.

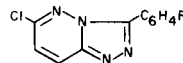
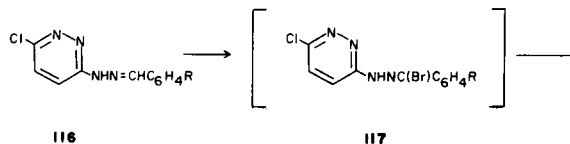
Hydrazidoyl chlorides **114** were reported to cyclize (61) upon treatment with triethylamine in benzene to give the corresponding pyrazolo[1,5-*c*]-*s*-triazole derivatives **115**.



R: COOEt; Ac; CONHC₆H₄OMe-*o*

12. *s*-Triazolo[4,3-*b*]pyridazines.

3-Aryl-6-chloro-*s*-triazolo[4,3-*b*]pyridazines **118** have been prepared from arylidene derivatives of 3-hydrazino-6-chloropyridazine **116** by treating the latter compound with bromine in acetic acid (43). The intermediate hydrazidoyl bromide **117** was not isolated, however.

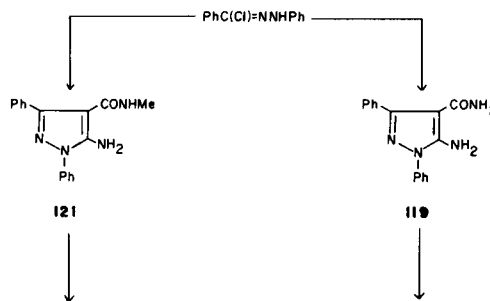


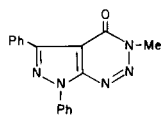
118

R: a) H; b) *p*-Cl; c) *p*-MeO

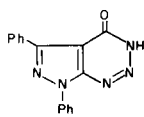
13. Pyrazolo[4,5-*e*]triazines.

N-Phenylbenzhydrazidoyl chloride reacts with cyanoacetamide in the presence of sodium ethoxide to give 1,3-diphenyl-5-aminopyrazole-4-carboxamide **119** in 80% yield. Diazotization of the latter resulted in a self-coupling giving **120** in 90% yield (60). *N*-Methylcyanoacetamide reacts similarly to yield **121** which upon diazotization gives **122**.





122



120

A number of 3,4,7-trisubstituted pyrazolo[1,5-*c*]-as-triazines **124a-b** have also been prepared by treating the hydrazidoyl chlorides **123** with methylamine or hydrazine hydrate in aqueous media (61).



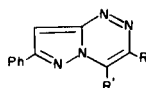
123

124

R: Ac; COOEt

R'/R: a) OH/OH; b) OH/Me

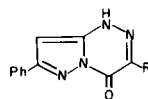
Treatment of **124** with potassium cyanide in ethanolic aqueous medium was reported to give the pyrazolo[1,5-*c*]-as-triazines **124c-e** (61).



124

R'/R: c) NH₂/COOEt; d) Me/CN; e) NH₂/2-MeOC₆H₄NHCO

Compound **124** (R = COOEt) has also been reported (61) to react with thiophenols and sodium benzenesulfinate in ethanol, giving pyrazolo[1,5-*c*]-as-triazin-7-one derivatives **125a-c**.

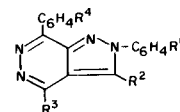


125

R: a) SPh; b) SC₆H₄Me-*p*; c) SO₂Ph

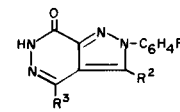
14. 2*H*-Pyrazolo[3,4-*d*]pyridazines.

A number of substituted 2*H*-pyrazolo[3,4-*d*]pyridazines **126**, 2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)ones **127**, and 2*H*-pyrazolo[3,4-*d*]pyridazin-4,7(5*H*,6*H*)diones **128**, have been synthesized from *C*-aroyl- and *C*-ethoxycarbonyl-*N*-arylhydrazidoyl halides (17). In this synthesis, the halides were treated with sodium salts of β-diketones, β-keto esters or β-cyanoketones in ethanol to give the corresponding 3,4-diacyl-, 3-ethoxycarbonyl-4-cyano-, and 3,4-diethoxycarbonylpyrazole derivatives (Table I). Hydrazinolysis of the latter pyrazole derivatives with hydrazine hydrate gives the 2*H*-pyrazolo[3,4-*d*]pyridazines **126-128**.



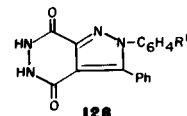
126

R¹/R²/R³/R⁴: a) H/Me/Me/*p*-Me h) H/Ph/Ph/*p*-Br
 b) *p*-Me/Me/Me/H i) H/Ph/Me/H
 c) *p*-Cl/Me/Me/H j) *p*-Me/Ph/Me/H
 d) H/Ph/Ph/H k) *p*-Cl/Ph/Me/H
 e) *p*-Me/Ph/Ph/H l) H/Ph/Me/*p*-Me
 f) *p*-Cl/Ph/Ph/H m) H/Ph/Me/*p*-Br
 g) H/Ph/Ph/*p*-Me n) H/Ph/NH₂/H



127

R¹/R²/R³: a) H/Ph/Ph f) H/Me/Me
 b) *p*-MeO/Ph/Ph g) *p*-Me/Me/Me
 c) *p*-Cl/Ph/Ph h) *p*-MeO/Me/Me
 d) H/Ph/NH₂ i) *p*-Cl/Me/Me
 e) *p*-MeO/Ph/NH₂ j) *p*-Cl/Ph/NH₂

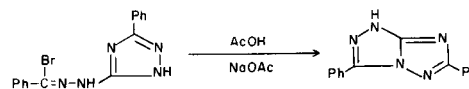


128

R¹: a) H; b) *p*-Me; c) *p*-Cl

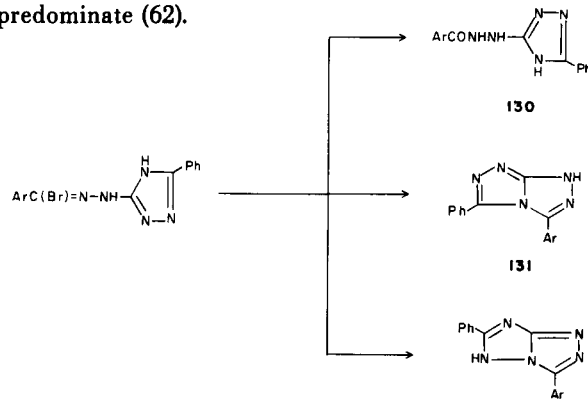
15. *s*-Triazolo[1,5-*c*]triazoles.

N-(3-Phenyl-1,2,4-triazol-5-yl)benzhydrazidoyl bromides, when refluxed in acetic acid in presence of equivalent amount of sodium acetate, were reported to give 2,6-diphenyl-7*H-s*-triazolo[1,5-*c*]-s-triazoline (**129**) in poor yield (62).



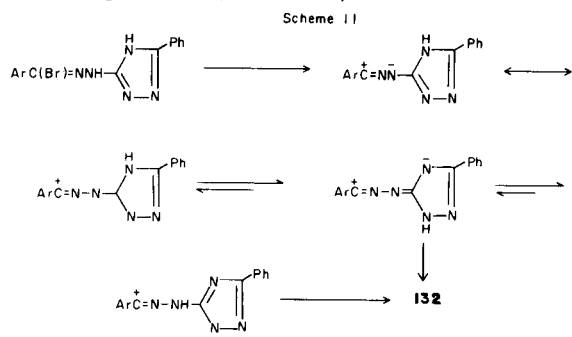
129

The cyclization of *N*-(5-phenyl-1,2,4-triazol-3-yl)benzhydrazidoyl bromides in mixed aqueous organic solvents was found to depend on the acidity of the medium. In a strongly acid medium, *N*-(5-phenyl-1,4-triazol-3-yl)benzhydrazides **130** are formed as the major products. At pH in the 3-6 range, 3-aryl-5-phenyl-1*H-s*-triazolo[3,4-*c*]-s-triazoles **131** were formed exclusively. In basic media, the isomeric 3-aryl-6-phenyl-5*H-s*-triazolo[4,3-*b*]-s-triazoles **132** predominate (62).



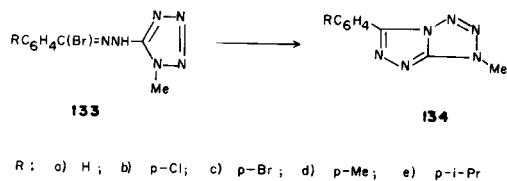
132

The product **132** is considered to result from a 1,5-dipolar cycloaddition involving the triazolyl anion as the nucleophile (63) (Scheme 11).

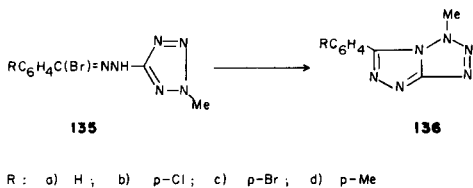


16. *s*-Triazolo[4,3-*d*]tetrazoles.

When the hydrazidoyl bromides **133** were solvolyzed in 50% (v/v) dioxane-water or acetone-water containing one equivalent of sodium acetate, they gave 3,5-disubstituted *s*-triazolo[4,3-*d*]tetrazoles **134** in a 70% yield (64,65). When the solvolysis of **133** was performed in the absence of sodium acetate, the yield of **134** was reduced to 50%.



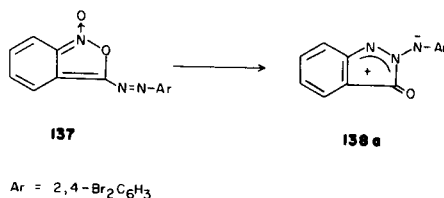
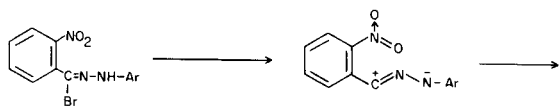
Similarly, when the isomeric hydrazidoyl bromides **135** were solvolyzed in aqueous acetone, good yields (60%) of the *s*-triazolo[4,3-*d*]tetrazoles **136** were obtained (65).



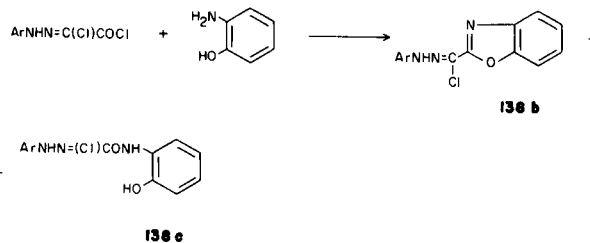
B. Nitrogen- and Oxygen-Containing Rings.

1. Benz[*c*]isoxazoles and Benz[*d*]oxazoles.

Treatment of *N*-2,4-dibromophenylbenzhydrazidoyl bromide with a base catalyst results in the formation of 3-(2,4-dibromophenylazo)anthranil 1-oxide (**137**), possibly *via* a nitrile imine intermediate. Reduction of **137** was reported (66) to give the mesoionic 2-(2,4-dibromophenyl-imino)indazenone **138a**.

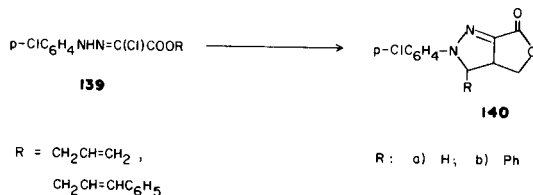


The reaction of *N*-aryl-*C*-chlorocarbonylhydrazidoyl chlorides with *o*-aminophenol was reported to give a mixture of 2-substituted benz[*d*]oxazoles **138b** together with the substitution products **138c** (90,91).

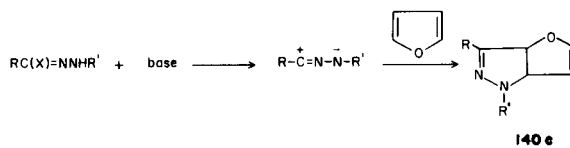


2. Furo[3,4-*c*]pyrazoles and Furo[2,3-*d*]pyrazoles.

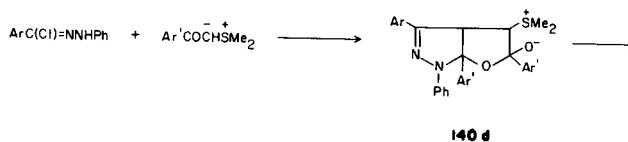
Hydrazidoyl chlorides of the type **139**, when treated with a large excess of triethylamine in benzene or toluene, were reported to undergo an intramolecular cycloaddition reaction and give 2-aryl-6-oxo-2,3,3a,6-tetrahydro-4*H*-furo[3,4-*c*]pyrazoles **140a-b**.

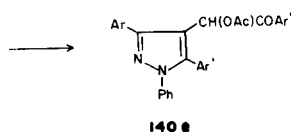


Dehydrohalogenation of hydrazidoyl halides in the presence of furan was reported (93) to give furo[2,3-*d*]pyrazoles **140c** as a result of the 1,3-cycloaddition of furan to the corresponding nitrile imines.



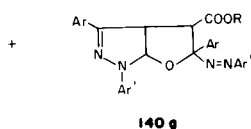
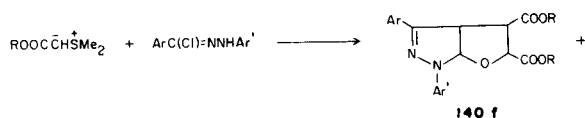
The reaction between *N*-phenylbenzenecarbohydrazidoyl chlorides and dimethylsulfonium phenacylide was reported (95) to give furo[2,3-*d*]pyrazole derivatives **140d**. The latter were converted into the corresponding pyrazoles **140e** when dissolved in acetic acid (95).





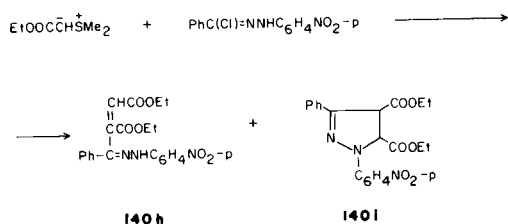
Ar/Ar': Ph/Ph; p-MeC₆H₄/Ph; Ph/p-MeC₆H₄

Carboalkoxymethylene sulfonium ylids were also reacted with hydrazidoyl chlorides to give a mixture of the furo[2,3-*d*]pyrazole derivatives **140f** and **140g** (96) in various yields according to the substituents in the ring residues of the hydrazidoyl halide used.



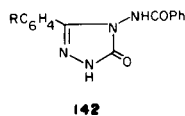
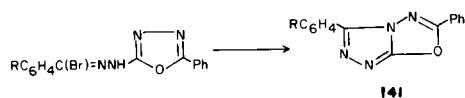
Ar/Ar': Ph/Ph; Ph/p-ClC₆H₄; p-MeC₆H₄/Ph R = Me or Et

A variation of the reaction was observed (96) with *N*-*p*-nitrophenylhydrazidoyl chloride. In this case, the reaction leads to the formation of **140h** and **140i** in 18 and 22% yields, respectively (96).



3. *s*-Triazolo[3,4-*b*]oxadiazoles.

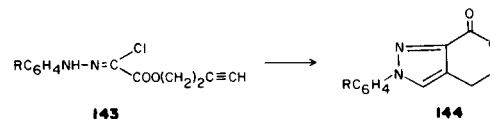
Scott and co-workers (68) reported that 2-phenyl-1,3,4-oxadiazol-5-ylbenzhydrazidoyl bromides when treated with triethylamine in benzene, undergo a facile cyclization and give a 95% yield of *s*-triazolo[3,4-*b*]-1,3,4-oxadiazoles **141**. The latter were converted into 4-benzoylamino-3-aryl-1,2,4-triazolin-5-ones **142** by refluxing them briefly in glacial acetic acid.



R: a) H; b) m-Br; c) p-Cl; d) p-Br; e) p-NO₂

4. Pyrano[3,4-*c*]pyrazoles.

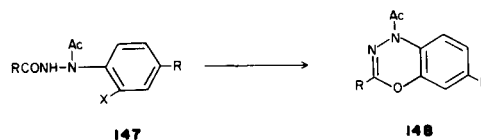
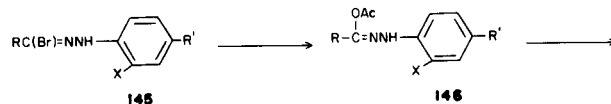
Fusco and co-workers reported recently (69) that hydrazidoyl chlorides of type **143** can be converted into 2-aryl-4,5-dihydro-7-oxopyrano[3,4-*c*]pyrazoles **144** in 25-49% yields by boiling them in toluene for 48 hours in the presence of triethylamine.



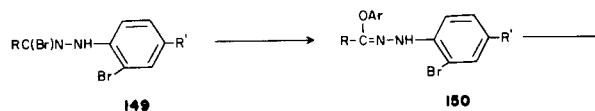
R: a) p-Cl; b) p-NO₂

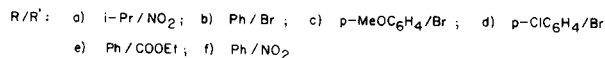
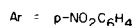
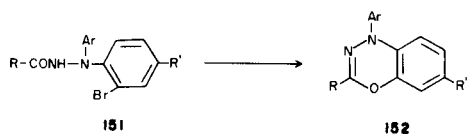
5. 4*H*-1,3,4-Benzoxadiazines.

Elliott and Gibson (70) reported a convenient synthesis of 4-acetyl-4*H*-1,3,4-benzoxadiazines **148** from *N*-(2-halo-4-substituted phenyl)-benzhydrazidoyl bromides **145**. Treatment of **145** with sodium acetate in glacial acetic acid was reported to give 1-aryl-2-acetyl-2-arylhydrazines **147**, probably *via* the *O*-acetylhydrazidates **146**. When the latter were refluxed in dimethylformamide in the presence of triethylamine and sodium hydroxide, they underwent cyclization and afforded 4-acetyl-4*H*-1,3,4-benzoxadiazine derivatives **148** in 39-93% yields. In this reaction the *ortho* fluorine is more readily displaced than bromine. Treatment of **145** (R = Ph, R' = NO₂, X = Br) with anhydrous sodium acetate in dimethylformamide at reflux temperature of the reaction mixture gave **148** directly.



More recently Shawali and co-workers (71) and Elliott and co-workers (34) reported the synthesis of 4-aryl-2,7-disubstituted 4*H*-1,3,4-benzoxadiazines **152** from hydrazidoyl bromides **149** by converting them first to aryl hydrazidates **150**. Thermolysis of the latter or treatment with a base catalyst results in their rearrangement to 1-aryl-2,2-diarylhydrazines **151**. Under basic conditions, the rearranged hydrazides **151** can be cyclized to 4-aryl-2,7-disubstituted-4*H*-1,3,4-benzoxadiazines **152**.

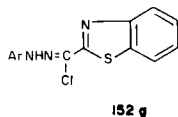




C. Nitrogen- and Sulfur-Containing Rings.

1. Benzo[d]thiazoles.

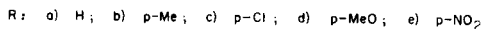
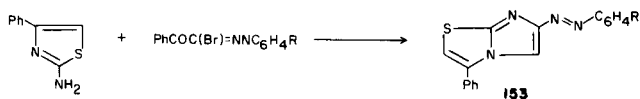
o-Aminothiophenol reacts with *C*-chlorocarbonyl hydrazidoyl chlorides and gives the expected amides and benzo[d]thiazoles **152g** (90,91). The latter products probably result from dehydration of the former.



152g

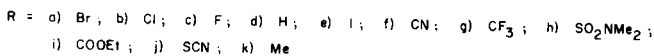
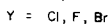
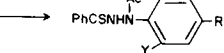
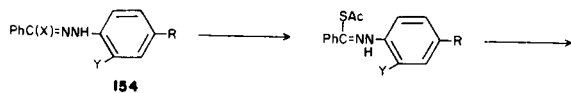
2. Imidazo[1,5-*b*]thiazoles.

Condensation of *C*-royl-*N*-arylhyaazidoyl bromides with 4-phenyl-2-aminothiazole in ethanol has been found (56) to yield 2-arylo-3-phenyl-3,5-diarylimidazo[1,5-*b*]thiazole derivatives **153** in good yield.

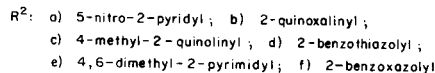
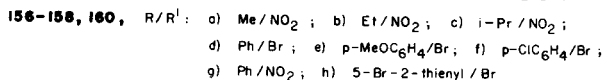
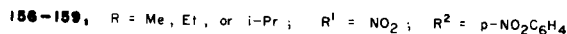
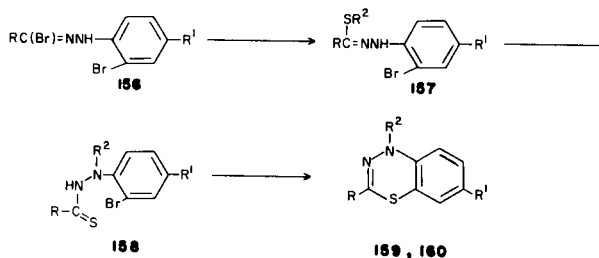


3. 4*H*-1,3,4-Benzothiadiazines.

A large number of 4-acetyl-4*H*-1,3,4-thiadiazines **155** were prepared from hydrazidoyl halides of type **154** by boiling the latter with potassium thioacetate in acetonitrile. The yield of **155** was found to depend on the *ortho* halogen atom in **154** (72). The ease of displacement of the *ortho* halogen is $\text{F} > \text{Br} > \text{Cl}$ (72-74).



Recently, Shawali and co-workers (71) and Elliott and co-workers (75) prepared several examples of 4-aryl-4*H*-1,3,4-benzothiadiazine derivatives **159-160** from hydrazidoyl halides **156** by converting the latter into the corresponding aryl thiohydrazidates **157**. Treatment of these esters with triethylamine in ethanol leads to a Smiles-type rearrangement (76) and gives the thiohydrazides **158**. The latter undergo cyclization in the presence of triethylamine and yield 4*H*-1,3,4-benzothiadiazines **159-160**.

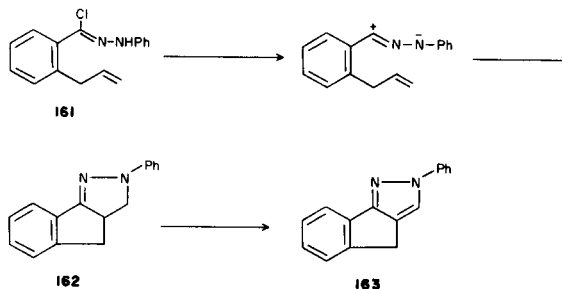


IV. Tricyclic Systems.

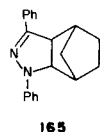
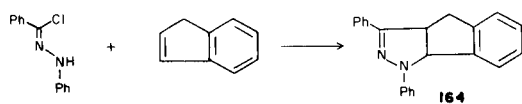
A. Nitrogen-Containing Rings.

1. Indeno[1,2-*c*]pyrazoles and Indazoles.

Reaction of *N*-phenyl *o*-allylbenzhydrazidoyl chloride **161** with triethylamine in benzene was reported (77) to give 2,3,3a,4-tetrahydro-2-phenylindeno[1,2-*c*]pyrazole **162**. Oxidation of **162** with DDQ results in 2,4-dihydro-2-phenylindeno[1,2-*c*]pyrazole **163** (77).

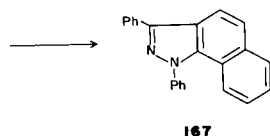
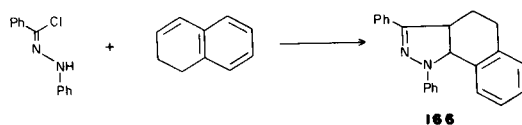


4*H*-Indeno[1,2-*c*]pyrazole **164** was also obtained from interaction of *N*-phenyl benzhydrazidoyl chloride with indene in benzene in the presence of triethylamine (25). Similar treatment of the same hydrazidoyl chloride with bicycloheptadiene leads to the formation of 1,3-diphenyl-4,7-methano-3a,4,7,7a-tetrahydroindazole **165** (25).

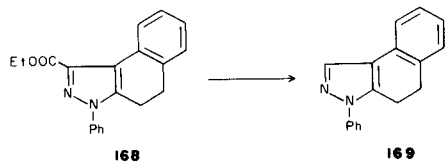
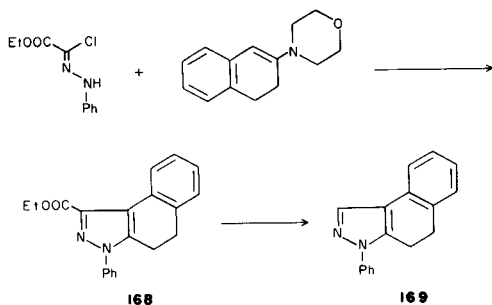


2. Naphtho[1,2-c]pyrazoles.

Interaction of *N*-phenylbenzhydrazidoyl chloride with 1,2-dihydronaphthalene in benzene in the presence of triethylamine was reported (25) to give 1,3-diphenyl-3a,4,5,9b-tetrahydronaphtho[1,2-c]pyrazole (**166**), which upon dehydrogenation yielded 1,3-diphenylnaphtho[1,2-c]pyrazole (**167**).

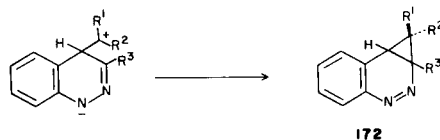
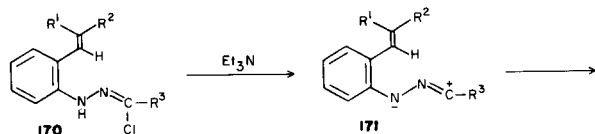


Reaction of *C*-ethoxycarbonyl-*N*-phenylhydrazidoyl chloride with 2-morpholino-3,4-dihydronaphthalene also gives the naphthopyrazole derivative **168**, which upon hydrolysis and decarboxylation yields 1-phenyl-8,9-dihydronaphtho[1,2-c]pyrazole (**169**) (28).



3. 1*H*-Cyclopropa[*c*]cinnolines.

Hydrazidoyl chlorides **170** afford 1a,7b-dihydro-1*H*-cyclopropa[*c*]cinnolines **172** when treated with triethylamine in benzene, through an intramolecular cycloaddition reaction of the generated 1,3-nitrile imine intermediate **171** (78,88).



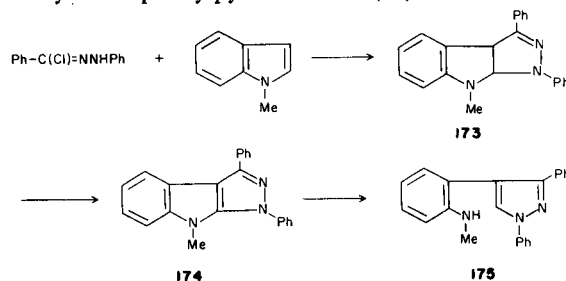
R^2 : COOEt

R^1/R^3 : a) Me / COOEt
b) Ph / COOEt
c) Me / Ac
d) Me / PhCO

e) Me / *p*-NO₂C₆H₄
f) Ph / Ac
g) Ph / PhSO₂

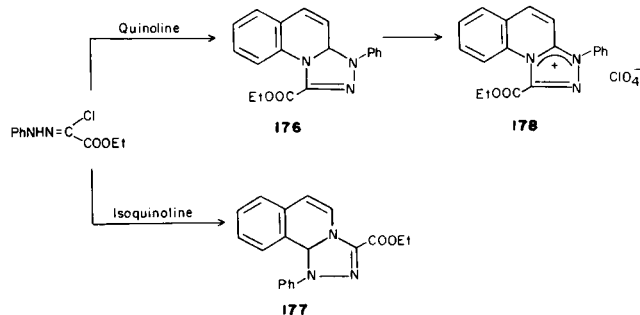
4. Pyrazolo[3,4-*b*]indoles.

Condensation of *N*-phenylbenzhydrazidoyl chloride with *N*-methylindole in tetrahydrofuran in the presence of triethylamine was reported (79) to give 8-methyl-3a,8a-dihydropyrazolo[3,4-*b*]indoles **173**. Oxidation of **173** with lead tetracetate in dichloromethane gave 8-methylpyrazolo[3,4-*b*]indoles **174**. Acid hydrolysis of **174** by heating in glacial acetic acid afforded 1,3-diaryl-4-*N*-methylaminophenylpyrazoles **175** (79).

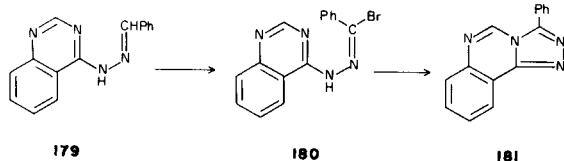


5. Triazino[4,5-*a*]quinolines.

Treatment of *C*-ethoxycarbonyl-*N*-phenylhydrazidoyl chloride with an equivalent amount of quinoline in the presence of triethylamine gave 3-ethoxycarbonyl-1-phenyl-4,11-dihydrotriazino[4,5-*a*]quinoline (**176**) in a high yield. Isoquinoline reacts similarly with the same hydrazidoyl chloride to give the isomeric product **177** (80). Compound **176**, when oxidized with chromic oxide in acetic acid followed by addition of perchloric acid, gave **178**.

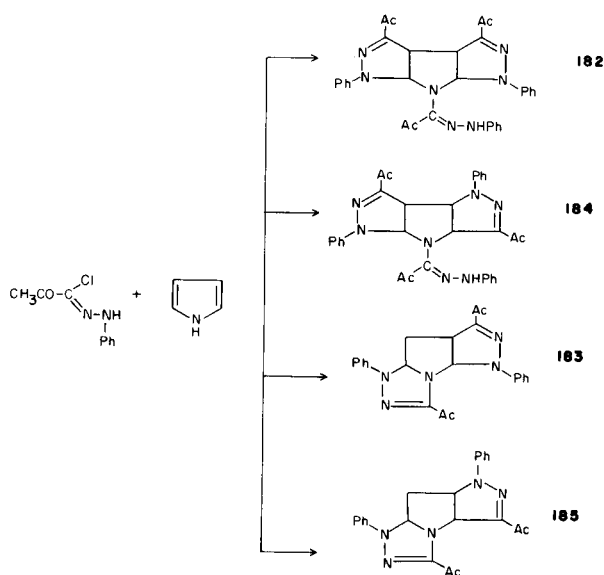


Bromination of benzylidene-4-quinazolyldiazine (**179**) with bromine in acetic acid in the presence of sodium acetate was reported to give 3-phenyl-*s*-triazolo[4,3-*c*]quinazolines **181**, probably *via* the hydrazidoyl bromide **180** which was not isolated (57).



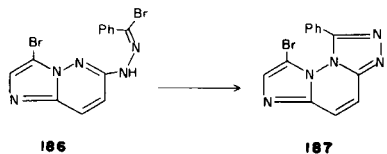
6. 1*H*-Pyrrolo[2,3-*c*:4,5-*c'*]dipyrazoles and Pyrazolo[3',4':4,5]pyrrolo[2,1-*c*]-s-triazoles.

Ruccia and co-workers (81) have reported recently that treatment of the *C*-acetyl-*N*-phenylhydrazidoyl chloride with pyrrole at room temperature yields, among other products, the ring systems **182** and **183** and their isomers **184** and **185**, respectively. The yields of the latter products were very poor (1.2-5%), however.



7. Imidazo[1,2-*b*]-s-triazolo[4,3-*f*]pyridazines.

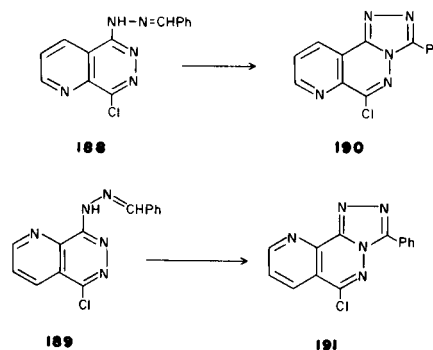
When *N*-(3-bromoimidazo[1,2-*b*]pyridazin-6-yl)benzhydrazidoyl bromide (**186**) was treated with 10% aqueous sodium hydroxide solution at 50°, it gave 1-phenyl-8-bromoimidazo[1,2-*b*]-s-triazolo[3,4-*f*]pyridazine (**187**) in 62% yield (82).



8. Pyrido[3,2-*d*]-s-triazolo[4,3-*b*]pyridazines.

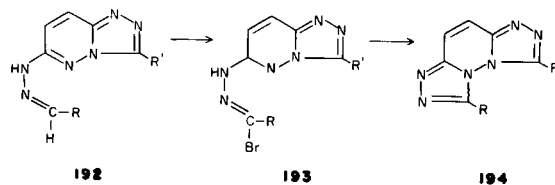
Two such fused three-ring systems have been synthesized from the corresponding arylidene derivatives of 5-hydrazinopyrido[2,3-*d*]pyridazine (**188**) and 8-hydrazino[2,3-*d*]pyridazines **189**. Treatment of **188** and **189** with bromine in acetic acid in presence of sodium acetate gave 6-chloro-3-phenylpyrido[3,2-*d*]-s-triazolo[4,3-*b*]pyridazine

190 and its isomer **191**, respectively (83). The intermediate hydrazidoyl bromides were not isolated.

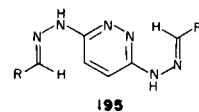


9. Bis-*s*-triazolo[4,3-*b*:3',4'-*f*]pyridazines.

The route described for the synthesis of *s*-triazolo[4,3-*b*]pyridazines **190-191** was extended to the preparation of bis-*s*-triazolo[4,3-*b*:3',4'-*f*]pyridazines **194**. Thus, alkylidene or arylidene derivatives of 6-hydrazino-*s*-triazolo[4,3-*b*]pyridazines **192** were converted into the fused tricyclic systems **194** by bromine in acetic acid in the presence of sodium acetate (84). The intermediate hydrazidoyl bromide **193** was not isolated.



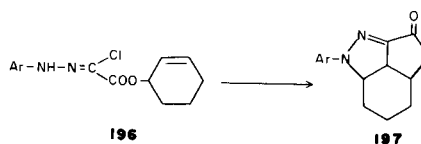
Alternatively, the latter ring system **194** was obtained by direct cyclization of bis-arylidene derivative **195** with bromine in acetic acid (84).



B. Nitrogen- and Oxygen-Containing Rings.

1. Octahydrofuro[4,3,2-*c,d*]indazoles.

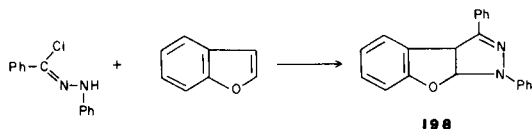
Treatment of the hydrazidoyl chloride **196** with a large excess of triethylamine in toluene for several hours was reported (63) to give 4-*p*-chlorophenyl-2-oxo-2,4,4a,5,6,7,7a,7b-octahydrofuro[4,3,2-*c,d*]indazole (**197**).



2. Benzofuro[2,3-*d*]pyrazolines.

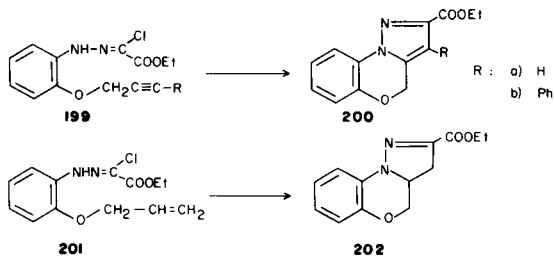
Interaction between *N*-phenylbenzhydrazidoyl chloride

and benzofuran in tetrahydrofuran in presence of triethylamine affords 1,3-diphenylbenzofuro[2,3-*d*]- Δ^2 -pyrazoline (**198**) (85).

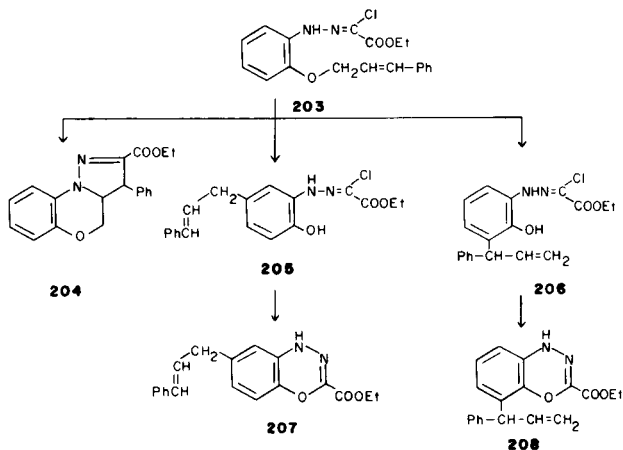


3. 4*H*-Pyrazolo[5,1-*c*][1,4]benzoxazines.

2-Ethoxycarbonyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]-benzoxazine **200** has been synthesized from hydrazidoyl chloride **199** by refluxing the latter in toluene in presence of excess triethylamine (69). Similar treatment of hydrazidoyl chloride **201** resulted in 2-carbethoxy-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**202**) (69,77). However, hydrazidoyl chloride **203**, upon refluxing in toluene in

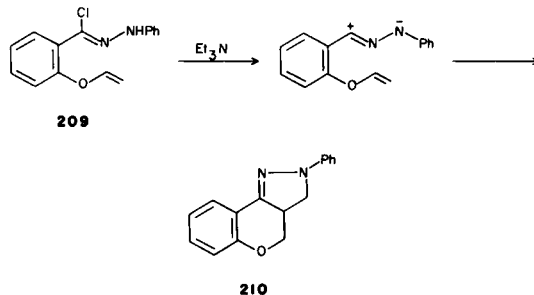


presence of triethylamine, gives a mixture of 2-carbethoxy-3-phenyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**204**), 2-carbethoxy-6-(1-phenylpropen-3-yl)-4*H*-1,3,4-benzoxadiazine (**207**), and 2-carbethoxy-8-(3-phenyl-propen-3-yl)-4*H*-1,3,4-benzoxadiazine (**208**). The products **207** and **208** are considered to arise from a preliminary Claisen type rearrangement of **203** to the isomeric phenols **205** and **206**, according to the known behavior of aryl allyl ethers. Owing to the presence of triethylamine, the corresponding phenoxide ion intramolecularly displaces the halogen giving the products **207** and **208**. Control experiments showed that **203** rearranges in boiling toluene to produce **205** and the latter readily cyclizes in the presence of triethylamine and gives **207** (69).



4. Benzopyrano[4,3-*c*]pyrazoles.

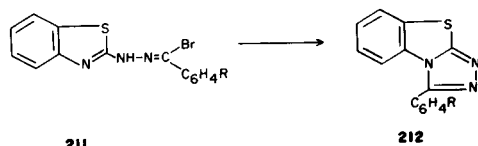
Padwa and co-workers (77) have recently reported that reaction of *N*-phenyl-*o*-allyloxybenzhydrazidoyl chloride (**209**) with triethylamine in benzene solution at 80° produces 2,3,3a,4-tetrahydro-2-phenyl(*l*)benzopyrano[4,3-*c*]pyrazole (**210**) in good yield.



C. Nitrogen- and Sulfur-Containing Rings.

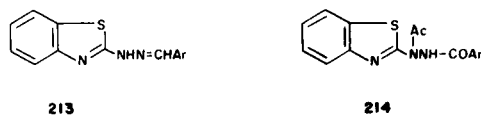
1. Triazolobenzothiazoles.

When the hydrazidoyl bromides **211** were treated with triethylamine in benzene, high yields (85-95%) of *s*-triazolo[1,2-*b*]benzo-1,3-thiazoles **212** were obtained. Cyclization of **211** into **212** can also be effected by solvolysis of **211** at ambient temperature in 70% (v/v) aqueous dioxane (86).



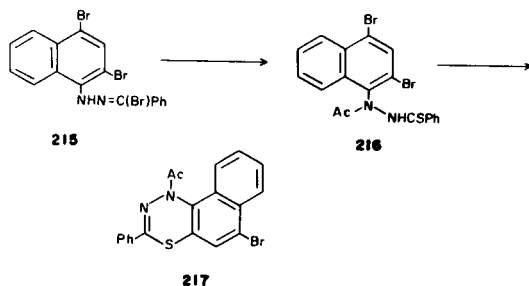
R: a) H; b) *p*-Me; c) *p*-NO₂; d) *p*-Cl; e) *p*-Br; f) *p*-*i*-Pr

Compounds **212** were also successfully obtained by slow addition of bromine in chloroform to a mixture of the parent hydrazone **213** in the same solvent containing sodium carbonate at ambient temperature, the yields range from 65 to 94%. When sodium acetate was used in place of sodium carbonate, mixtures of **212** and the hydrazides **214** were produced (86).



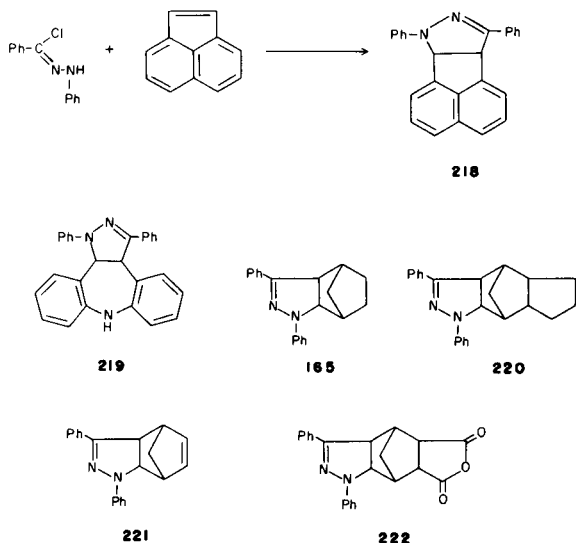
2. Naphtho[1,2-*e*]-1,3,4-thiadiazines.

Reaction of the hydrazidoyl bromide **215** with potassium thioacetate was reported (74) to give 2-phenyl-4-acetyl-9-bromo-4*H*-naphtho[1,2-*e*]-1,3,4-thiadiazine (**217**), probably *via* the thiohydrazone intermediate **216**.



V. Miscellaneous Polycyclic Systems.

Reaction of *N*-phenylbenzhydrazidoyl chloride with acenaphthylene in benzene in presence of triethylamine affords 6b,9a-dihydro-7,9-diphenylacenaphtho[1,2-*c*]pyrazole (**218**) in 60% yield (25). Similar interaction between the same hydrazidoyl chloride and dibenzo[*b,f*]azepine, norbornene, dicyclopentadiene, and *cis*-bicyclo[2,2,1]hept-5-ene-2,3-dicarboxylic acid anhydride results in the formation of the ring systems **219**, **165**, and **220-222**, respectively (25).



Note added in proof. A synthesis of an ethoxycarbonyl derivative of benzo[*e*]-1,2,4-triazine has been reported by base-catalyzed cyclization of the appropriate amino-substituted hydrazidoyl bromide (**99**). Triazolo[4,5-*f*]pyridazines were obtained by reaction of hydrazidoyl chlorides with pyridazine in chloroform in the presence of triethylamine (**100**). Similarly, pyrazine yielded triazolo[4,5-*a*]pyrazines (**100**), quinoxaline gave triazolo[4,5-*a*]quinoxalines (**100**), and phthalazine the corresponding triazolo[4,5-*b*]phthalazines (**100**). Several substituted indoles were shown to react with nitrile imines giving 3a,8a-dihydropyrazolo[3,4-*b*]indoles in addition to other products (**101**). Derivatives of pyrazolo[5,1-*a*]quinazolines were obtained by condensation of hydrazidoyl halides with

ethyl cyanoacetate, cyanoacetamide, and malononitrile in the presence of sodium ethoxide (**102**). Hydrazidoyl chlorides and 3-pyrrolidinobenzo[*b*]furan react in benzene in the presence of triethylamine and give a mixture of the tautomeric benzofuro[3,2-*c*]pyrazolines and 2-benzoylbenzo[*b*]furan arylhydrazines (**103**). 2-Ethoxycarbonyl-4*H*-1,2,4-triazolo[5,1-*c*]-1,4-benzoxazine was obtained by ring closure from the appropriately substituted hydrazidoyl chloride (**104**). In analogous reactions, the 2-ethoxycarbonyl derivatives of 4*H*-1,3,4-benzothiadiazine, 4*H*-1,2,4-triazolo[5,1-*c*]benzothiazine, and 1,2,4-triazolo[1,5-*f*]phenanthridine were obtained (**104**).

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