Synthesis of 3(5)-(1′-Pyrazolyl)pyrazoles from 1,4-Dinitropyrazole by Cine Substitution Reaction. Structure Determination[1]

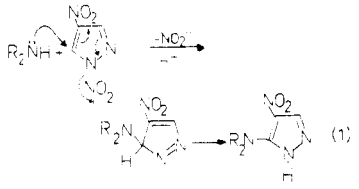
Pauline Cohen-Fernandes,* C. Erkelens, C. G. M. van Eendenburg, J. J. Verhoeven, and Clarisse L. Habraken*

Gorlaeus Laboratory, The University, Leiden, The Netherlands

Received April 03, 1979

The cine substitution of 1,4-dinitropyrazoles **1a–b** with pyrazoles **2–7** as nucleophiles provides a convenient method of synthesis of 4-nitro-3(5)-(1′-pyrazolyl)pyrazoles **8a–g** and **9a–d**. Reduction of the 4-nitro group and deamination afford the 3(5)-(1′-pyrazolyl)pyrazoles **12a–b**, **12d–e**, and **13a–d**. Structure assignments are based on ^1H and ^{13}C NMR spectra. The ^{13}C spectra of 1,1′-dimethylbipyrazoles are reported.

Recently we reported on the cine substitution reaction of the 1,4-dinitropyrazoles **1a–b** with secondary amines as nucleophiles, affording 3(5)-*N*,*N*-dialkyl-substituted aminopyrazoles in good yields[2] (eq 1). In this reaction, i.e.,



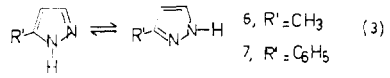
(1)

nucleophilic aromatic substitution of the 1,2-addition–elimination type as described by Miller,[3] the entering group comes in ortho to the leaving group, resulting in the initial formation of a 3*H*-pyrazole. The ultimate product is formed in a subsequent fast 1,5 hydride shift.

The present paper is concerned both with the extension of the scope of this cine substitution reaction by using pyrazoles as nucleophiles and with its utility for the preparation of C–N coupled bipyrazoles. C–N coupled bipyrazoles have been scarcely reported in the literature,[4] and we now found that the cine substitution reaction provides an approach to that class of compounds.

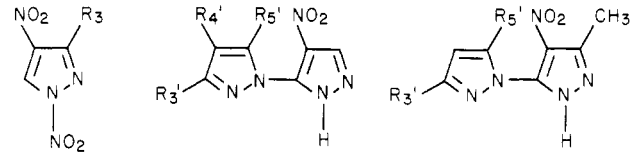
The reaction of 1,4-dinitropyrazole (**1a**) and pyrazole (**2**) in refluxing ethanol for 2 h gave the bipyrazole **8a** in 90% yield (eq 2). Likewise, the reaction of **1a** with 3,5-dimethylpyrazole (**3**), 4-ethylpyrazole (**4**) and 4-bromopyrazole (**5**) respectively afforded the accordingly substituted bipyrazoles **8d–f**, and the reaction of **2** and **3** with 3-methyl-1,4-dinitropyrazole (**1b**) gave the bipyrazoles **9a** and **9d** (see Chart I). For the unsymmetrically substituted 3(5)-methylpyrazole **6** and 3(5)-phenylpyrazole **7** consisting of equilibrium mixtures of tautomers (eq 3), reaction with

(2)



(3)

Chart I[a]



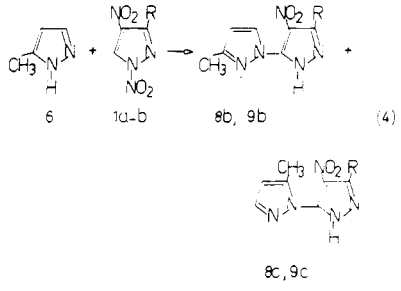
1a, R_3 = H
b, R_3 = Me

8a, R = H
b, $R_{3'}$ = Me
c, $R_{5'}$ = Me
d, $R_{3'}$ = $R_{5'}$ = Me
e, $R_{4'}$ = Et
f, $R_{4'}$ = Br
g, $R_{3'}$ = C_6H_5

9a, R = H
b, $R_{3'}$ = Me
c, $R_{5'}$ = Me
d, $R_{3'}$ = $R_{5'}$ = Me

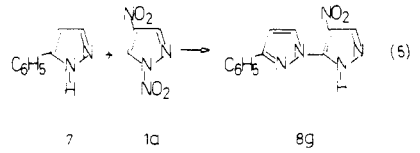
[a] R = H unless otherwise stated.

1a might in turn be expected to result in the formation of two isomeric bipyrazoles. According to this expectation, the reaction of **1a** with **6**, having a methyl group in the 3(5)-position, afforded a 4:1 mixture of the isomeric compounds **8b** and **8c**, and the reaction of **1b** with **6** gave **9b** and **9c** in the ratio of 2:1 (eq 4). However, from the



(4)

reaction of **1a** with **7**, possessing the bulkier phenyl group in the 3(5)-position, only **8g** was obtained (eq 5).



(5)

The structure assignments of the isomer pairs **8b,c** and **9b,c** were based on their proton NMR spectra and on steric considerations. The major compounds present in the product mixtures were considered to be the sterically less hindered 1,3-substituted isomers **8b** and **9b**. Consequently, **8g**, the sole product obtained from the reaction of **1a** and 3(5)-phenylpyrazole **7**, was also assigned as the 1,3-substituted compound.

Reduction of the 4-nitro group of **8a–e** and **9a–d** and subsequent deamination afforded the parent compound 3(5)-(1′-pyrazolyl)pyrazole **12a** and the alkyl substituted derivatives **12b,d,e** and **13a–d** (Chart II). Since we did not succeed in the separation of the isomer pairs **8b,c** and **9b,c**, the mixtures were subjected to reduction. Deamina-

(1) Pyrazoles, Part 17. Part 16: C. L. Habraken and S. M. Bonser, *Heterocycles*, **7**, 259 (1977).

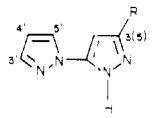
(2) Pyrazoles, Part 15, C. L. Habraken and E. K. Poels, *J. Org. Chem.*, **42**, 2893 (1977).

(3) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968.

(4) (a) The synthesis of 3(5)-methyl-5(3)-(3′,4′,5′-trimethyl-1′-pyrazolyl)pyrazole from 1-acetyl-3,5,5-trimethylpyrazoline is reported by A. N. Kost, G. A. Golubeva, L. A. Sviridova, I. I. Grandberg, and N. B. Chernyshova, *Dokl. Akad. Nauk SSSR*, **179**(2), 332 (1968). (b) C–N-coupled bipyrazolyls have been isolated as byproducts of the halogenation both of 4-substituted pyrazoles and of their silver salts: R. Hüttel, H. Wagner, and P. Jochum, *Justus Liebigs Ann. Chem.*, **593**, 179 (1953); H. Reimlinger, A. Noels, J. Jadot, and A. Overstraeten, *Chem. Ber.*, **103**, 1942 (1970); H. Reimlinger, A. Noels, and J. Jadot, *ibid.*, **103**, 1949 (1970).

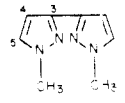
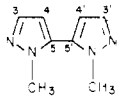
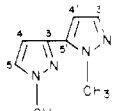
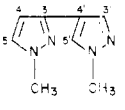
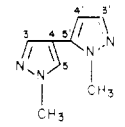
0022-3263/79/1944-4156$01.00/0

Table I. ^{1}H Chemical Shift Data for 12a and 13a (Parts Per Million Relative to Me_4Si) and J values (Hz)



		position of H							
	solv	C-4	C-4′	C-3(5)	C-3′	C-5′	NH	$J_{3'4'}$	$J_{4'5'}$
12a, R = H	$CDCl_3$	6.56	6.44	7.61	7.73	8.07	11.56	1.8	2.5
	Me_2SO	6.46	6.46	7.68	7.82	8.22	12.81	1.7	2.4
	HMPA	6.37	6.46	7.60	7.80	8.14	13.80		
13a, R = CH_3	$CDCl_3$	6.32	6.41		7.69	8.05	9.49	1.4	2.1
	Me_2SO	6.23	6.44		7.64	8.17	12.47	1.5	2.4
	HMPA	6.15	6.42		7.57	8.09	13.40	1.3	2.5

Table II. ^{13}C Chemical Shifts of 1,1′-Dimethylbipyrazolyls[a, b, e]

compd	C-3	C-4	C-5	C-3′	C-4′	C-5′	C-1 CH_3	C-1′ CH_3
 14	146.6	103.3	130.8				38.8	
 15	138.7	107.7	132.2				37.3	
 16	142.6	105.2[c]	130.8	138.2	105.3[c]	136.3	38.6[d]	39.1[d]
 17	144.8	102.7	131.0	136.9	116.4	127.1	38.7[d]	38.9[d]
 18	138.3[c]	112.2	128.6	138.5[c]	105.2	135.3	37.4	39.1

[a] See ref 7 for the synthesis. [b] In parts per million relative to Me_4Si. [c,d] The assignments of these carbons are not certain and may be reversed. [e] Solvent is $CDCl_3$ for all compounds.

tion of **11b,c** afforded the isomers **13b,c**, whereas in deamination of **10b,c** the minor compound **12c** was lost in the process.

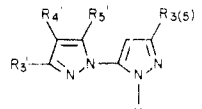
To support the above structure assignments, we first investigated the solvent effects on the proton NMR spectra of **12a** and **13a** (Table I). From the investigations of Elguero and Jacquier[5] it is known that in solvents such as $CDCl_3$ and C_6D_6 the C-5 proton resonance signal of 1-methyl-substituted pyrazoles is distinguished from the signal of the C-3 proton by appearing at higher field and with a larger coupling constant ($J_{45} > J_{34}$). In addition, the C-5 proton resonance signal shows a pronounced solvent effect consisting of a shift to lower external field in going from nonpolar to polar solvents such as Me_2SO and HMPA.[6] For the C-3 proton signal, on the contrary, no such shift or only a much smaller one to higher field is observed. Previously we employed this method for the structure assignments in the series of the C–C coupled 1,1′-dimethylbipyrazoles **14–18**.[7] In the case of compound **13a** the NMR spectrum in $CDCl_3$ (see Table I) shows a doublet at lower field with a larger coupling constant (J = 2.1–2.5 Hz) than the doublet at higher field (J = 1.3–1.5 Hz). However, neither doublet shows any pronounced solvent effect. The same holds for compound **12a**. An explanation may lie in the possibility of internal hydrogen bonding in compounds **12a** and **13a**.

Therefore, we could not employ this technique to assign the structures **12b** and **13b,c** nor confirm the structure assignments of the isomer pairs **8b,c** and **9b,c**. We then examined the ^{13}C NMR spectra of bipyrazole compounds.

It was reported[8-10] that the ^{13}C spectra of N-substituted pyrazoles gave three signals: (1) the carbon (C-5) next to the pyrrolic N at approximately 130 ppm, (2) the carbon (C-3) adjacent to the pyridinic N downfield at 140 ppm, and (3) the C-4 signal due to its larger shielding at high field (105 ppm). In addition, it was shown that methylation of a N-substituted pyrazole at C-3 or C-5 causes a downfield shift of about 9–10 and 12–13 ppm, respectively. Comparison of the ^{13}C chemical shifts of some 1,1′-dimethylbipyrazoles (**14–18**)[7] gave the same overall pattern (see Table II). We thus decided to use this technique to elucidate the structures of **12b** and the isomers **13b,c** (Ta-

(5) J. Elguero, R. Jacquier, and Hong Cung N. Tien Duc, *Bull. Soc. Chim. Fr.*, 3727 (1966).
(6) J. Elguero and R. Jacquier, *J. Chim. Phys. Phys.-Chim. Biol.*, **63**, 1242 (1966).
(7) P. B. M. W. M. Timmermans, A. P. Uyttewaal, and C. L. Habraken, *J. Heterocycl. Chem.*, **9**, 1373 (1972).
(8) J. Elguero, Claude Marzin, and J. D. Roberts, *J. Org. Chem.*, **39**, 357 (1974).
(9) S. Gelin, R. Gelin, and D. Hartmann, *J. Org. Chem.*, **43**, 2665 (1978).
(10) R. A. Earl, J. Pugmire, Ganapatti R. Revankar, and L. B. Townsend, *J. Org. Chem.*, **40**, 1822 (1975).

Table III. ^{13}C Chemical Shifts of Some 3(5)-(1′-Pyrazolyl)pyrazoles[a,b,d]



	compd	C-4	C-3(5)	C-5(3)	C-4′	C-3′	C-5′	$R_{3(5)}$	$R_{3'}$	$R_{4'}$	$R_{5'}$
R = H[b]	12a	95.3	130.6	149.7	107.1	140.9	127.5				
$R_{3'}$ = Me	12b	95.0	130.4	149.6	107.0	150.4	128.2		13.6		
$R_{3'}$ = $R_{5'}$ = Me	12d	98.4	129.8	148.6	106.9	149.4	140.5		13.5		12.4
$R_{4'}$ = Et	12e	95.0	130.5	149.9	125.1	140.4	125.1			17.4 (CH_2), 15.0 (Me)	
$R_{3(5)}$ = Me	13a	95.1	141.4	150.0	106.9	140.8	127.3	11.0			
$R_{3(5)}$ = $R_{3'}$ = Me	13b	94.4	141.0	149.6	106.9	150.3	127.8	11.1	13.6		
$R_{3(5)}$ = $R_{5'}$ = Me	13c	98.3	140.6[c]	148.5	106.7	140.0	139.6[c]	11.0			12.4
$R_{3(5)}$ = $R_{3'}$ = $R_{5'}$ = Me	13d	98.3	140.7[c]	148.9	106.7	149.2	140.4[c]	10.7	13.4		12.3

[a] In ppm relative to Me_4Si. [b] R = H unless otherwise stated. [c] The assignments of these carbons are not certain and may be reversed. [d] The solvent was $CDCl_3$ for all compounds.

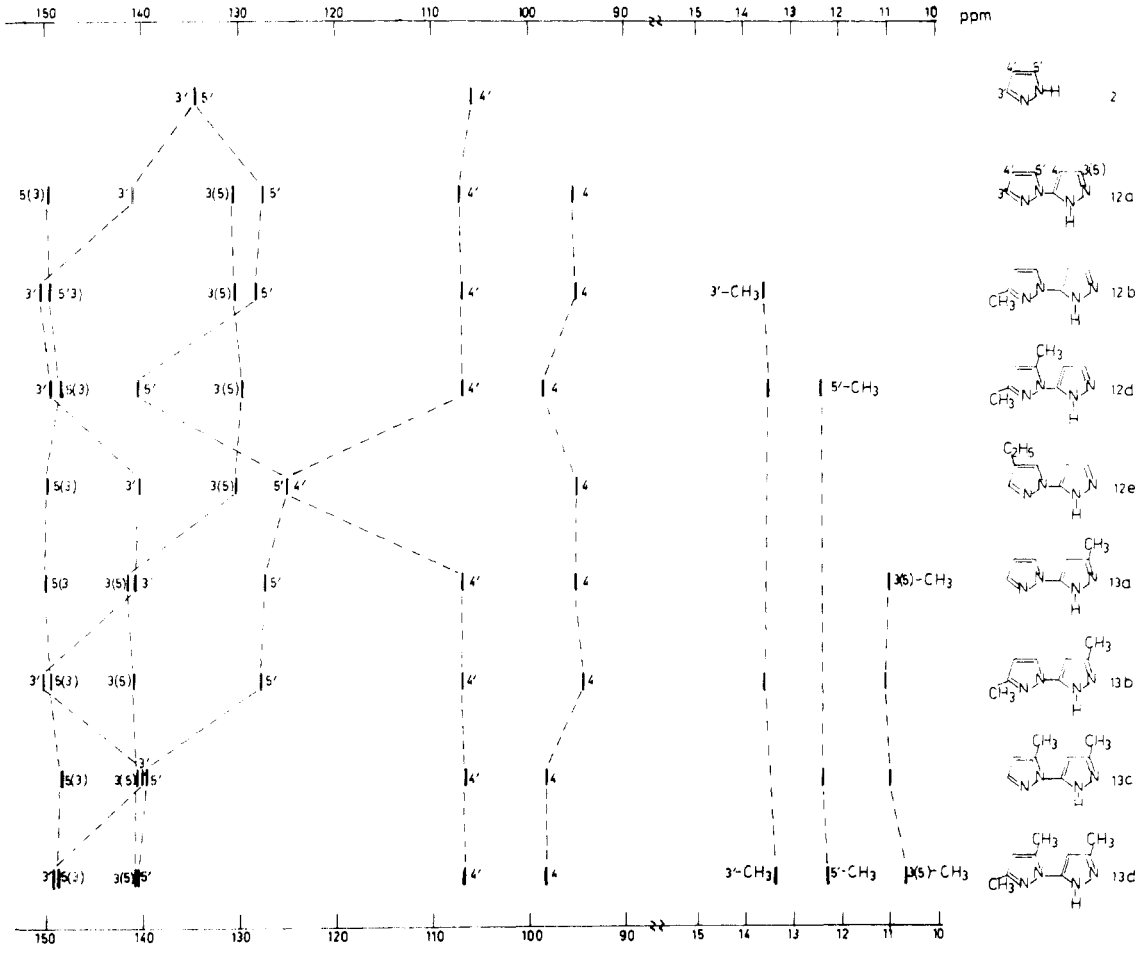
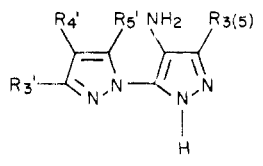
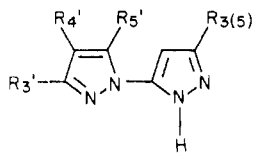


Figure 1. Carbon-13 resonance patterns for some 3(5)-(1′-pyrazolyl)pyrazole derivatives.

Chart II[a]





10a, R = H
b, $R_{3'}$ = Me
c, $R_{5'}$ = Me
d, $R_{3'}$ = $R_{5'}$ = Me
e, $R_{4'}$ = Et

11a, $R_{3(5)}$ = Me
b, $R_{3(5)}$ = $R_{3'}$ = Me
c, $R_{3(5)}$ = $R_{5'}$ = Me
d, $R_{3(5)}$ = $R_{3'}$ = $R_{5'}$ = Me

12a, R = H
b, $R_{3'}$ = Me
d, $R_{3'}$ = $R_{5'}$ = Me
e, $R_{4'}$ = Et

13a, $R_{3(5)}$ = Me
b, $R_{3(5)}$ = $R_{3'}$ = Me
c, $R_{3(5)}$ = $R_{5'}$ = Me
d, $R_{3(5)}$ = $R_{3'}$ = $R_{5'}$ = Me

[a] R = H unless otherwise stated.

ble III). From these data compounds **12b** and **13b** could be identified as the C-3′ CH_3 structure, the respective C-3′ signals being shifted downfield to 150.4 and 150.3 ppm. Compound **13c** had to be the C-5′ CH_3 isomer, the C-5′ signal being as expected at 140 ppm. Further proof of the assignment was obtained from the comparison of the C-3′ CH_3 and C-5′ CH_3 signals in **12b** and **13b,c** with the model systems 1,3- and 1,5-dimethylpyrazole and 1,3,5-trimethylpyrazole:[8] the C-3′ CH_3 signal is at 13.4–13.6 ppm in **12b** and **13b** and the C-5′ CH_3 at 12.4 ppm in **13c**.

Studying the ^{13}C resonance patterns of **12a–e** and **13a–d** presented in Figure 1, one observes that the signal at 10.7–11.1 ppm must be assigned to the C-3(5) CH_3. The chemical shift of C-3(5) moves downfield with methyl substitution from 130 ppm in the series **12a–e** to 141 ppm in the series **13a–d**. Comparison of the spectrum of **12e** (ethyl substitution at C-4′) with those of **12a–d**, **13a–d** made the

assignment of the signal at 95–98 ppm for C-4 and that of 105–108 ppm for C-4′ possible. Spectra with the decoupler turned off supported the assignment of C-3′ and C-5(3) in compounds **12b**, **12d**, **13b**, and **13d**. Long-range coupling gave for C-3′ a quartet of doublets and for C-5(3) a doublet of doublets. This method was of no avail in the assignment of C-3(5) and C-5′ in **13c** and **13d**, both carbons being substituted by a CH_3 group, and these assignments may be reversed.

In conclusion, the nucleophilic aromatic cine substitution reaction of 1,4-dinitropyrazoles with pyrazoles provides a useful method for the synthesis of the virtually unknown C–N-coupled[4] bipyrazoles.

Experimental Section

General Methods. ^1H NMR spectra (expressed in parts per million) were recorded on a JEOL PS-100. All carbon-13 magnetic resonance spectra were recorded on a JEOL PFT-100 spectrometer, equipped with a JEOL-EC 100 data processing unit. The compounds were examined as ca. 2% wt/vol solutions. Chemical shifts are given relative to that of internal Me_4Si with an accuracy of 0.1 ppm. The spectra were taken under conditions of proton-noise decoupling and proton-CW off-resonance decoupling. IR spectra (KBr) were recorded on a Beckman IR-10 instrument; mass spectra were taken on an AEI type MS-902 instrument, operated at 70 eV, source temperature 130 °C. The sample was introduced via an all-glass heated inlet system (160 °C). Elemental analyses were performed by Mr. W. J. Buis (TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands). For the separation of products the short-column chromatography technique of Hunt and Rigby[16] was used on silica gel H (Merck) according to Stahl. Spraying with Rhodamine B solution (0.05% in ethanol) was used for detection of nitropyrazoles on TLC. All melting points are uncorrected. *N*-Nitropyrazoles **1a,b** were prepared as has been previously described;[11] these compounds must be stored under exclusion of moisture to prevent slow hydrolysis.

Caution. Although we have never experienced detonations when working with the 1,4-dinitropyrazoles **1a,b**, investigations by J. Verhoeff, J. H. M. van Liempt, and J. Rooseboom (Prins Maurits Laboratorium, TNO, Delft) showed that **1a** is an explosive substance which can deflagrate and probably detonate. The sensitivity for explosion, however, is much lower than for primary explosives.

General Procedure for the Synthesis of 4-Nitro-3(5)-(1′-pyrazolyl)pyrazole Derivatives 8a–g and 9a–d. To a solution of 10 mmol of the *N*-nitropyrazole (**1a,b**) in 20 mL of ethanol was added a solution of 2 equiv of the appropriate pyrazole in 20 mL of ethanol slowly with stirring. The solution then was refluxed for 1–3 h. Completion of the reaction was determined by TLC (9:1 chloroform–methanol). For removal of the nitrous acid, a solution of 10 mmol of sulfamic acid in 20 mL of water was added slowly. After the evolution of nitrogen had stopped, the solvent was evaporated under reduced pressure. The residue consisted of the desired products **8a–g** and **9a–d** and an equal amount of the respective pyrazole sulfate. The residue was taken up in a little water. The insoluble compound (**8a–g**, **9a–d**) was collected on a Buchner funnel and crystallized from the appropriate solvent. The yields varied from 80 to 95%.

Reduction of Compounds 8a–e and 9a–d into the Respective 4-Amino-3(5)-(1′-pyrazolyl)pyrazole Derivatives 10a–e and 11a–d.[12] To a solution of 5.6 mmol of the nitro compounds **8a–e** and **9a–d** and 5% palladized charcoal (0.11 g) in 15 mL of ethanol was added a solution of 60% hydrazine hydrate (2.7 mL) slowly with stirring. The solution then was refluxed for 2 h. The catalyst was filtered off and the filtrate evaporated to small volume and diluted with water. The yellow solid of the product (**10a–e**, **11a–d**) was collected, washed with cold water, and dried. When exposed to light it discolors on standing. The crystals were used without further purification. The yields varied from 60 to 80%.

3(5)-(1′-Pyrazolyl)pyrazole Derivatives 12a,b,d,e and 13a–d from Deamination of 10a–e and 11a–d.[13] A solution of 1 g (20 mmol) of sodium nitrite in 3 mL of water was added with agitation during 30 min to a solution consisting of 6.71 mmol of **10a–e** or **11a–d**, 2 g (15 mmol) of 50% hypophosphorous acid, 1.1 mL of concentrated hydrochloric acid and 6.5 mL of water. The temperature was maintained at 35–40 °C. At this stage the solution was found to contain azolediazonium chloride salts (IR 2270 cm^{-1}) and diazoazoles (IR 2190 cm^{-1}).[14,15] To decompose these rather stable intermediates,[14,15] we gently heated the solution. After being allowed to stand overnight at 100 °C, the solution was allowed to cool and poured onto crushed ice. The solution was neutralized with sodium bicarbonate and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform extract yielded a pale yellow solid. The deamination of a mixture of the compounds **10b** and **10c** led to appreciable quantities of tarry products while the presence of **12c** could not be demonstrated. Crystallization and sublimation gave the pure compounds **12a,b,d,e** and **13a–d**. The yields varied from 30 to 60%.

4-Nitro-3(5)-(1′-pyrazolyl)pyrazole (8a): pale green, mp 181 °C (from ethanol–water); IR 3160 and 2970 (CH and NH), 1515 and 1370 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 6.52 (m, 1, C-4′ H), 7.77 (d, 1, C-3′ H), 8.15 (d, 1, C-5′ H), 8.96 (s, 1, C-3(5) H). Anal. Calcd for $C_6H_5N_5O_2$: C, 40.23; H, 2.81; N, 39.10. Found: C, 40.23; H, 3.02; N, 39.0].

4-Nitro-3(5)-(3′-methyl-1′-pyrazolyl)pyrazole (8b) and 4-nitro-3(5)-(5′-methyl-1′-pyrazolyl)pyrazole (8c): mixture of isomeric compounds **8b,c** (ratio 4:1); pale yellow solid; IR 3150, 2950, and 2820 (CH and NH), 1515 and 1390 cm^{-1} (NO_2); NMR (**8b**, Me_2SO-d_6) δ 2.23 (s, 3, C-3′ CH_3), 6.32 (m, 1, C-4′ H), 8.05 (d, 1, C-5′ H), 8.90 (s, 1, C-3(5) H); NMR (**8c**, Me_2SO-d_6) δ 2.15 (s, 3, C-5′ CH_3), 6.32 (m, 1, C-4′ H), 7.60 (d, 1, C-3′ H), 9.03 (s, 1, C-3(5) H).

4-Nitro-3(5)-(3′,5′-dimethyl-1′-pyrazolyl)pyrazole (8d): light brown needles, mp 265–267 °C (from 1:1 ethanol–water); IR 3150 and 2800 (CH and NH), 1500 and 1380 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 2.11 (s, 3, CH_3), 2.16 (s, 3, CH_3), 6.10 (s, 1, C-4′ H), 9.03 (s, 1, C-3(5) H). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.35; N, 33.82. Found: C, 46.33; H, 4.55; N, 33.62.

4-Nitro-3(5)-(4′-ethyl-1′-pyrazolyl)pyrazole (8e): white crystals, mp 166–168 °C (from ethanol–water); IR 2980 and 3140 (CH and NH), 1505 and 1380 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 1.21 (t, 3, CH_3), 2.36 (q, 2, CH_2), 7.62 (s, 1, C-3′ H), 7.93 (s, 1, C-5′ H), 8.92 (s, 1, C-3(5) H). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.35; N, 33.82. Found: C, 46.15; H, 4.45; N, 33.59.

4-Nitro-3(5)-(4′-bromo-1′-pyrazolyl)pyrazole (8f): light brown crystals, mp 197 °C (from ethanol–water and benzene respectively); IR 2950 and 3150 (CH and NH), 1505 and 1385 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 7.92 (s, 1, C-3′ H), 8.45 (s, 1, C-5′ H), 9.00 (s, 1, C-3′(5′) H). Anal. Calcd for $C_6H_4N_5O_2Br$: Br, 30.98. Found: Br, 30.72.

4-Nitro-3(5)-(3′-phenyl-1′-pyrazolyl)pyrazole (8g): dark yellow crystals (from benzene), IR 2950 and 3160 (CH and NH), 1500 and 1385 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 7.01 (d, 1, C-4′ H), 8.22 (d, 1, C-5′ H), 8.97 (s, 1, C-3(5) H), 7.30 (m, 3, *m*- and *p*-H), 7.80 (m, 2, *o*-H). Anal. Calcd for $C_{12}H_9N_5O_2$: C, 56.47; H, 3.55; N, 27.44. Found: C, 56.58; H, 3.53; N, 27.29.

3(5)-Methyl-4-nitro-5(3)-(1′-pyrazolyl)pyrazole (9a): white crystals, mp 172 °C (from ethanol–water); IR 3200 (CH and NH), 1510 and 1375 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 2.59 (s, 3, C-3(5) CH_3), 6.53 (m, 1, C-4′ H), 7.78 (d, 1, C-3′ H), 8.13 (d, 1, C-5′ H); ($CDCl_3$) δ 2.66 (s, 3, C-3(5) CH_3), 6.54 (m, 1, C-4′ H); 7.80 (d, 1, C-3′ H), 8.15 (d, 1, C-5′ H). Anal. Calcd for $C_7H_7N_5O_2 \cdot H_2O$: C, 39.81; H, 4.30; N, 33.17. Found: C, 40.32; H, 4.04; N, 33.57.

3(5)-Methyl-4-nitro-5(3)-(3′-methyl-1′-pyrazolyl)pyrazole (9b) and 3(5)-methyl-4-nitro-5(3)-(5′-methyl-1′-pyrazolyl)-pyrazole (9c): mixture of isomeric compounds **9b,c** (ratio 2:1); white solid; IR 3100–2800 (CH and NH), 1370 and 1550 cm^{-1} (NO_2); NMR (**9b**, $CDCl_3$) δ 2.34 (s, 3, C-3′ CH_3), 2.57 (s, 3, C-3(5) CH_3), 6.29 (d, 1, C-4′ H), 8.00 (d, 1, C-5′ H); NMR (**9c**, $CDCl_3$) δ 2.17 (s, 3, C-5′ CH_3), 2.57 (s, 3, C-3(5) CH_3), 6.29 (d, 1, C-4′ H), 7.68 (d, 1, C-3′ H).

3(5)-Methyl-4-nitro-5(3)-(3′,5′-dimethyl-1′-pyrazolyl)-

(11) J. W. A. M. Janssen, and C. L. Habraken, *J. Org. Chem.*, **38**, 1777 (1973).
(12) I. L. Finar, and R. J. Hurlock, *J. Chem. Soc.*, 3259 (1958).
(13) R. A. Henry, and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 291 (1954).
(14) R. A. Henny, and W. G. Finnegan, *Chem. Ber.*, **94**, 1037 (1961).
(15) J. Vilarrasa, E. Mêlendez, and J. Elguero, *Tetrahedron Lett.*, 1609 (1974).
(16) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).

pyrazole (9d): white crystals, mp 210 °C (from 1:1 ethanol–water); IR 2750–3100 (CH and NH), 1545 and 1380 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 2.09 (s, 3, C-3′(5′) CH_3), 2.15 (s, 3, C-5′(3′) CH_3), 2.58 (s, 3, C-3(5) CH_3), 6.10 (s, 1, C-4′ H); ($CDCl_3$) δ 2.21 (s, 3, C-3′(5′) CH_3), 2.35 (s, 3, C-5′(3′) CH_3), 2.55 (s, 3, C-3(5) CH_3), 6.33 (s, 1, C-4′ H). Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.82; H, 4.89; N, 31.67.

4-Amino-3(5)-(1′-pyrazolyl)pyrazole (10a): pale yellow crystals, mp 143 °C; IR 3380 and 1615 cm^{-1} (NH_2); NMR (Me_2SO-d_6) δ 4.3 (s, 2, NH_2), 6.46 (m, 1, C-4′ H), 7.73 (d, 1, C-3′ H), 8.14 (d, 1, C-5′ H), 7.24 (s, 1, C-3(5) H).

4-Amino-3(5)-(3′-methyl-1′-pyrazolyl)pyrazole (10b) and 4-amino-3(5)-[5′-methyl-1′-pyrazolyl]pyrazole (10c): mixture of isomeric compounds **10b,c** (ratio 5:1); brown solid; IR 3360 cm^{-1} (NH_2); NMR (**10b**, Me_2SO-d_6) δ 5.2 (s, 2, NH_2), 6.24 (m, 1, C-4′ H), 7.26 (s, 1, C-3(5) H), 8.04 (d, 1, C-5′ H), 2.26 (s, 3, C-3′ CH_3); NMR (**10c**, Me_2SO-d_6) δ 5.2 (s, 2, NH_2), 6.24 (m, 1, C-4′ H), 7.26 (s, 1, C-3(5) H), 7.60 (d, 1, C-3′ H), 2.36 (s, 3, C-5′ CH_3).

4-Amino-3(5)-(3′,5′-dimethyl-1′-pyrazolyl)pyrazole (10d): white crystals; IR 3370 (NH_2), 3175 cm^{-1} (CH and NH); NMR (Me_2SO-d_6) δ 2.16 (s, 3, C-3′(5′) CH_3), 2.25 (s, 3, C-5′(3′) CH_3), 5.98 (s, 1, C-4′ H), 7.20 (s, 1, C-3(5) H).

4-Amino-3(5)-methyl-5(3)-(1′-pyrazolyl)pyrazole (11a): white crystals; IR 3380 (NH_2), 3120 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 2.16 (s, 3, C-3(5) CH_3), 6.41 (m, 1, C-4′ H), 7.69 (d, 1, C-3′(5′) H), 8.05 (d, 1, C-5′(3′) H).

4-Amino-3(5)-methyl-5(3)-(3′-methyl-1′-pyrazolyl)pyrazole (11b) and 4-amino-3(5)-methyl-5(3)-(5′-methyl-1′-pyrazolyl)pyrazole (11c): mixture of isomeric compounds **11b,c** (ratio 3:1); pale yellow solid; IR 3370 cm^{-1} (NH_2); NMR (**11b**, $CDCl_3$) δ 2.15 (s, 3, C-3(5) CH_3), 2.35 (s, 3, C-3′ CH_3), 6.17 (d, 1, C-4′ H), 7.92 (d, 1, C-5′ H). NMR (**11c**, $CDCl_3$) δ 2.15 (s, 3 C-3(5) CH_3), 2.45 (s, 3, C-5′ CH_3), 6.17 (d, 1, C-4′ H), 7.58 (d, 1, C-3′ H).

4-Amino-3(5)-methyl-5(3)-(3′,5′-dimethyl-1′-pyrazolyl)-pyrazole (11d): pale yellow solid; IR 3340 (NH_2), 3150 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 2.09, 2.25, 2.37 (s, 9, C-3(5), C-3′, C-5′ CH_3), 5.87 (s, 1, C-4′ H).

3(5)-(1′-Pyrazolyl)pyrazole (12a): white crystals, mp 90 °C (from diisopropyl ether, sublimation); IR 3180, 3020, and 2950 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 6.44 (m, 1, C-4′ H), 6.56 (d, 1, C-4 H), 7.61 (d, 1, C-3(5) H), 7.73 (d, 1, C-3′ H), 8.06 (d, 1, C-5′ H), 11.56 (s, 1, NH); (Me_2SO-d_6) δ 6.46 (s, 2, C-4 and -4′ H), 7.68 (d, 1, C-3′ H), 7.81 (d, 1, C-3(5) H), 8.22 (d, 1, C-5′ H), 12.81 (s, 1, NH); (HMPA) δ 6.37 and 6.46 (m, 2, C-4 and -4′ H), 7.60 (s, 1, C-3′ H), 7.80 (s, 1, C-3(5) H), 8.14 (s, 1, C-5′ H), 13.79 (s, 1, NH). Anal. Calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.66. Found: C, 53.67; H, 4.59; N, 41.59.

3(5)-(3′-Methyl-1′-pyrazolyl)pyrazole (12b): white crystals, mp 120 °C (sublimation); IR 2940 and 3150 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 6.17 and 6.42 (d, 2, C-4 and -4′ H), 7.51 (d, 1, C-3(5) H), 7.90 (d, 1, C-5′ H), 2.31 (s, 3, C-3′ CH_3); (Me_2SO-d_6) δ 6.22 and 6.41 (d, 2, C-4 and -4′ H), 7.76 (m, 1, C-3(5) H), 8.06 (d, 1, C-5′ H), 2.20 (s, 3, C-3′ CH_3), 12.40 (s, 1, NH). Anal. Calcd for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found: C, 56.46; H, 5.43; N, 37.65.

3(5)-(3′,5′-Dimethyl-1′-pyrazolyl)pyrazole (12d): yellow oil; IR 2920 and 3140 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 5.95 (s, 1, C-4′ H), 6.36 (d, 1, C-4 H), 7.45 (d, 1, C-3(5) H), 2.29 (s, 3, C-3′(5′) CH_3), 2.37 (s, 3, C-5′(3′) CH_3). Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 58.83; H, 6.23; N, 32.93. High-resolution mass spectrum: calcd for $C_8H_{10}N_4$, *m/e* 162.0905; found, *m/e* 162.0907.

3(5)-(4′-Ethyl-1′-pyrazolyl)pyrazole (12e): light yellow oil; IR 2960 and 3160 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 6.36 (d, 1, C-4 H), 7.11 (s, 1, C-3′ H), 7.70 (s, 1, C-5′ H), 7.41 (d, 1, C-3(5) H), 1.21 (t, 3, CH_3), 2.48 (q, 2, CH_2). The mass spectrum showed slight contamination with 4-ethylpyrazole. High-resolution mass spectrum: calcd for $C_8H_{10}N_4$, *m/e* 162.0905; found, *m/e* 162.0907.

3(5)-Methyl-5(3)-(1′-pyrazolyl)pyrazole (13a): light yellow crystals, mp 108 °C [petroleum ether (bp 60–80 °C), sublimation]; IR 2960 and 3140 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 6.32 (s, 1, C-4 H), 6.41 (m, 1, C-4′ H), 7.69 (d, 1, C-3′ H), 8.05 (d, 1, C-5′ H), 2.26 (s, 3, C-3(5) CH_3), 9.49 (s, 1, NH); (Me_2SO-d_6) δ 6.23 (s, 1, C-4 H), 6.44 (m, 1, C-4′ H), 7.64 (d, 1, C-3′ H), 8.17 (d, 1, C-5′ H), 12.47 (s, 1, NH); (HMPA) δ 6.15 (s, 1, C-4 H), 6.42 (m, 1, C-4′ H), 7.57 (d, 1, C-3′ H), 8.09 (d, 1, C-5′ H), 13.40 (s, 1, NH). Anal. Calcd for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found: C, 56.64; H, 5.28; N, 37.51.

3(5)-Methyl-5(3)-(3′-methyl-1′-pyrazolyl)pyrazole (13b): light yellow crystals, mp 154 °C (from water); IR 2950, 3120, 3150, and 3180 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 6.17 (d, 1, C-4′ H), 6.25 (s, 1, C-4 H), 7.92 (d, 1, C-5′ H), 2.24 and 2.33 (s, 6, C-3(5) and C-3′ CH_3). Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 58.87; H, 6.25; N, 34.65.

3(5)-Methyl-5(3)-(5′-methyl-1′-pyrazolyl)pyrazole (13c): from mixture with **13b**; NMR ($CDCl_3$) δ 6.17 (d, 1, C-4′ H), 6.25 (s, 1, C-4 H), 7.58 (d, 1, C-3′ H), 2.24 (s, 3, C-3(5) CH_3), 2.42 (s, 3, C-5′ CH_3).

3(5)-Methyl-5(3)-(3′,5′-dimethyl-1′-pyrazolyl)pyrazole (13d): light yellow crystals, mp 115 °C (from 85:15 ethanol–water, sublimation); IR 2920, 2980, 3160 and 3200 cm^{-1} (CH and NH); NMR ($CDCl_3$) δ 5.97 (s, 1, C-4(4′) H), 6.20 (s, 1, C-4′(4) H), 2.22, 2.28, and 2.40 (s, 9, C-3′, C-5′, and C-3(5) CH_3 respectively). Anal. Calcd for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.80. Found: C, 61.52; H, 7.02; N, 31.67.

Acknowledgment. We thank Ralf Tadema Wieland for a literature search of C–N-coupled bipyrazolyls[4] and Ursula Wagner for performing the synthesis of **12e**. We also express our thanks to Dr. J. van Thuyl, J. van Houte, and W. C. M. Luyten for the mass spectral analyses and to J. Stikkelorum for IR spectral data.

Registry No. 1a, 35852-77-8; **1b**, 62563-09-1; **2**, 288-13-1; **3**, 67-51-6; **4**, 17072-38-7; **5**, 2075-45-8; **6**, 1453-58-3; **7**, 2458-26-6; **8a**, 71426-21-6; **8b**, 71426-22-7; **8c**, 71426-23-8; **8d**, 71426-24-9; **8e**, 71426-25-0; **8f**, 71426-26-1; **8g**, 71426-27-2; **9a**, 71426-28-3; **9b**, 71426-29-4; **9c**, 71426-30-7; **9d**, 71426-31-8; **10a**, 71426-32-9; **10b**, 71463-29-1; **10c**, 71426-33-0; **10d**, 71426-34-1; **10e**, 71463-30-4; **11a**, 71426-35-2; **11b**, 71426-36-3; **11c**, 71426-37-4; **11d**, 71426-38-5; **12a**, 71426-39-6; **12b**, 71426-40-9; **12d**, 71426-41-0; **12e**, 71426-42-1; **13a**, 71426-43-2; **13b**, 71426-44-3; **13c**, 71426-45-4; **13d**, 71426-46-5.

New Synthesis of 1,2,4-Triazoles and 1,2,4-Oxadiazoles

Yang-i Lin,* Stanley A. Lang, Jr., Maurice F. Lovell, and Nancy A. Perkinson

American Cyanamid Company, Medical Research Division, Pearl River, New York 10965

Received June 05, 1979

A new synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles has been developed. *N′*-Acyl-*N,N*-dimethylamidines, which were prepared in excellent yields by reactions of amides with *N,N*-dimethylalkanamide dimethyl acetals, reacted with hydrazines or hydroxylamine in acetic acid to give 1,2,4-triazoles or 1,2,4-oxadiazoles, respectively, in excellent yields.

In a previous investigation,[1] we reported a novel synthesis of pyrazoles and isoxazoles by utilization of the (dimethylamino)-2-propen-1-one moiety as a masked β-keto aldehyde. This experience with the (dimethyl-

0022-3263/79/1944-4160$01.00/0