Synthesis of Pyrazoles and Condensed Pyrazoles

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This review introduces the synthesis of various pyrazoles reported by us and some other research groups during 1989-1998. Some of papers in this review deal with the development of potent pyrazoles or with the synthesis of potential pyrazoles aiming at agrochemicals and/or drugs.

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This review contains the following contents.

1. Introduction.

In our previous review [2], we described the synthesis of pyrazoles reported by us and some other research groups in 1981-1989. Continuously, this review summarizes the pyrazole syntheses provided by us and several other research groups in 1989-1998. Some research introduced in this review relates to patents or experiments to develop potent pyrazoles as well as studies on a new or efficient method for the synthesis of potential pyrazoles aiming at agrochemicals and/or drugs.

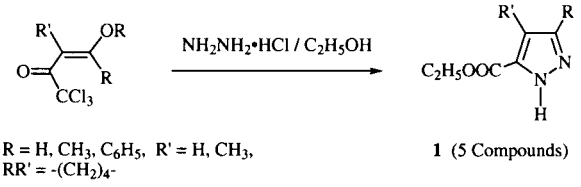
2. Synthesis of Pyrazoles.

2-1. Pyrazoles from β-Alkoxyvinyl Trichloromethyl Ketones.

The reaction of β-alkoxyvinyl trichloromethyl ketones with hydrazine hydrochloride (1.2 equivalents) in ethanol gave ethyl pyrazolecarboxylates **1** in good yields (Scheme 1) (5 compounds, 70-90%) [3]. The advantages of this method are an improved one-pot procedure, ready access to the precursors, high yields, and relatively short reaction times under mild conditions.

The 3(5)-alkoxycarbonylpyrazoles are important intermediates in the preparation of agrochemicals, microbicides, herbicides [3,4], plant growth regulators, and plant protectants [3,5].

Scheme 1



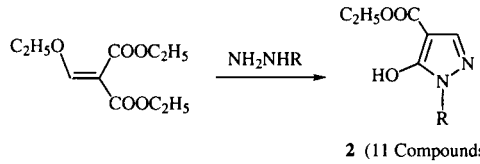
R = H, CH_3, C_6H_5, R' = H, CH_3, RR' = -$(CH_2)_4$-

1 (5 Compounds)

2-2. Pyrazoles from Diethyl Ethoxymethylenemalonate.

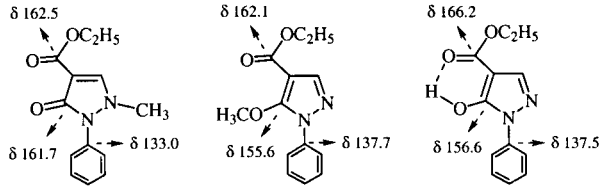
The reaction of diethyl ethoxymethylenemalonate with various hydrazines afforded the 5-hydroxypyrazole-4-carboxylates **2** (Scheme 2), whose 5-hydroxy tautomeric form was supported by the nmr spectral data in deuteriochloroform or deuteriodimethyl sulfoxide solution [6]. From the comparison of the chemical shifts shown in Chart 1, a hydrogen bond between the C_5-hydroxyl group and C_4-ester C=O group was suggested in a deuteriochloroform solution of compound **2a**.

Scheme 2



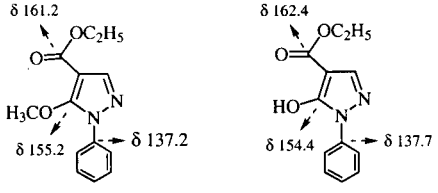
2 (11 Compounds)
R = Aryl, Heteroaryl, SO_2Aryl

Chart 1



3 [a] **4** [a] **2a** [a]

[a] Measured in deuteriochloroform.



4 [b] **2a** [b]

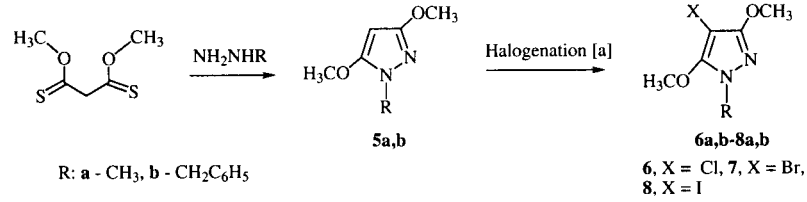
[b] Measured in deuteriodimethyl sulfoxide.

sium iodide afforded the 4-chloro **6a,b**, 4-bromo **7a,b**, and 4-iodo **8a,b** derivatives, respectively (Scheme 3) [7]. The C_4-carbon chemical shifts of the 4-iodo derivatives **8a,b** were considerably shielded [δ 26.6 ppm (**8a**), δ 27.6 ppm (**8b**)] in comparison with other derivatives [δ 70.3 ppm (**5a**), δ 70.8 ppm (**5b**); δ 78.3 ppm (**6a**), δ 79.1 ppm (**6b**); δ 62.4 ppm (**7a**), δ 63.2 ppm (**7b**)].

2-4. Pyrazoles from Ethyl Ethoxymethylenecyanoacetate.

The ester group of the tetrahydroquinoxaline **9** was hardly converted into the carboxamides **10** in an ordinary reaction with aliphatic and aromatic amines. However, the carboxamides **10** were elaborated from compound **9** *via* compounds **11** and **12**, as follows. The reaction of compound **9** with a 10-fold molar amount of hydrazine hydrate gave the hydrazide **11**, whose reaction with ethyl ethoxymethylenecyanoacetate afforded the 1-acylpyrazole **12** (Scheme 4) [8,9]. The reaction of compound **12** with aniline derivatives provided the carboxamides **10**, wherein the pyrazole moiety was a good leaving group.

Scheme 3



5a,b

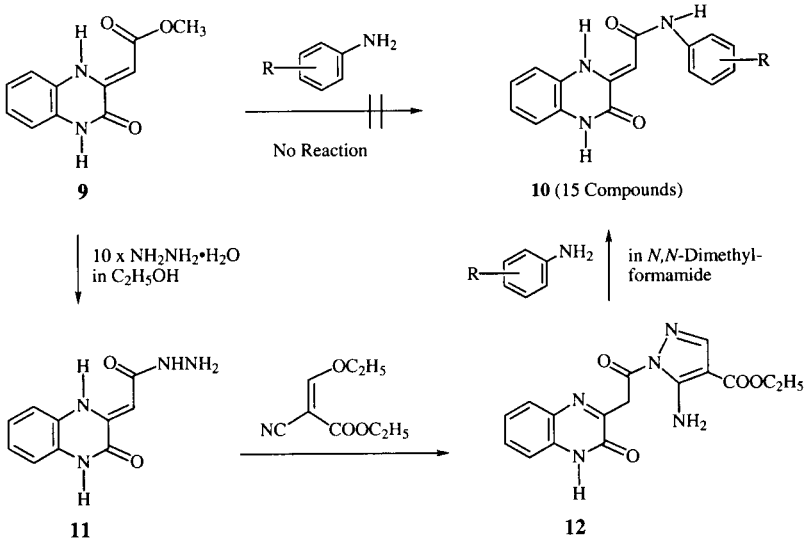
R: **a** - CH_3, **b** - $CH_2C_6H_5$

6a,b-8a,b

6, X = Cl, **7**, X = Br, **8**, X = I

[a] *N*-Chlorosuccinimide/Benzoyl Peroxide, Br_2, or I_2/KI

Scheme 4



9 **10** (15 Compounds)

11 **12**

2-3. Pyrazoles from Dimethyl Dithiomalonate.

The reaction of dimethyl dithiomalonate with methylhydrazine or benzylhydrazine gave 1-methylpyrazole **5a** or 1-benzylpyrazole **5b**, whose reaction with *N*-chlorosuccinimide/benzoyl peroxide, bromine, and iodine/potas-

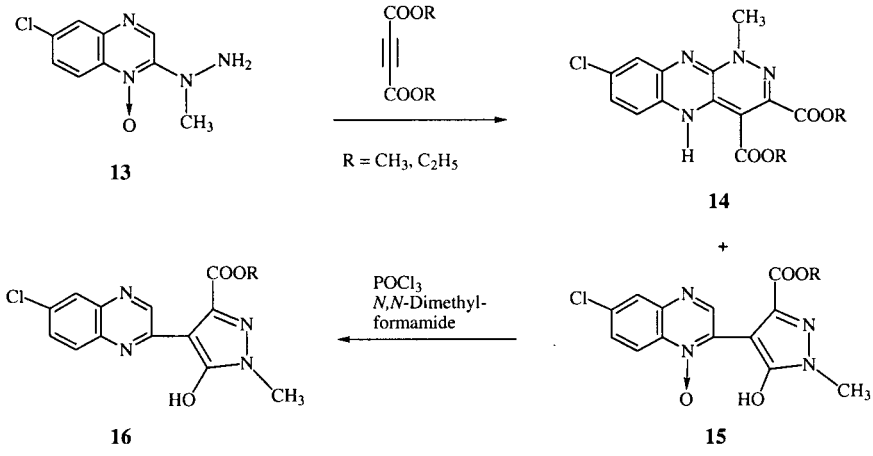
2-5. Pyrazoles from Acetylenedicarboxylates.

The reaction of the quinoxaline *N*-oxide **13** with acetylenedicarboxylates gave the pyridazino[3,4-*b*]quinoxalines **14** and 2-(pyrazol-4-yl)quinoxaline *N*-oxides **15** (Scheme 5) [10]. The reaction of compounds **15** with phosphoryl

chloride/*N,N*-dimethylformamide resulted in deoxygenation to provide compounds **16**. Concerning the tautomeric structure of the pyrazole moiety, compounds **15** and **16** were supported to exist as the 5-hydroxy form, but not as the 5-oxo form, from the nmr spectral data. The mechanism for the formation of compounds **15** is shown in Scheme 6.

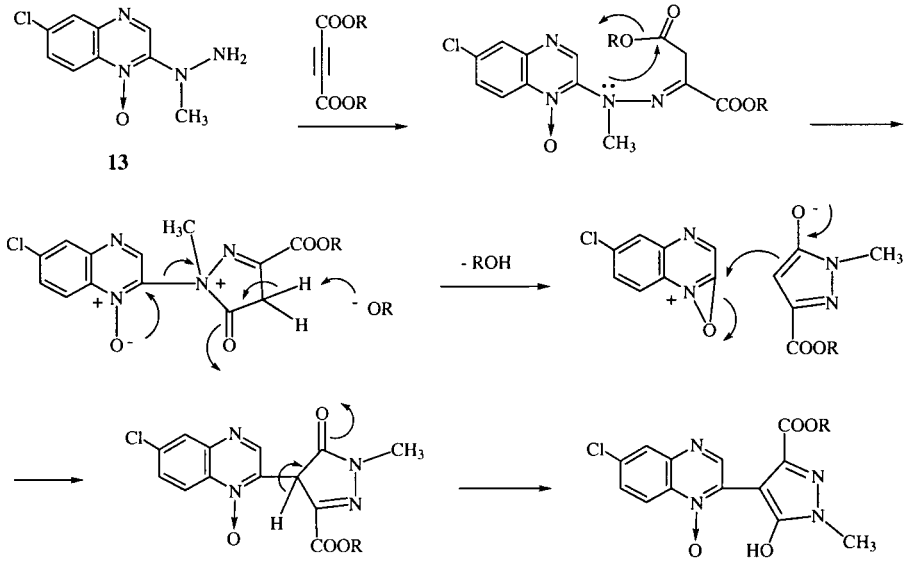
The reaction of the 5-unsubstituted pyrazoles **18** with lithium diisopropylamide or *n*-butyllithium gave the 5-lithio intermediate **19**, whose reaction with sulfur dioxide afforded the lithium pyrazole-5-sulfinates **20** (Scheme 7) [12]. Subsequent reaction of the lithium sulfinates **20** with *N*-chlorosuccinimide followed by ammonolysis

Scheme 5



13 14 + 16 15

Scheme 6

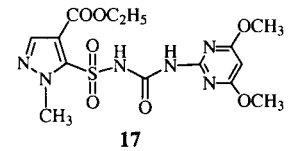


13 15

2-6. Pyrazole-5-sulfonamides from C_5-Unsubstituted Pyrazoles.

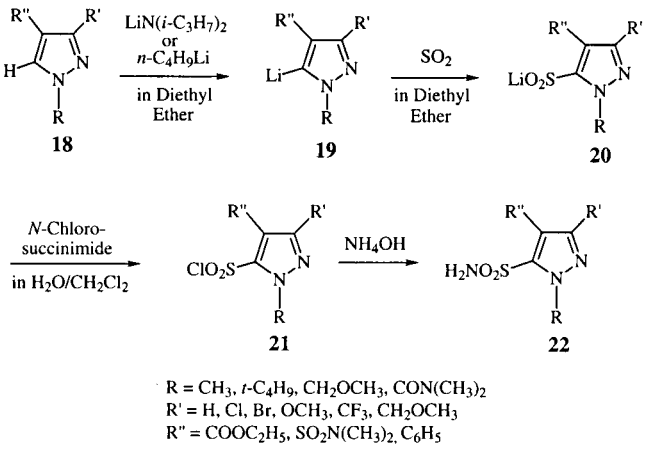
Pyrazosulfron-ethyl **17** (Chart 2) (developed and patented by Nissan Chemical Industries, Ltd.) is a potent and selective herbicide for paddy weeds without phytotoxicity to the rice plant [11]. In order to improve a method for the synthesis of pyrazosulfron-ethyl **17**, a new route to pyrazole-5-sulfonamides **22** was devised as follows.

Chart 2



17

Scheme 7



provided the pyrazole-5-sulfonamides **22** *via* the sulfonyl chlorides **21**.

2-7. 1-Fluoromethylpyrazoles and 1-Fluoromethylpyrazole-5-sulfonamides.

In continuation of the above works, further research was carried out to prepare the 1-difluoromethylpyrazole **24**, 1-trifluoromethylpyrazole **26**, 1-fluoromethyl-, 1-difluoromethyl-, and 1-trifluoromethylpyrazole-5-sulfonamides **28a-c** leading to the synthesis of the fluorinated pyrazosulfron-ethyl analogues **29a-c** in the expectation of improvement of biological activity.

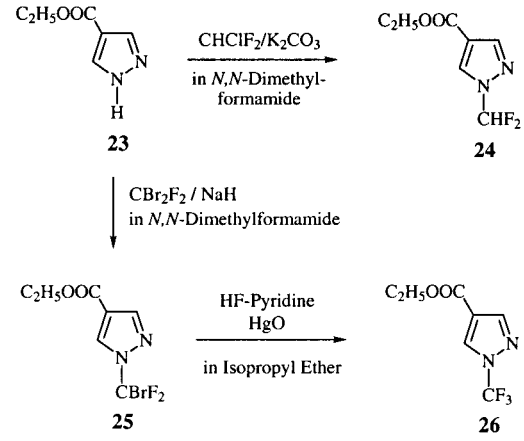
The reaction of the pyrazole-4-carboxylate **23** with difluorocarbene gave the 1-difluoromethylpyrazole-4-carboxylate **24**, while the reaction of compound **23** with dibromodifluoromethane/sodium hydride afforded the 1-bromodifluoromethylpyrazole-4-carboxylate **25** whose reaction with poly(hydrogen fluoride)pyridine/mercuric oxide provided the 1-trifluoromethylpyrazole-4-carboxylate **26** (Scheme 8) [13].

The 1-monofluoromethyl **27**, 1-difluoromethyl **24**, and 1-trifluoromethyl **26** derivatives were converted into the 1-monofluoromethyl-, 1-difluoromethyl-, and 1-trifluoromethyl-5-sulfamoylpyrazole-4-carboxylates **28a-c**, respectively (Scheme 9) [13], by the procedure shown in Scheme 7. Compounds **28a-c** were converted into the monofluoromethyl, difluoromethyl, and trifluoromethyl analogues **29a-c** of pyrazosulfron-ethyl.

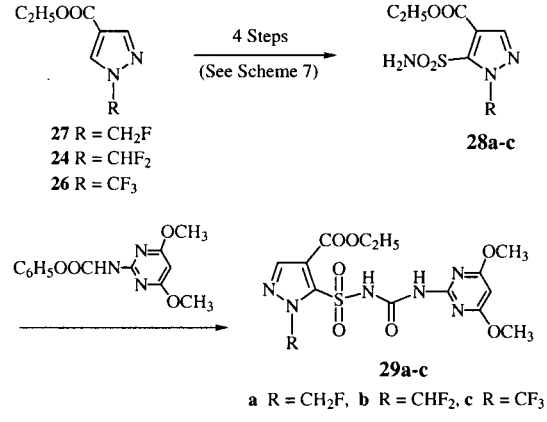
2-8. 1-(4-Fluorophenyl)pyrazoles.

The pyrazole-3-carboxylic acid **31** was synthesized from the acetophenone **30** by 4 steps (Scheme 10) [14]. The reaction of compound **31** with phosphorus pentachloride and then ammonia gave the pyrazole-3-carboxamide **32**, whose reaction with methanesulfonyl chloride/pyridine afforded 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile **33** (developed by Fujisawa Pharmaceutical Co., Ltd.), which is an antiinflammatory

Scheme 8



Scheme 9

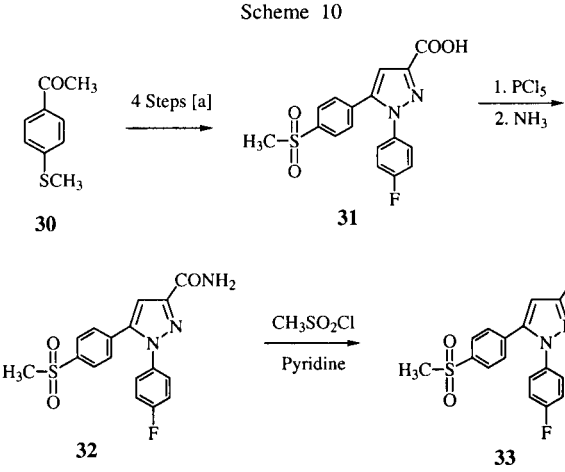


agent with fewer side effect than existing nonsteroidal antiinflammatory drugs.

2-9. Pyrazoles by Ring Transformation.

The reaction of the 1,2,4-oxadiazolylmethylenedioxolanes **34a-d** with 2-hydroxyethylhydrazine gave the

Scheme 10

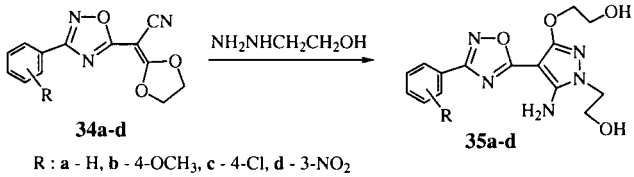


4-(1,2,4-oxadiazol-5-yl)pyrazoles **35a-d**, respectively (Scheme 11) [15].

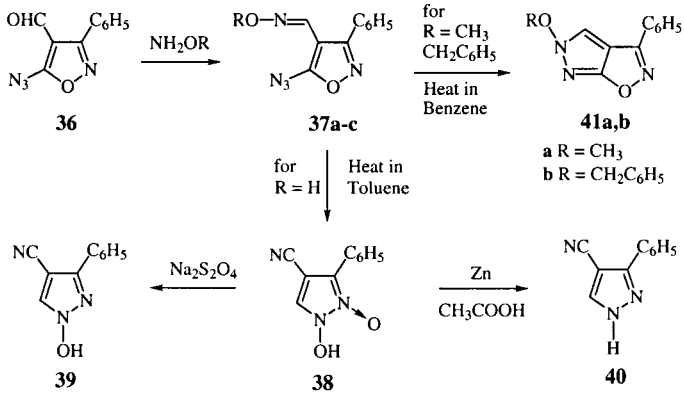
The reaction of the 5-azidoisoxazole **36** with methoxylamine hydrochloride, *O*-benzylhydroxylamine hydrochloride, and hydroxylamine hydrochloride in pyridine afforded the 5-azidoisoxazole-4-carbaldehyde *O*-methyloxime **37a**, *O*-(phenylmethyl) oxime **37b**, and oxime **37c**, respectively (Scheme 12) [16]. Reflux of compound **37c** (R = H) resulted in ring transformation to provide the 1-hydroxypyrazole-4-carbonitrile 2-oxide **38**, whose reduction with sodium hydrosulfite or zinc/acetic acid gave the deoxygenated pyrazole **39** or **40**, respectively. On the other hand, the thermolysis of compound **37a** (R = CH_3) afforded the pyrazolo[4,3-*d*]isoxazole **41a**, while the thermolysis of compound **37b** (R = $CH_2C_6H_5$) provided the pyrazolo[4,3-*d*]isoxazole **41b** and pyrazole **40**.

Moreover, the thermolysis of the hydrazone **42** gave the pyrazolo[4,3-*d*]isoxazole **43** and pyrazole 2-oxide **44** (Scheme 13) [16]. The reduction of compound **44** with zinc/acetic acid afforded the deoxygenated pyrazole **45**. Concerning the reaction mechanism, the nitrene **46** or open-chain species **47** was speculated to be an intermediate from isoxazole to the pyrazolo[4,3-*d*]isoxazole or to the pyrazole 2-oxide (Chart 3) [16].

Scheme 11



Scheme 12



Heating of the dichloropyridazine **48** in sodium hydride/-*N*,*N*-dimethylformamide effected ring transformation to give the 5-(quinoxalin-2-yl)pyrazole **49** (Scheme 14) [17].

The reaction of the 5-hydroxyimino-4-oxothiophene-3-carboxylates **50a-c** with methylhydrazine, phenylhydrazine, and *t*-butylhydrazine gave the 3-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylates **51a-c** or 5-(*N*-hydroxyaminothiocarbonyl)-1*H*-pyrazole-4-carboxylates **52b,c** (Scheme 15) [18]. The detailed reaction mechanisms are shown in the original paper.

Scheme 13

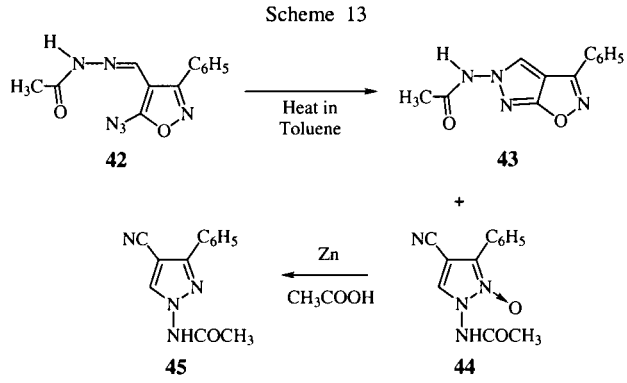
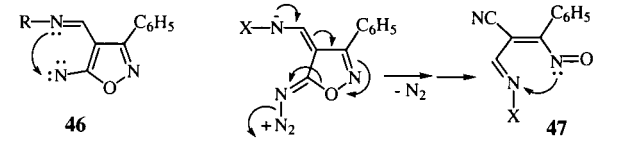
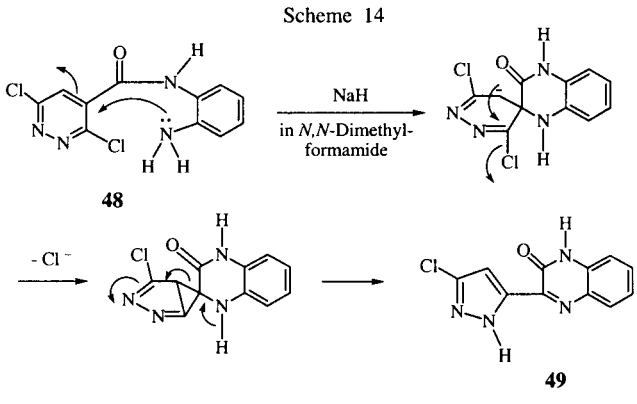


Chart 3



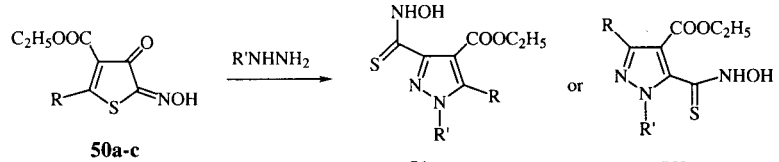
Scheme 14



2-10. Modification of Pyrazoles in Side Chain.

The reaction of the 1-aryl-1*H*-pyrazole-4-methanols **53a-j** with hydrobromic acid/acetic acid and then with potassium cyanide gave the 1-aryl-1*H*-pyrazole-4-acetonitriles **54** and 5-substituted 4-methyl-1-phenyl-1*H*-pyrazole-3-carbonitriles **55** (Scheme 16) [19]. When the substituent R is H or *t*-butyl group, only the 4-acetonitrile **54** or 3-carbonitrile **55** is obtained, respectively. When the substituent R is other groups shown in Scheme 16, mixtures of the 4-acetonitrile **54** and 3-carbonitrile **55** are found to be produced from the nmr spectral data. Compounds **54a,b,f,h-j** and **55c-i** were isolated, and the 1-aryl-1*H*-pyrazole-4-acetic acids **56a,b,i,j** and 1-phenyl-1*H*-pyrazole-3-carboxylic acid **57** were obtained by alkaline hydrolysis. The original paper [19] exhibits the species **58** as an intermediate to the 3-carbonitriles **55**.

Scheme 15



50a-c

a H
b CH_3
c C_6H_5

51a-c

a R = H, R' = CH_3, C_6H_5, t-C_4H_9
b R = R' = CH_3
c R = C_6H_5, R' = CH_3

52b,c

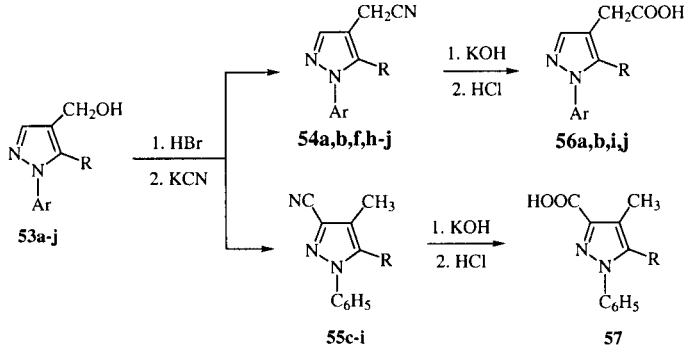
b R = CH_3, R' = C_6H_5
c R = R' = C_6H_5

Compounds **56a,b,i,j** exhibited appreciable analgesic properties, and compound **57** showed a statistically significant antiinflammatory activity.

The reaction of the 5-aminopyrazoles **59** with thiophosgene provided the 5-isothiocyanatopyrazoles **60**, whose reaction with methylhydrazine or phenylhydrazine gave the 2-substituted 4-(pyrazol-5-yl)thiosemicarbazides **61** (Scheme 17) [20]. The reaction of compounds **61** with formic acid/acetic anhydride or triethyl orthoacetate/acetic anhydride afforded the 4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **62**.

Compounds **62** have been synthesized as lead molecules to be explored as potential herbicides, and biological tests of compounds **62** are in progress, according to the original paper [20].

Scheme 16



53a-j

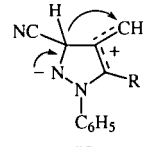
54a,b,f,h-j

55c-i

56a,b,i,j

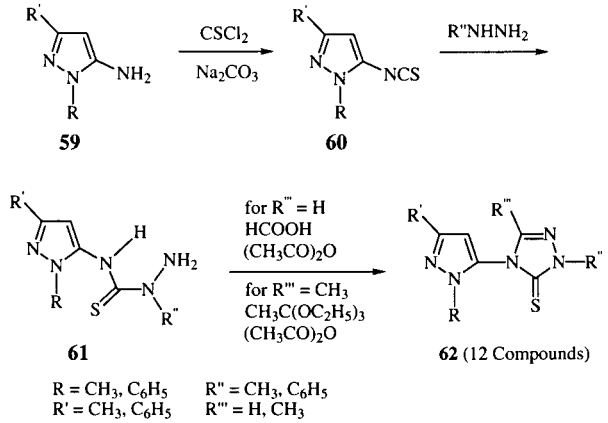
57

	Ar	R
a	C_6H_5	H
b	C_6H_4-4-F	H
c	C_6H_5	CH_3
d	C_6H_5	C_2H_5
e	C_6H_5	$(CH_2)_2CH_3$
f	C_6H_5	$CH(CH_3)_2$
g	C_6H_5	$C(CH_3)_3$
h	C_6H_5	$CH_2C_6H_5$
i	C_6H_5	C_6H_5
j	C_6H_4-4-F	C_6H_5



58

Scheme 17



59

60

61

R = CH_3, C_6H_5
R' = CH_3, C_6H_5
R" = CH_3, C_6H_5
R"' = H, CH_3

62 (12 Compounds)

3. Synthesis of Condensed Pyrazoles.

3-1. Bicyclic Condensed Pyrazoles.

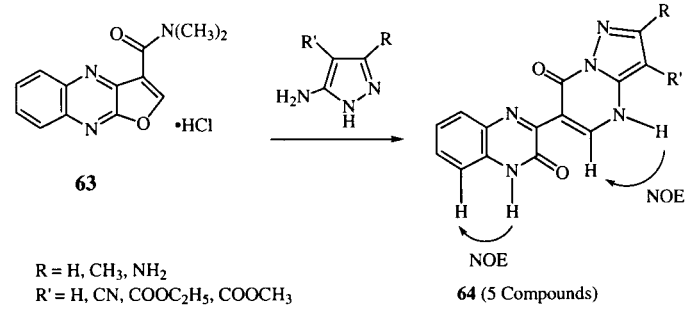
3-1-1. Pyrazolo[1,5-*a*]pyrimidin-7-ones.

The reaction of the furo[2,3-*b*]quinoxaline hydrochloride **63** with some 5-aminopyrazole derivatives in pyridine/1-butanol resulted in ring transformation to give the 6-(quinoxalin-2-yl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ones **64** (Scheme 18) [21,22]. Compounds **64** were found to occur as the 4,7-dihydro-7-oxo form **65**, but not as the 1,7-dihydro-7-oxo form **66** or 7-hydroxy form **67** (Chart 4), which was supported by the NOE spectral data between the N_4-H and C_5-H protons [NOE (2.3-5.5%) measured in deuteriodimethyl sulfoxide].

Pyrazolo[1,5-*a*]pyrimidines **70a-f** were synthesized from the interest in physiological and biological activities [23,24].

The reaction of 5-amino-3-arylpyrazoles **68a-f** with methoxymethylene derivative of Meldrum's acid gave the 5-pyrazolylaminomethylene derivatives of Meldrum's acid **69a-f**, whose reflux in nitrobenzene to afford the pyrazolo-[1,5-*a*]pyrimidin-7-ones **70a-f**, respectively (Scheme 19) [23]. The selected proton and carbon chemical shifts for compounds **70a-f** are shown in Table, and the detailed proton

Scheme 18

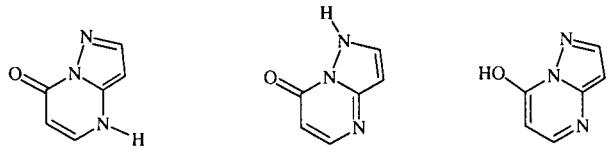


63

R = H, CH_3, NH_2
R' = H, CN, $COOC_2H_5$, $COOCH_3$

64 (5 Compounds)

Chart 4

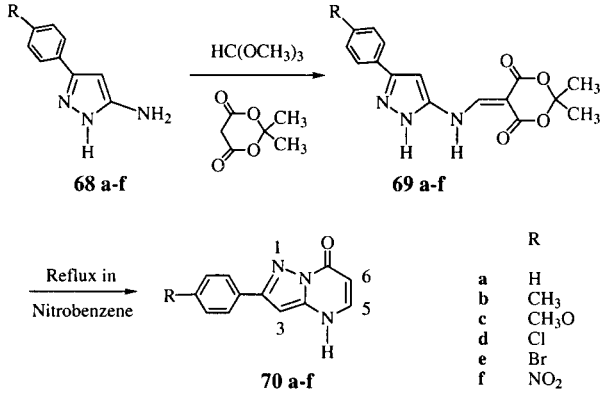


65 4,7-Dihydro-7-oxo Form

66 1,7-Dihydro-7-oxo Form

67 7-Hydroxy Form

Scheme 19



Table

Chemical Shift (δ ppm) for Compounds **70a-f**

C_3 - H	C_5 - H	C_6 - H
6.58-6.71	7.04-7.93	5.71-5.82
C_3	C_5	C_6
96.2-96.7	143.4-148.3	86.4-88.3

and carbon signals for compounds **69** and **70a-f** are shown in the original paper [23].

3-1-2. Pyrazolo[5,1-*b*]thiazoles.

The reaction of the 3-aminorhodanines **71** with ethyl 2-bromo-3,3-diethoxypropionate gave the 2,3-dihydropyrazolo[5,1-*c*]thiazoles **72** *via* a tandem condensation-sulfur extrusion (Scheme 20) [25].

This convenient synthesis was found in continuation of a study to prepare the rhodanine derivatives having some biological activity such as antimicrobial [25, 26], antiinflammatory [25, 27], or antihyperglycemic activity [25, 28].

3-1-3. Pyrazolo[1,5-*a*][1,3]diazepines.

Several pyrazolo[1,5-*a*]pyrimidines have been known to be active on the central nervous system (CNS) [29]. Some pyrazolodiazepines were synthesized herein to evaluate the biological activity in comparison with the above pyrazolo[1,5-*a*]pyrimidines with CNS activity.

The 5-ethylaminopyrazole **74** was synthesized by the acetylation and then reduction of the 5-aminopyrazole **73** (Scheme 21) [30]. The reaction of compound **74** with succinic, maleic, cyclohexanedicarboxylic, and cyclohexenedicarboxylic anhydrides in the presence of 1,3-dicyclohexylcarbodiimide gave the bicyclic and tricyclic pyrazolo[1,5-*a*][1,3]diazepines **75-78**, respectively.

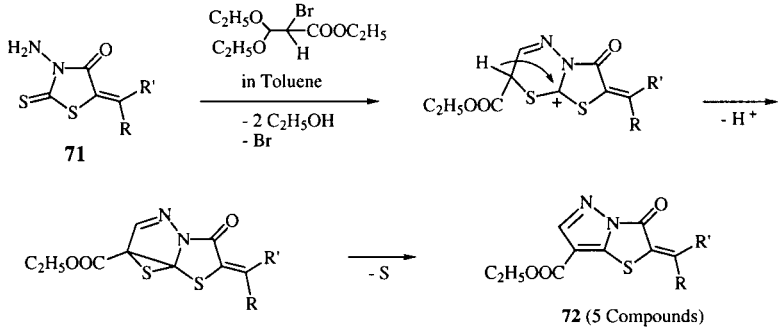
Compounds **75-77** were tested according to the Irwing technique, but none of them showed any particular symptomatology.

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

The reaction of the 3-methoxypyrazoles **79a,b** with chlorotrimethylsilane/sodium iodide in acetonitrile gave the 3-oxopyrazoles **80a,b** (Scheme 22) [31]. The reaction of compound **80b** with formamide gave the pyrazolo-[3,4-*d*]pyrimidine-3,4-dione **81**, which was also obtained by treatment of the 3-methoxypyrazolo[3,4-*d*]pyrimidin-4-one **82** with chlorotrimethylsilane/sodium iodide. The reaction of the 3-methoxypyrazolo[3,4-*d*]pyrimidine **83** or 3-methoxy-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]-pyrimidin-4-one **85** with chlorotrimethylsilane/sodium iodide afforded the pyrazolo[3,4-*d*]pyrimidin-3-one **84** or 1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine-3,4-dione **86**, respectively (Schemes 23, 24) [31].

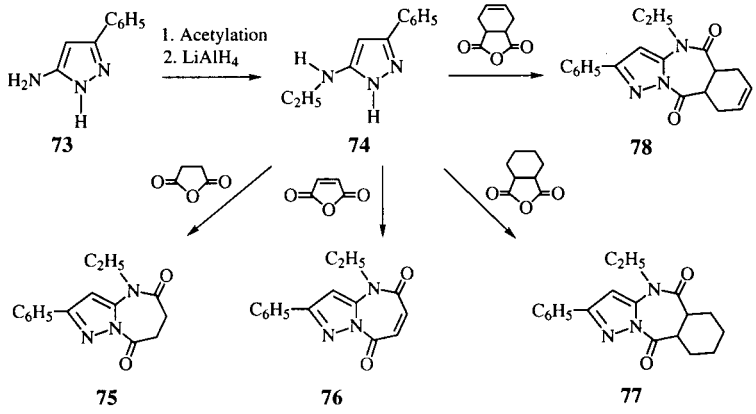
Compounds **81** and **84** and deacetylated derivatives of compounds **85** and **86** were tested *in vitro* for antiviral activity against several virus strains including rhinovirus, influenza, and adenovirus, but no antiviral activity was exhibited.

Scheme 20

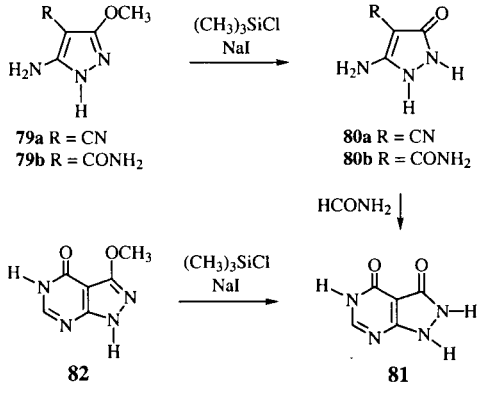


R = $C_6H_4OCH_3$, C_6H_5, $C_6H_4NO_2$, 5-Br-2-Thienyl, CH_3 R' = H, CH_3

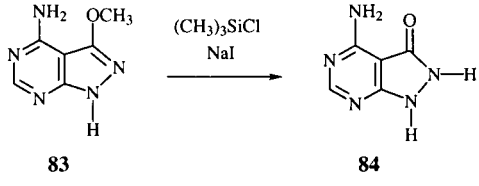
Scheme 21



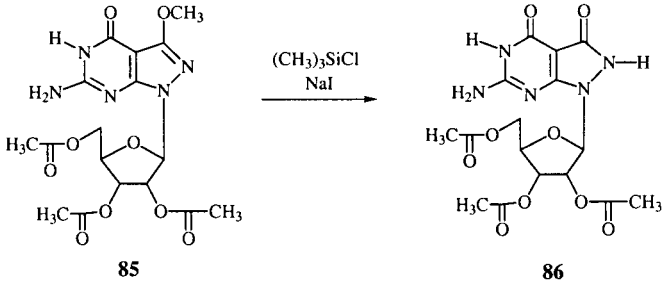
Scheme 22



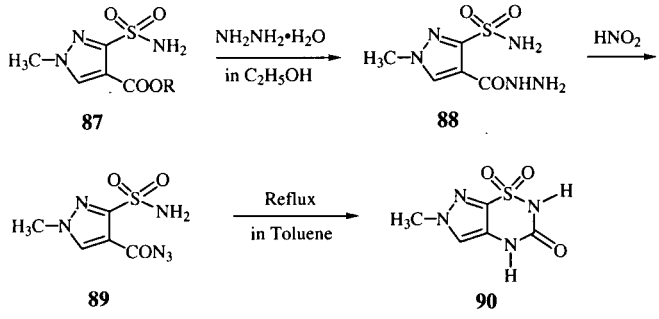
Scheme 23



Scheme 24



Scheme 25



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

The sulfamoylpyrazole-4-carboxylate **87** was converted into the hydrazide **88** and then the azide **89**, whose reflux in toluene provided the 1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*]-[1,2,4]thiadiazine **90** (Scheme 25) [32].

3-2. Tricyclic Condensed Pyrazoles.

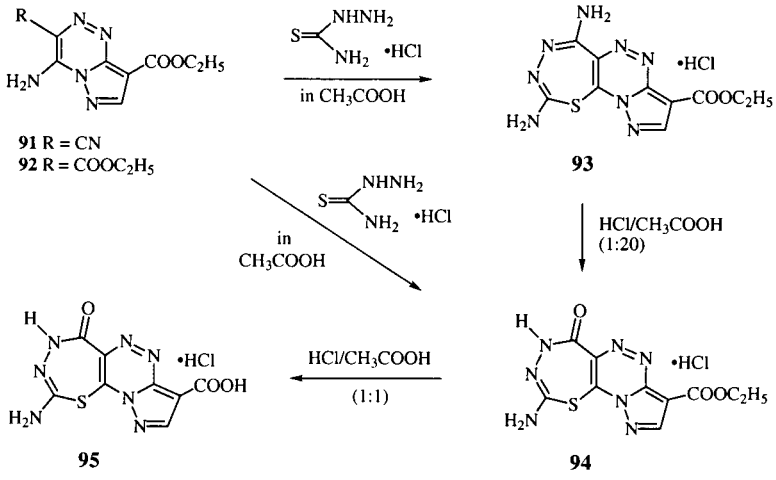
3-2-1. Pyrazolo[5',1':3,4][1,2,4]triazino[6,5-*f*][1,3,4]-thiadiazepines.

The reaction of the pyrazolo[5,1-*c*][1,2,4]triazine **91** or **92** with thiosemicarbazide hydrochloride gave the 2,5-diaminopyrazolo[5',1':3,4][1,2,4]triazino[6,5-*f*][1,3,4]thiadiazepine-8-carboxylate hydrochloride **93** or 2-amino-5-oxopyrazolo[5',1':3,4][1,2,4]triazino[6,5-*f*][1,3,4]-thiadiazepine-8-carboxylate hydrochloride **94**, respectively (Scheme 26) [33]. Hydrolysis of compound **93** or **94** in hydrochloric acid/acetic acid (1:20) or (1:1) afforded compound **94** or 2-amino-5-oxopyrazolo[5',1':3,4][1,2,4]-triazino[6,5-*f*][1,3,4]thiadiazepine-8-carboxylic acid hydrochloride **95**, respectively.

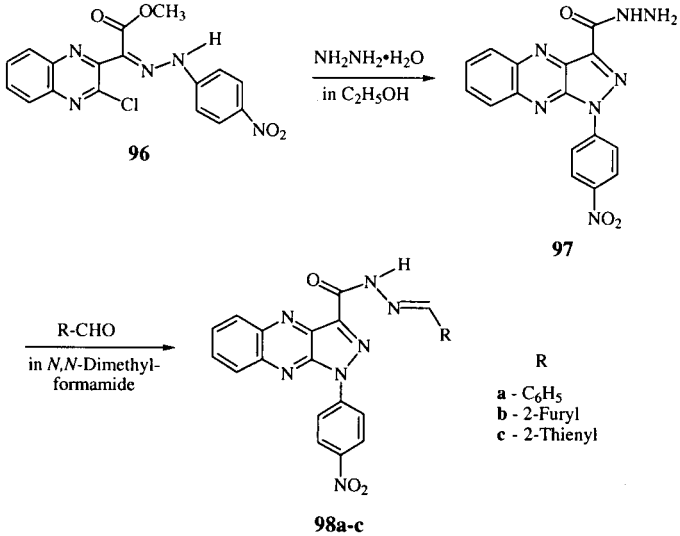
3-2-2. Pyrazolo[3,4-*b*]quinoxalines.

The reaction of the 3-hydrazonomethylquinoxaline **96** with hydrazine hydrate gave the pyrazolo[3,4-*b*]quinoxaline **97**, which was converted into the hydrazone derivatives **98a-c** (Scheme 27) [34].

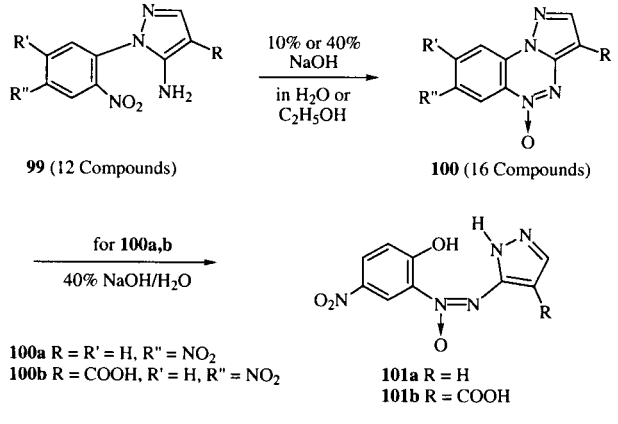
Scheme 26



Scheme 27



Scheme 28



Compound **97** showed a relatively high antibacterial activity, wherein the MIC value was 25 μg/ml against *Bacillus licheniformis* and *Cellulomonas* sp., while compounds **98a-c** did not exhibit any antibacterial activity against the above bacteria.

3-2-3. Pyrazolo[5,1-*c*][1,2,4]benzotriazine 5-Oxides.

The cyclization of the 1-(2-nitrophenyl)-5-aminopyrazoles **99** in sodium hydroxide solution gave the pyrazolo[5,1-*c*]-[1,2,4]benzotriazine 5-oxides **100** (Scheme 28) [35]. When compound **100a** (R = R' = H, R" = NO_2) or **100b** (R = COOH, R' = H, R" = NO_2) was refluxed in 40% sodium hydroxide solution, the 5(3)-(2-hydroxy-5-nitrophenyl-*ONN*-azoxy)pyrazole **101a** or **101b** was obtained respectively.

The original paper describes that a biological investigation of compounds **100** is now in progress to evaluate the affinity for benzodiazepine (BDZ) receptor and the *in vivo* CNS activity.

3-2-4. Pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-4-ones.

From the pharmaceutical interest [36], pyrazolotriazolopyrimidin-4-ones were synthesized as shown below.

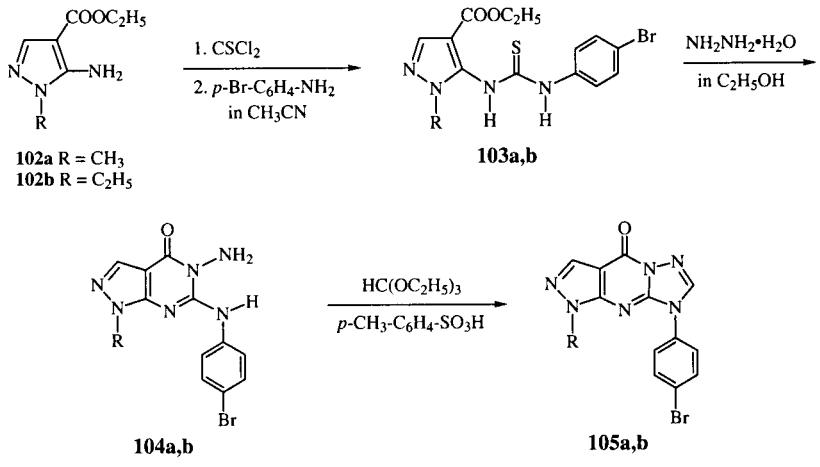
The reaction of the 5-aminopyrazoles **102a,b** with thiophosgene and then *p*-bromoaniline gave the *N*-pyrazolyl-*N'*-arylthioureas **103a,b**, whose reaction with hydrazine hydrate afforded the pyrazolo[3,4-*d*]pyrimidin-4-ones **104a,b** (Scheme 29) [37]. The reaction of compounds **104a,b** with triethyl orthoformate/*p*-toluenesulfonic acid provided the 1-methyl-1*H*- and 1-ethyl-1*H*-pyrazolo[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-4-ones **105a,b**.

The 2-methyl-2*H*- and 2-ethyl-2*H*-pyrazolo[3,4-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-4-ones **109a,b** were also obtained in a similar manner from the 3-aminopyrazoles **106a,b** *via* compounds **107a,b** and **108a,b** (Scheme 30) [37].

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

Pyrazolobenzothiazepines were synthesized in order to develop pharmacologically active compounds with a new ring system.

Scheme 29



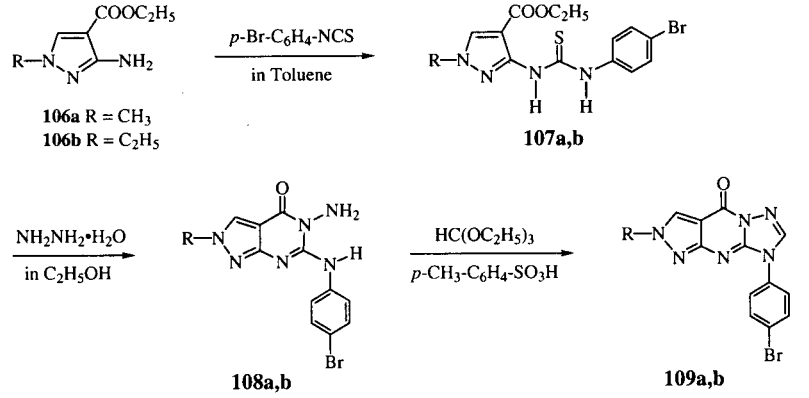
102a R = CH_3
102b R = C_2H_5

103a,b

104a,b

105a,b

Scheme 30



106a R = CH_3
106b R = C_2H_5

107a,b

108a,b

109a,b

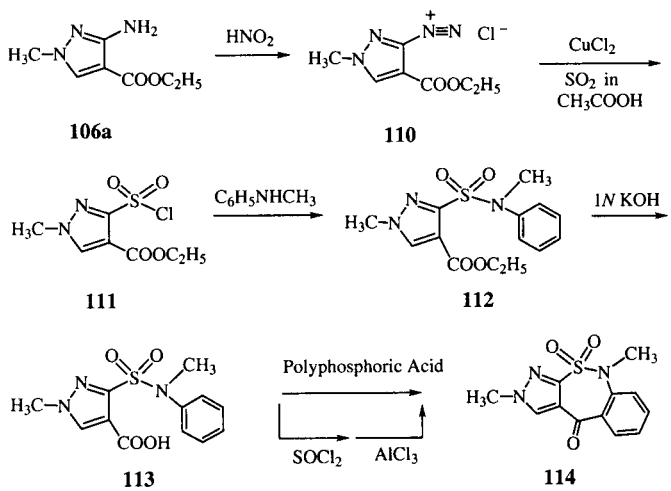
The reaction of the 3-aminopyrazole **106a** with nitrous acid and then sulfur dioxide and cupric chloride in acetic acid gave the 3-chlorosulfonylpyrazole **111** *via* the diazonium salt **110** (Scheme 31) [38]. The reaction of compound **111** with *N*-methylaniline afforded the 3-sulfamoylpyrazole **112**, whose hydrolysis provided the 3-sulfamoylpyrazole-4-carboxylic acid **113**. The reaction of compound **113** with polyphosphoric acid gave the 2*H*-pyrazolo-[3,4-*c*][2,1]benzothiazepine 10,10-dioxide **114**, which was also obtained by the Friedel-Crafts reaction.

The 1*H*-pyrazolo[3,4-*c*][2,1]benzothiazepine 10,10-dioxide **116** was obtained by the same method from 5-aminopyrazole **115** (Scheme 32) [38].

The reaction of compound **116** with alkyl sulfate or alkyl halide in aqueous sodium hydroxide (Method 1) gave the 2-alkyl-2*H*-isomers **114**, **117**, **118** and 1-alkyl-1*H*-isomers **120**, **121**, **122** (Scheme 33) [39], wherein the yields of the 2-alkyl-2*H*-isomers were better than those of the 1-alkyl-1*H*-isomers. Under phase-transfer conditions (Method 2) (aqueous sodium hydroxide/ammonium salt/toluene), the 1-ethyl, 1-benzyl, and 1-phenethyl derivatives were not obtained, but only the 1-methyl derivative was produced. Method 2 provided all the 2-alkyl derivatives **114**, **117**, **118**, **119**.

The structure of the 2-alkyl-2*H*-isomers was differentiated from that of the 1-alkyl-1*H*-isomers by the nmr spectral data (Chart 5). Namely, the NOE was observed between the C_3-H and the methylene protons in compound **117**, while the methylene protons of the N_1-ethyl group

Scheme 31



106a

110

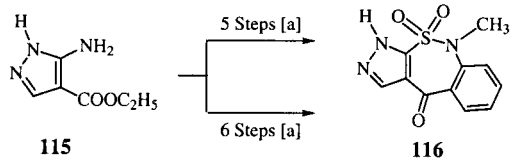
111

112

113

114

Scheme 32



[a] See steps in Scheme 31.

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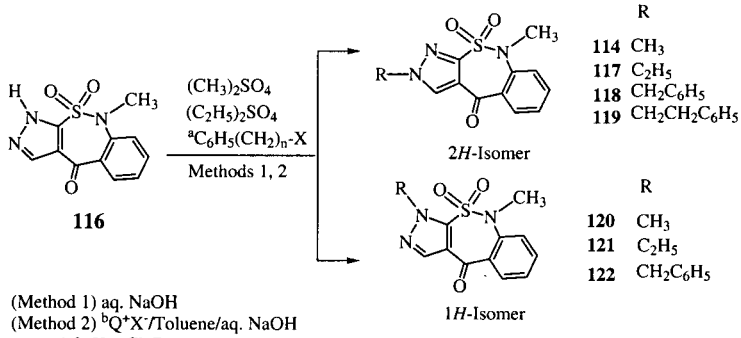
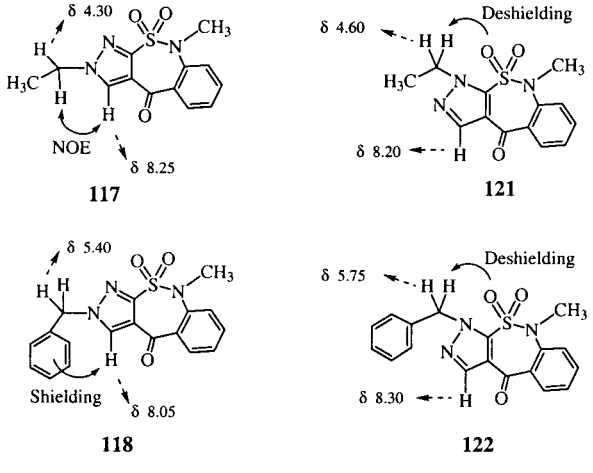
Scbeme 33



(Method 1) aq. NaOH
(Method 2) $^{b}Q^{+}X^{-}$/Toluene/aq. NaOH
a: n = 1,2, X = Cl, Br
b: $Q^{+}X^{-}$ = $(C_4H_9)_4NBr$, $(C_4H_9)_4NHSO_4$, $(C_2H_5)_3(C_6H_5CH_2)NBr$

Chart 5



were deshielded by the sulfone moiety in compound **121**. Moreover, the C_3-H proton of compound **118** was shielded by the benzene ring, while the methylene protons of compound **122** were deshielded by the sulfone moiety.

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