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This review summarizes the synthesis of various pyrazoles reported by us and some other research groups in 1981-1989.

This review contains the following contents:

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1. Introduction.

A great many papers have been reported so far concerning the synthesis or biological activity of pyrazole derivatives. These numerous papers have been occasionally summarized in some monographs [1] and reviews [2], which have been useful for the biologists and chemists engaged in the development of new drugs or in other important works. However, a sufficient number of reviews have not been provided at the present time because of the accumulating papers on the pyrazole chemistry annually. In this review, we summarize the literature on pyrazole chemistry investigated by us and some other research groups during 1981-1989.

2. Synthesis of Pyrazoles.

2-1. Pyrazoles from β-Keto-β-sulfonylenamines.

The reaction of the β-keto-β-sulfonylenamines **1** with substituted hydrazines gave the 1,5-disubstituted 4-sulfonylpyrazoles **2** (Scheme 1) [3]. Subsequent reaction of pyrazole **2a** with *n*-butyllithium (Chart 1) produced the β-cyano-β-sulfonylenamine [δ (CN) 116.4 ppm]. These results ascertained a facile route to the 1,5-disubstituted 4-sulfonylpyrazoles **2** from the β-keto-β-sulfonylenamines **1**.

Scheme 1

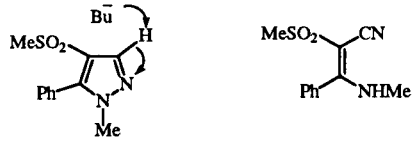
1 **2** (8 Compounds)

R = Ph, p-Tolyl, R' = Me, Ph, C_6H_4-*p*-Cl, C_6H_4-*p*-NO_2

2-2. Pyrazoles from Arylazomethylenetriphenylphosphoranes.

The reaction of arylazomethylenetriphenylphosphoranes **3a-e** with chloroform/50% sodium hydroxide solution, under phase transfer condition using benzyltriethylammo-

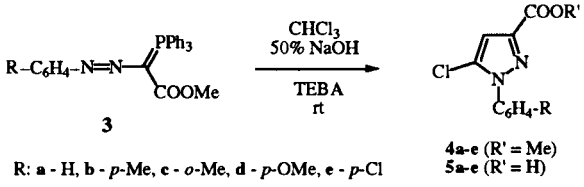
Chart 1



2a β-Cyano-β-sulfonylenamine

nium chloride, afforded the 1-aryl-5-chloropyrazole-3-carboxylates **4a-e** and 1-aryl-5-chloropyrazole-3-carboxylic acids **5a-e** (Scheme 2) [4].

Scheme 2



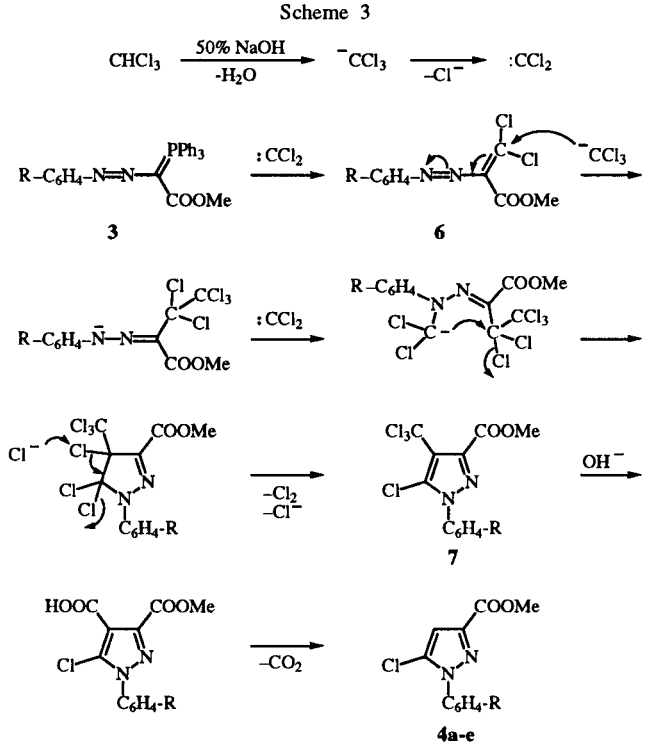
3

R: **a** - H, **b** - *p*-Me, **c** - *o*-Me, **d** - *p*-OMe, **e** - *p*-Cl

4a-e (R' = Me)
5a-e (R' = H)

The reaction mechanism is shown in Scheme 3, wherein compounds **6** and **7** are isolated in an alternate experiment.

Scheme 3

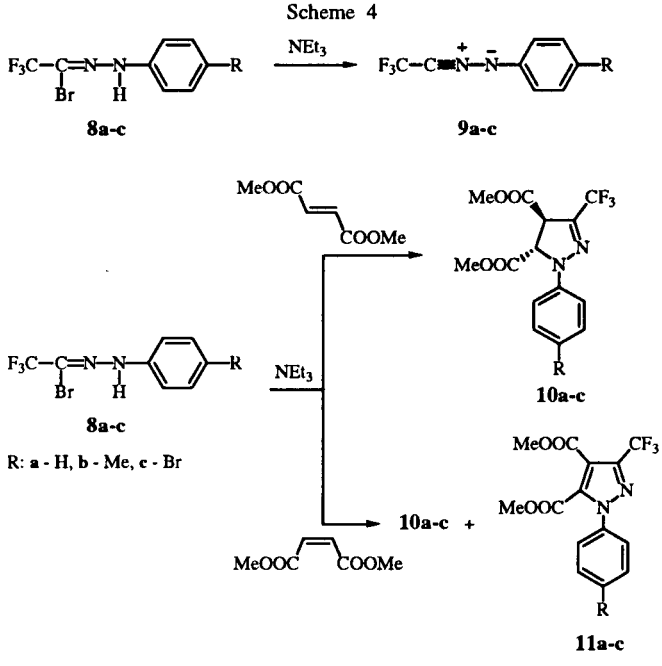


3 **6** **7** **4a-e**

2-3. 3-Trifluoromethylpyrazoles and 3-Trifluoromethyl-2-pyrazolines from Nitrilimines

The reaction of *N*-aryltrifluoroacetohydrazonyl bromides **8a-c** with triethylamine is known to give the nitrilimines **9a-c**, whose reaction with dimethyl fumarate affords the dimethyl 1-aryl-3-trifluoromethyl-2-pyrazoline-*trans*-4,5-dicarboxylates **10a-c** (Scheme 4) [5]. When dimethyl maleate was used in place of dimethyl fumarate, compounds **10a-c** and dimethyl 1-aryl-3-trifluoromethylpyrazole-4,5-dicarboxylates **11a-c** were obtained. The nitrilimine was also generated *in situ*, by the thermal decomposition of the oxadiazaphosphole **12** (Scheme 5) [5]. The reaction of compound **12** with dimethyl fumarate or maleate produced only *trans*-pyrazoline **10a**.

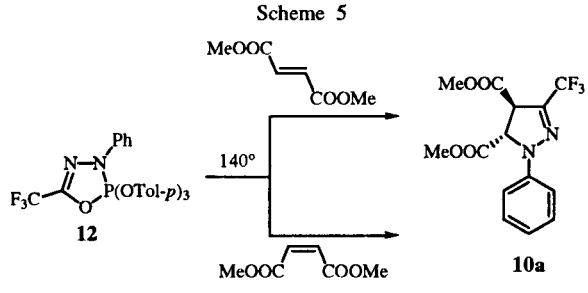
Scheme 4



8a-c **9a-c** **10a-c** **11a-c**

R: **a** - H, **b** - Me, **c** - Br

Scheme 5



12 **10a**

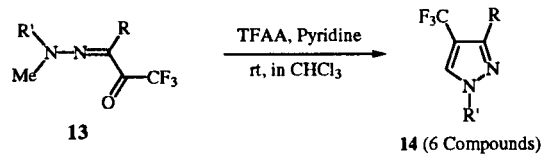
2-4. 4-Trifluoromethylpyrazoles from Trifluoroacetylhydrazones.

The reaction of trifluoroacetylhydrazones **13** with trifluoroacetic anhydride gave 4-trifluoromethylpyrazoles **14** (Scheme 6) [6]. The reaction mechanism is shown in Scheme 7.

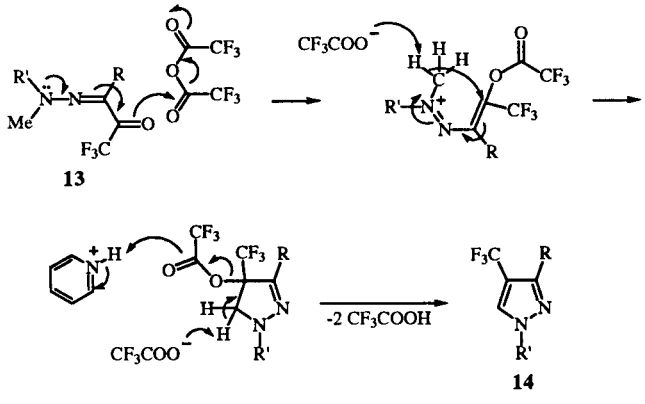
2-5. 5-Fluoropyrazoles and 1-Fluoromethylpyrazoles.

Fluorination of the 1-methylpyrazole-4-carboxylates **15a,b** with poly(hydrogen fluoride)/pyridine/triethylamine

Scheme 6

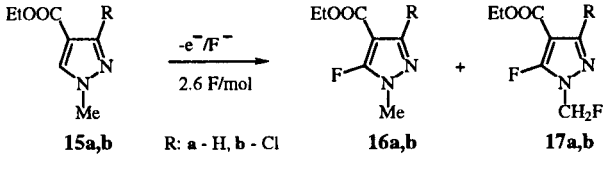


Scheme 7



complex under electrolytic anodic oxidation gave 5-fluoro-1-methylpyrazole-4-carboxylates **16a,b** and 5-fluoro-1-fluoromethylpyrazole-4-carboxylates **17a,b** (Scheme 8) [7]. Various reaction conditions and subsequent yields are described in the original paper [7].

Scheme 8



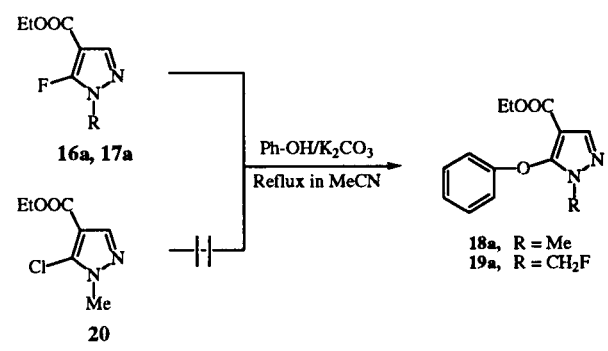
The reaction of C_5-fluoro derivatives **16a** and **17a** with phenolate anion provided the C_5-phenoxy derivatives **18a** and **19a**, respectively, while the C_5-chloro analogue **20** was not reactive to phenolate anion (Scheme 9) [7].

The reaction of the 1-hydroxymethylpyrazole-4-carboxylate **21** with cesium fluoride (4 equivalents)/methanesulfonyl fluoride (2 equivalents)/18-crown-6 (1 equivalent) afforded the 1-fluoromethylpyrazole-4-carboxylate **22** (Scheme 10) [8].

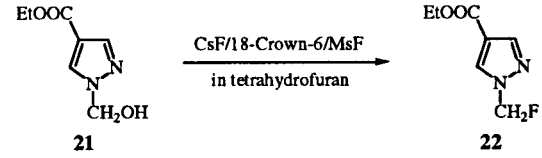
2-6. Reactivity of 4-Isopropylidene-2-pyrazolin-5-ones.

The reaction of the 4-arylidene **23a** or 4-isopropylidene **23b** derivatives of 1-aryl-3-methyl-2-pyrazolin-5-ones with 2,4-dinitrophenylhydrazine gave the 1-aryl-3-methyl-2-pyrazolin-5-one **24** and the 2,4-dinitrophenylhydrazone **25a** or **25b**, respectively (Scheme 11) [9]. The reaction of

Scheme 9

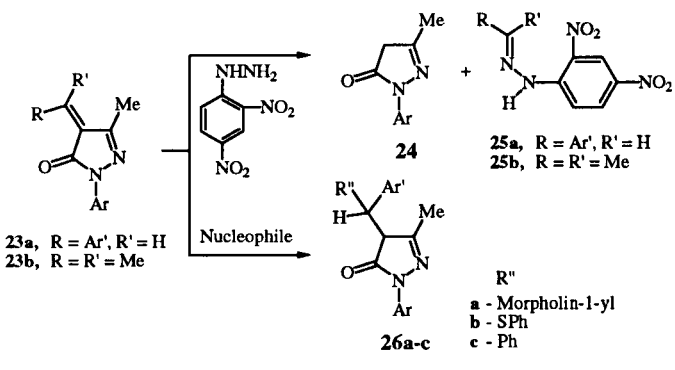


Scheme 10



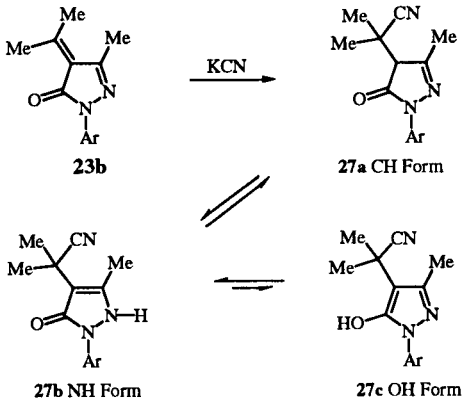
the 4-arylidene derivative **23a** with morpholine, thiophenol, and phenylmagnesium bromide afforded the adducts **26a-c**, respectively, while the reaction of the 4-isopropylidene derivative **23b** with thiol derivatives did not produce any adduct presumably due to a steric hindrance. On the other hand, the reaction of the 4-isopropylidene derivative **23b** with potassium cyanide provided the cyano derivative **27**, which was found to exist as the CH form **27a** and NH form **27b** in deuteriochloroform and as the NH form **27b** in deuteriodimethyl sulfoxide from the nmr spectral data (Scheme 12, Table). The OH form **27c** did not occur in either solvents.

Scheme 11



The reaction of the 4-isopropylidene derivative **23b** with hydrogen peroxide or *m*-chloroperbenzoic acid gave the spiroepoxides **28** and **29** (Scheme 13). The reaction of compound **28** with *m*-chloroperbenzoic acid did not afford compound **29**, so that the mechanism from compound **23b** to **29** was proposed as shown in Scheme 14.

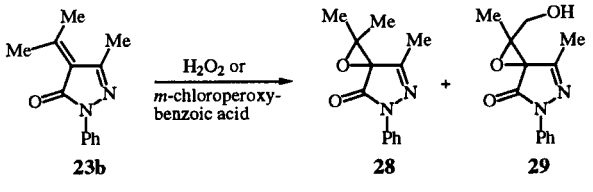
Scheme 12



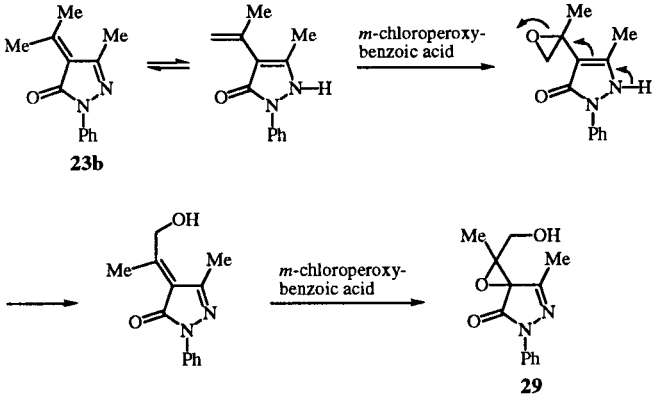
Table

Solvent	Tautomer Ratio (%) CH Form	NH Form	OH Form
dimethyl-d_6-sulfoxide	----	100	----
deuteriochloroform	63	37	----

Scheme 13



Scheme 14



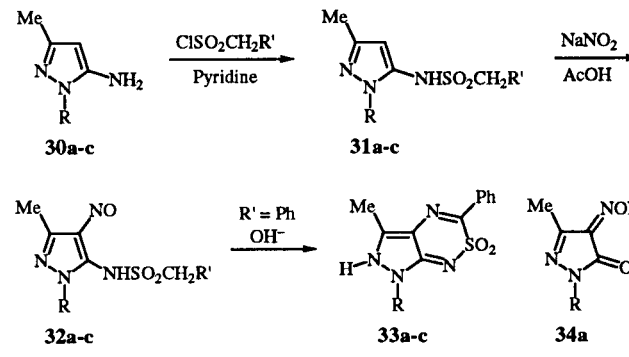
3. Synthesis of Condensed Pyrazoles.

3-1. Bicyclic Condensed Pyrazoles.

3-1-1. Pyrazolo[3,4-*c*][1,2,5]thiadiazine 2,2-Dioxides.

The 7-substituted 6*H*-pyrazolo[3,4-*c*][1,2,5]thiadiazine 2,2-dioxides **33a-c** were synthesized from the 1-substituted 5-aminopyrazoles **30a-c** *via* the 5-alkylsulfonamido **31a-c** and 5-alkylsulfonamido-4-nitroso (R' = Ph) **32a-c** derivatives (Scheme 15) [10]. On the other hand, the reaction of

Scheme 15



R: **a** - Ph, **b** - C_6H_4-*M*-Cl, **c** - Me R': H, Me, Ph

the 5-alkylsulfonamido-4-nitroso derivatives **32a-c** (R' = H, Me) with 1*N* sodium hydroxide resulted in hydrolysis to give 4-oximino-5-pyrazolone **34a**. The reaction product was dependent on the nature of the substituent R' linked to the methylene group.

3-1-2. Pyrazolo[3,4-*d*]pyrimidines and Pyrazolo[3,4-*d*]-[1,2,3]triazines.

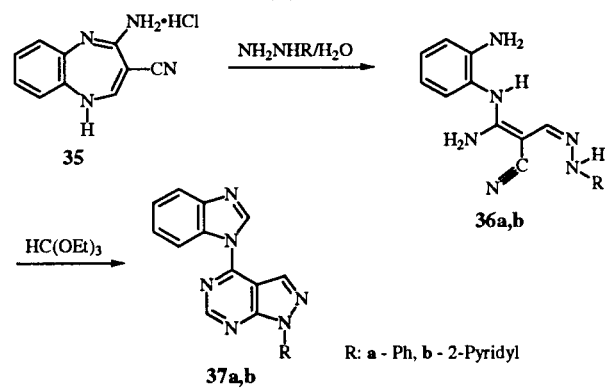
The reaction of the 1,5-benzodiazepine hydrochloride **35** with hydrazines provided the open-chain compounds **36a,b,** whose reaction with triethyl orthoformate gave the 4-(benzimidazol-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidines **37a,b,** respectively (Scheme 16) [11].

The reaction of the 5-aminopyrazoles **38a,b** with triethyl orthoformate afforded the 5-aminopyrazolo[3,4-*d*]pyrimidines **39a,b,** whose reaction with 5-nitro-2-furfural diacetate or 2,5-diethoxytetrahydrofuran provided the Shiff bases **40a,b** or 5-(pyrrol-1-yl) derivatives **41a,b,** respectively (Scheme 17) [12]. The reaction of the 5-aminopyrazoles **42a,b** with nitrous acid gave the pyrazolo[3,4-*d*][1,2,3]-triazines **43a,b.**

3-1-3. Pyrazolo[5,1-*c*]l[1,2,4]triazines from Pyrazole-5-diazonium Salts.

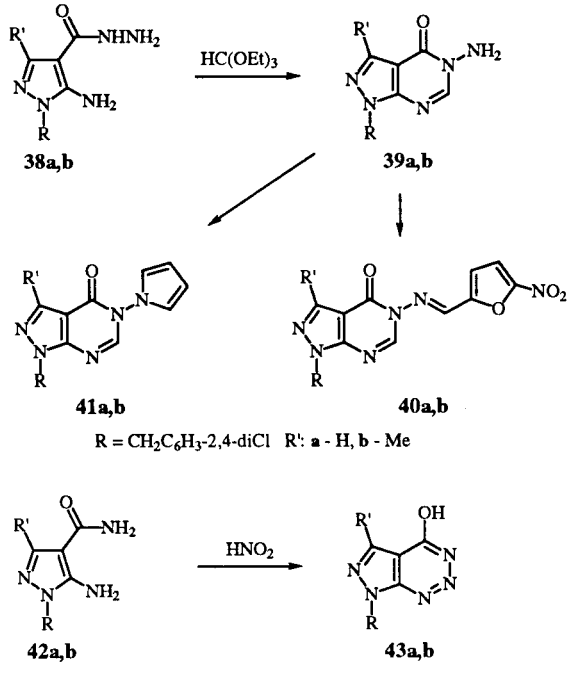
The synthesis of various pyrazolo[5,1-*c*]l[1,2,4]triazines has been summarized in a monograph [13]. Some of these

Scheme 16



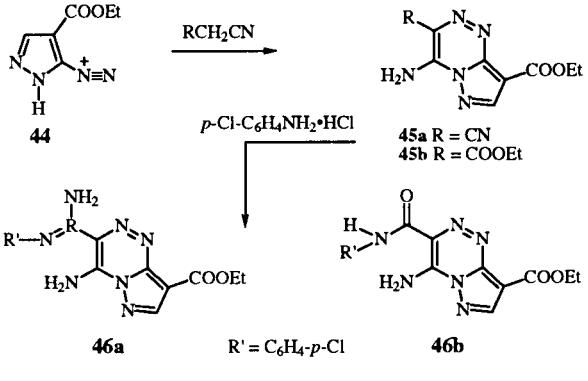
R: **a** - Ph, **b** - 2-Pyridyl

Scheme 17



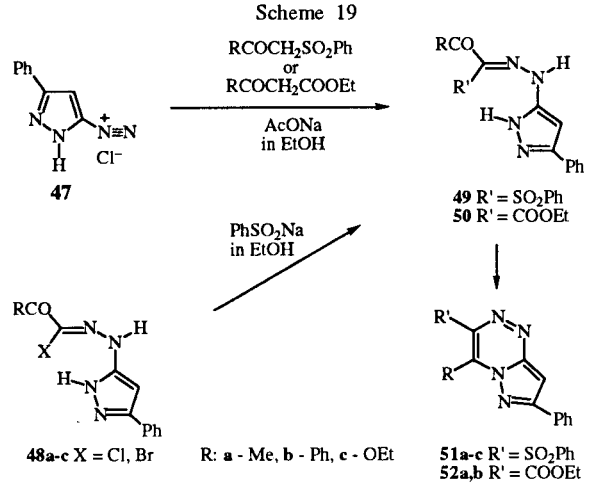
compounds reported by Partridge and Stevens [14] in 1966 were shown to be active inhibitors of tumor growth [14a]. Our review describes the synthesis of pyrazolo[5,1-*c*]-[1,2,4]triazines reported in 1981-1989. The reaction of the pyrazole-5-diazonium salt **44** with active methylene compounds gave the pyrazolo[5,1-*c*][1,2,4]triazines **45a,b** [15], whose reaction with *p*-chloroaniline hydrochloride afforded the 3-amidino **46a** and 3-carbamoyl **46b** derivatives, respectively (Scheme 18) [16].

Scheme 18



The reaction of the pyrazole-5-diazonium chloride **47** with benzenesulfonylacetone, benzenesulfonylacetophenone, and ethyl benzenesulfonylacetate gave the pyrazolo[5,1-*c*][1,2,4]-triazines **51a**, **51b**, and the hydrazone **49c**, respectively (Scheme 19) [17]. Compounds **51a, 51b, and 49c** were also obtained from the reaction of the hydrazidoyl halides **48a-c** with sodium benzenesulfinate, respectively. The reaction of the diazonium chloride **47** with ethyl acetoacetate or ethyl benzoylacetate afforded the hydrazones **50a,b**. Compounds **49c** and **50a,b** were converted into compounds **51c** and **52a,b**, respectively, thermally or under acidic condition.

Scheme 19



Scheme 20

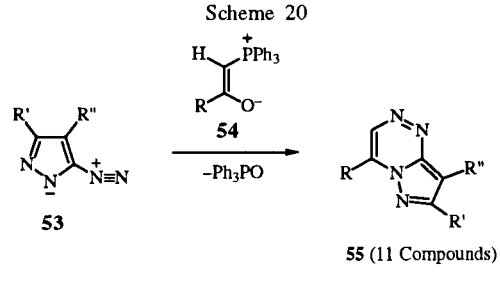
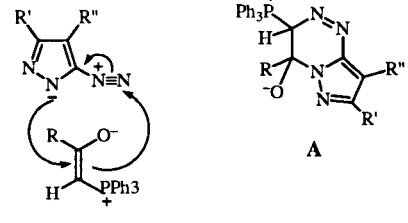


Chart 2

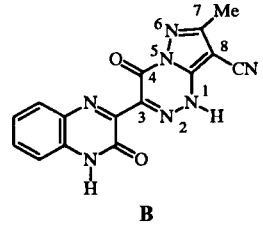


The reaction of the pyrazole-5-diazonium compounds **53** with the phosphonium ylides **54** provided the pyrazolo-[5,1-*c*][1,2,4]triazines **55** (Scheme 20) *via* an intermediate **A** produced by the cycloaddition reaction (Chart 2) [18].

The reaction of the pyrazole-5-diazonium salt **56** with quinoxaline **57** gave the hydrazone **58**, whose reflux in triethylamine/*N*,*N*-dimethylformamide afforded the 3-(quinoxalin-2-yl)-4,6-dihydropyrazolo[5,1-*c*][1,2,4]-triazine **59** (Scheme 21) [19]. Compound **59** existed as the 4,6-dihydro form in a dimethyl sulfoxide solution, which was supported by the NOE between the N_6-H and C_7-Me

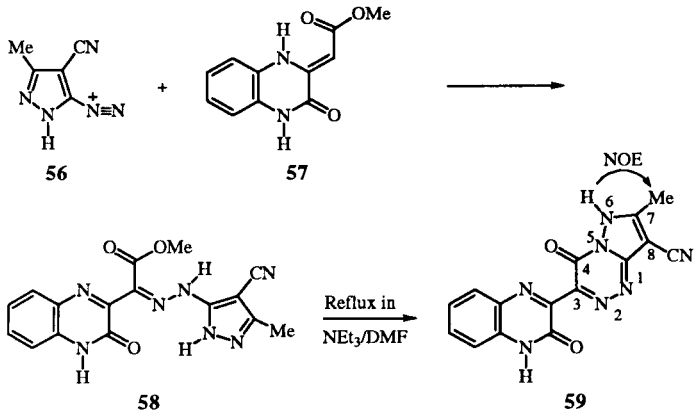
protons. Accordingly, the 1,4-dihydro form **B** (Chart 3) was not preferred in solution.

Chart 3



B

Scheme 21



56 **57** **58** **59**

3-2. Tricyclic Condensed Pyrazoles.

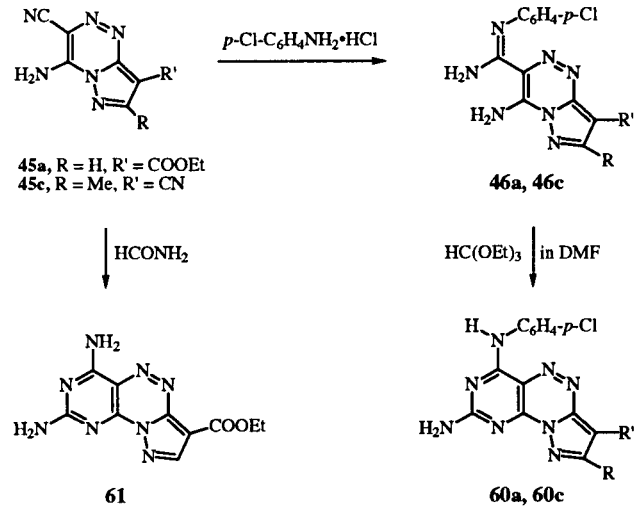
3-2-1. Pyrazolo[5',1':3,4][1,2,4]triazino[5,6-*d*]pyrimidines.

The reaction of the pyrazolo[5,1-*c*][1,2,4]triazines **45a,c** with *p*-chloroaniline hydrochloride gave the 3-amidinopyrazolo[5,1-*c*][1,2,4]triazines **46a,c**, respectively, whose reaction with triethyl orthoformate afforded the pyrazolo[5',1':3,4][1,2,4]triazino[5,6-*d*]pyrimidines **60a,c**, respectively (Scheme 22) [20]. The reaction of compound **45a** with formamide provided the 2,4-diaminopyrazolo[5',1':3,4][1,2,4]triazino[5,6-*d*]pyrimidine **61**. The reaction of the pyrazolo[5,1-*c*][1,2,4]triazine **45d** with hydrazine or phenyl isothiocyanate gave compound **62** or **63**, respectively (Scheme 23) [21].

3-2-2. Pyrazolo[4,3-e][1,2,4]triazolo[4,3-*c*]pyrimidines, Pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines, Pyrazolo[4,3-*e*]tetrazolo[4,5-*c*]pyrimidines, and Pyrazolo[4,3-*e*]imidazo[1,2-*c*]pyrimidines.

The reaction of the 4-hydrazinopyrazolo[3,4-*d*]pyrimidines **64** with triethyl orthoesters, carboxylic acids, and nitrous acid gave the pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **65**, pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidines **66**, and pyrazolo[4,3-*e*]tetrazolo[4,5-*c*]pyrimidines **67**, respectively (Scheme 24) [12]. The pyrazolo[4,3-*e*]imidazo[1,2-*c*]pyrimidine **69a** was synthesized

Scheme 22



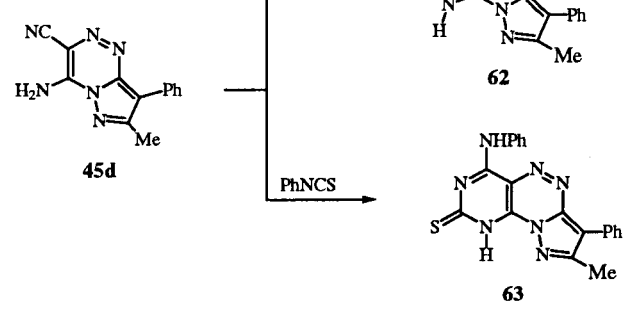
45a, R = H, R' = COOEt
45c, R = Me, R' = CN

46a, 46c

61

60a, 60c

Scheme 23

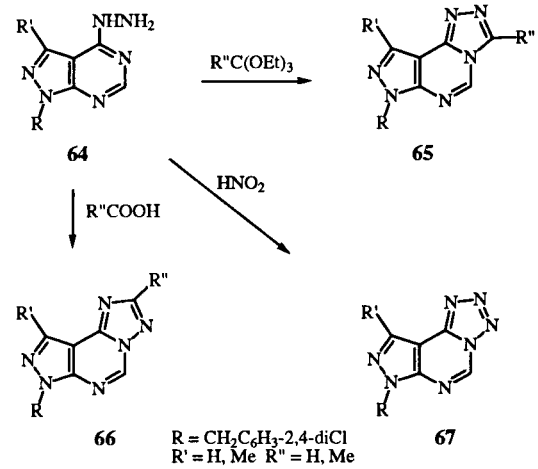


45d

62

63

Scheme 24

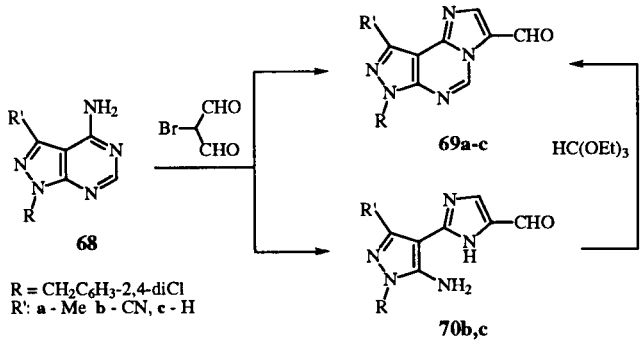


64 **65** **66** **67**

R = $CH_2C_6H_3$-2,4-diCl
R' = H, Me R" = H, Me

by the reaction of the pyrazolo[3,4-*d*]pyrimidine **68a** with bromomalondialdehyde, while the pyrazolo[4,3-*e*]imidazo[1,2-*c*]pyrimidines **69b,c** were obtained *via* the imidazolylpyrazoles **70b,c** (Scheme 25) [12].

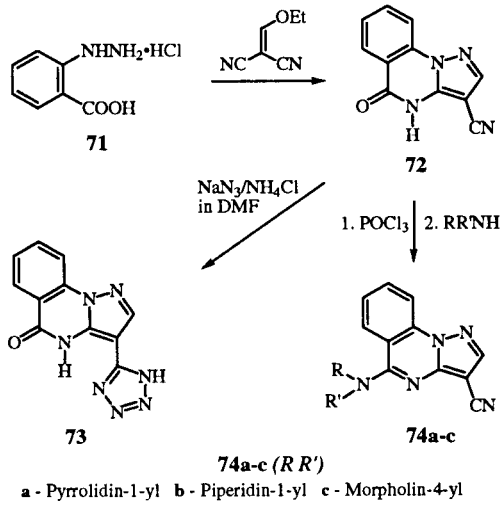
Scheme 25



3-2-3. Pyrazolo[1,5-*a*]quinazolines.

The reaction of 2-hydrazinobenzoic acid **71** with ethoxymethylenernalononitrile gave the pyrazolo[1,5-*a*]-quinazoline-3-carbonitrile **72**, whose reaction with sodium azide afforded the 3-(tetrazol-5-yl)pyrazolo[1,5-*a*]quinazoline **73** (Scheme 26) [22]. The reaction of compound **72** with phosphoryl chloride and then secondary amines provided the 5-substituted pyrazolo[1,5-*a*]quinazoline-3-carbonitriles **74a-c**.

Scheme 26



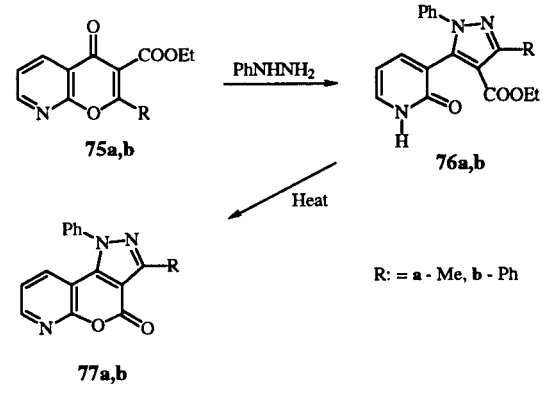
3-2-4. Pyrazolo[3',4':4,5]pyrano[2,3-*b*]pyridines.

The reaction of 4-oxopyrano[2,3-*b*]pyridine-3-carboxylates **75a,b** with phenylhydrazine gave the 5-(pyridin-3-yl)pyrazole-4-carboxylates **76a,b,** whose heating at the respective melting points provided the pyrazolo[3',4':4,5]-pyrano[2,3-*b*]pyridin-4-ones **77a,b** (Scheme 27) [23].

3-2-5. Pyrazolo[4,3-*c*]quinolin-4-ones.

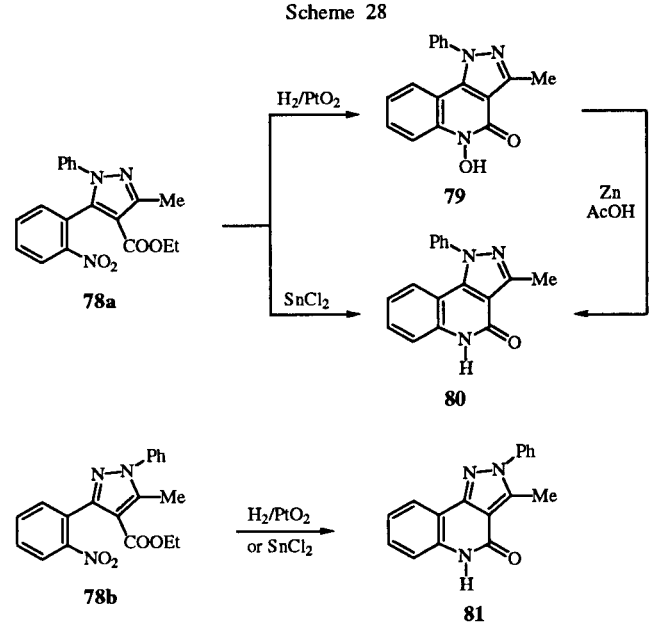
The reductive cyclization of the 5-(*o*-nitrophenyl)pyrazole **78a** with hydrogen/platinum oxide or stannous chloride gave the 5-hydroxypyrazolo[4,3-*c*]quinoline **79** or pyrazolo[4,3-*c*]-quinoline **80**, respectively [24]. The reduction of compound

Scheme 27



79 with zinc powder/acetic acid afforded compound **80**. The reduction of the 3-(*o*-nitrophenyl)pyrazole **78b** with hydrogen/platinum oxide or stannous chloride provided the pyrazolo[4,3-*c*]quinoline **81** (Scheme 28).

Scheme 28

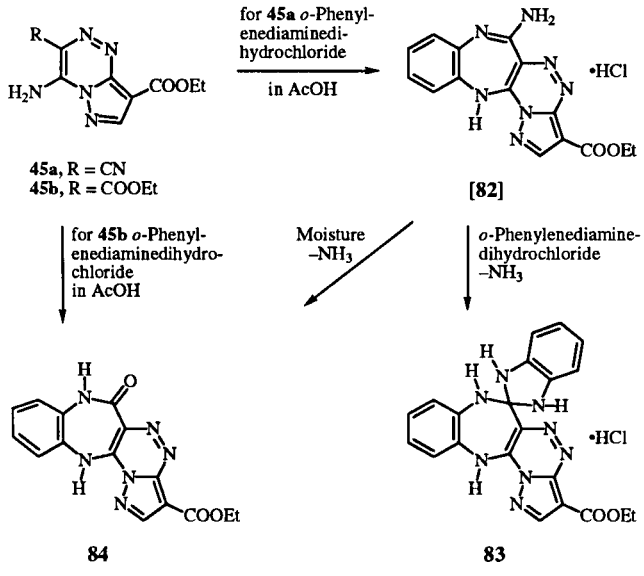


3-3. Tetracyclic Condensed Pyrazoles.

3-3-1. Pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepines.

The reaction of the pyrazolo[5,1-*c*][1,2,4]triazine-3-carbonitrile **45a** with *o*-phenylenediamine dihydrochloride gave the spiro[benzimidazole-6,2'-pyrazolo[1',5':3,4][1,2,4]-triazino[5,6-*b*][1,5]benzodiazepine hydrochloride **83** and pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzodiazepine **84** *via* an intermediate **82** (Scheme 29) [15,16]. Compound **84** was also obtained by the reaction of the pyrazolo[5,1-*c*]-[1,2,4]triazine-3-carboxylate **45b** with *o*-phenylenediamine dihydrochloride.

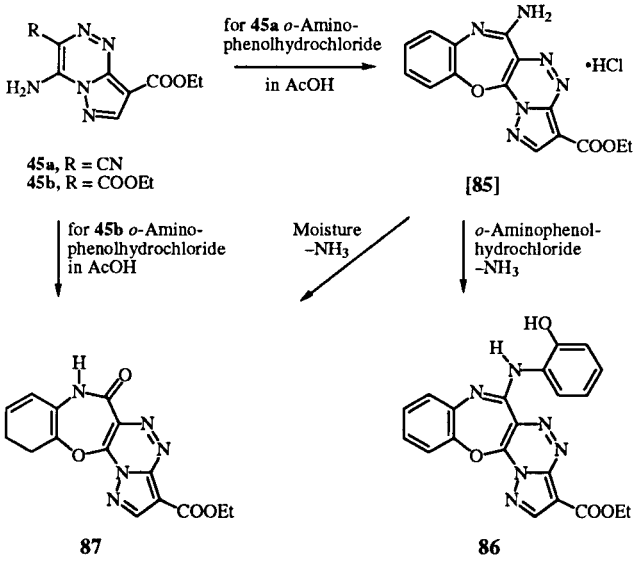
Scheme 29



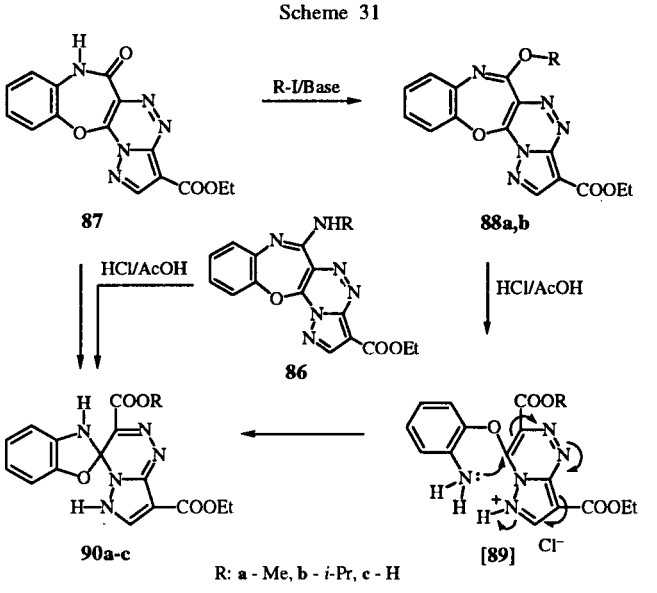
3-3-2. Pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines.

The reaction of the pyrazolo[5,1-*c*][1,2,4]triazine-3-carbonitrile **45a** with *o*-aminophenol hydrochloride gave the pyrazolo[1',5':3,4][1,2,4]triazino[5,6-*b*][1,5]benzoxazepines **86** and **87** *via* an intermediate **85** (Scheme 30) [25,26]. Compound **87** was also obtained by the reaction of the pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate **45b** with *o*-aminophenol hydrochloride. The alkylation of compound **87** with alkyl iodide/base afforded the *O*-alkyl derivatives **88a,b**, whose reflux in hydrochloric acid/acetic acid resulted in ring transformation to provide the spiro-[benzoxazole-2'(3*H*),4(1*H*)pyrazolo[5,1-*c*][1,2,4]triazines] **90a,b** (Scheme 31) [25,26]. Cbmpounds **86** and **87** were also transformed into compound **90c** under a similar condition to the above.

Scheme 30



Scheme 31



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