Synthesis of 4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazoles

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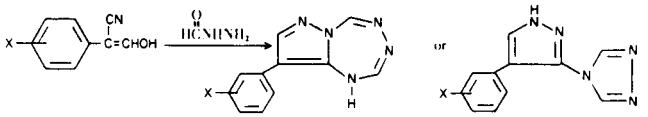
Received September 27, 1976

4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazoles and 4-phenyl-5-(4*H*-1,2,4-triazol-4-yl)-3-pyrazolols were prepared by the reaction of formylhydrazine on α-phenyl-α-cyanoacetaldehydes and ethyl α-phenyl-α-cyanoacetates.

J. Heterocyclic Chem., **14**, 65 (1977).

During an investigation of the synthesis and antiinflammatory activity of β-amino-β-phenylacrylonitriles (1), the reaction of α-phenyl-α-cyanoacetaldehyde with formyl hydrazine yielded a high melting white solid. Spectral evidence and analytical data suggested structures **2** or **3** as reasonable possibilities (Scheme I). The nmr spectrum,

Scheme I



1 2 3

(**3a**, X = H) showed one exchangeable proton (11.52 δ), singlets at 8.7 (2) and 8.2 (1) in addition to the aryl signals at 7.3 (2) and 7.2 (3). Exposure of the compound to deuterium chloride in deuterium oxide overnight caused the proton signal at 8.7 (2) to lose intensity. The structure for this product was established to be **3** on the basis of an X-ray diffraction analyses.

Crystals of **3b**, grown from methanol are monoclinic, space group $P2_1/a$, with unit cell dimensions a = 9.51A, b = 17.35A, c = 7.51A, $\beta = 97.17°$. The observed density is 1.32 gm cm^{-3}.

Three-dimensional intensity data were collected on a CAD-3 diffractometer to give 1769 independent reflections, in the range $3 < \theta < 60$, of which 1079 were classified as observed with $I > 2.5\sigma$ (I). The θ-2θ scan method was used with nickel filtered CuKα radiation.

The structure was solved by the symbolic addition method as applied to centrosymmetric crystals. Phases were determined for 145 of the 175 reflections with normalized structure factors greater than 1.70. An E-map based on these phases contained the complete structure. Initial least-squares refinement of the trial structure treating all ring atoms as carbons led to an R factor of 0.17. It was then possible to distinguish between nitrogen and carbon atoms on the basis of refined thermal parameters. Further isotropic refinement reduced R to 0.10; anisotropic refinement yielded a final R factor of 0.08. A difference electron density map showed peaks at all the positions anticipated for hydrogen atoms.

An ORTEP drawing of the structure is shown in Figure 1.

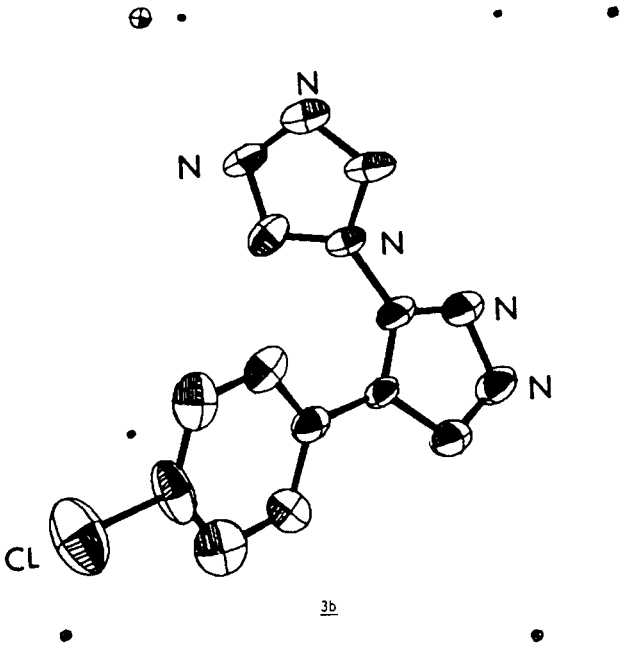
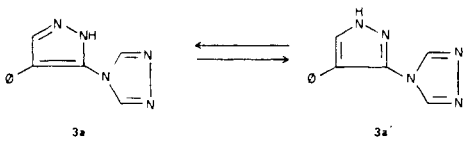


Figure 1

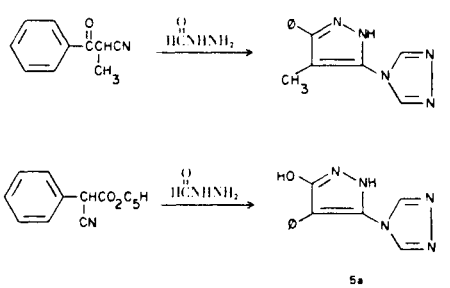
The X-ray analysis indicated that the proton on the pyrazole ring populates either nitrogen to an indistinguishable extent **3a** and **3a'** but for numbering, the structure is as written **3a**. The reaction with formyl hydrazine

Scheme II



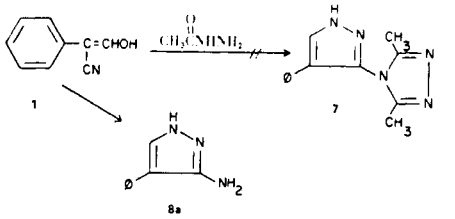
was demonstrated to be general and yielded similar products when this reagent was reacted with α-cyanoketones or α-cyanoesters of the type shown in Scheme III.

Scheme III



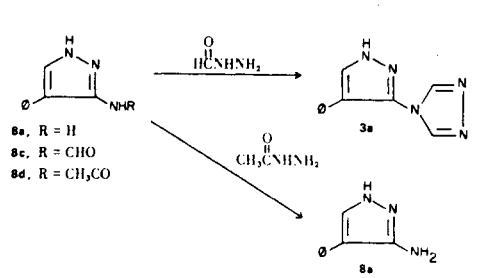
Attempted extension of this sequence to yield compounds substituted in the triazole ring by employment of acetylhydrazine did not give the desired materials **7**, but aminopyrazoles **8a** (Scheme IV).

Scheme IV



The reaction of 3-amino-4-phenylpyrazole (**8a**), its formate **8c** or acetate **8d** with formyl hydrazine or diformyl hydrazine in a melt or in ethylene glycol gave **3a**, 4-(4-phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole. The use of acetylhydrazine gave only recovered pyrazole (Scheme V).

Scheme V

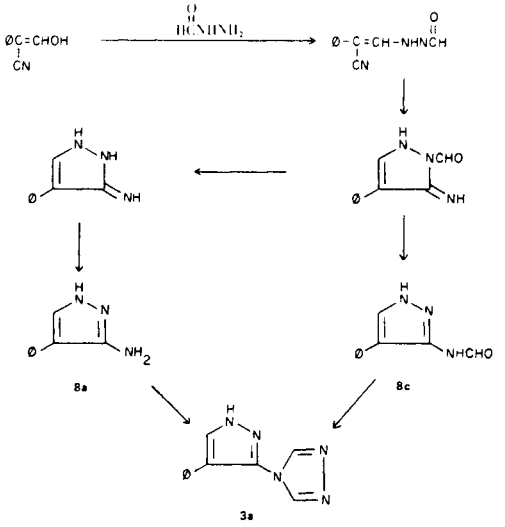


In terms of yield, the pyrazolyltriazoles were better synthesized in a two-step fashion. The aminopyrazoles (2) were prepared from the α-phenyl-α-cyanoacetaldehydes with hydrazine in ethanol and then reacted with formyl hydrazine in refluxing ethylene glycol.

The pyrazolyltriazoles form stable hydrochlorides (**6a**) and most can be acetylated. The acetylation yields a homogeneous material whose structure is assigned as **6c**. Most pyrazolyltriazoles which possess a methyl group in the 5-position of the pyrazole ring fail to acetylate. It is on this basis that the acetylation is assigned as occurring on the 1-position of pyrazole ring.

Mechanistically, the terminal amino of the formyl hydrazine is pictured (Scheme VI) as adding to the aldehyde

Scheme VI



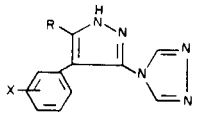
group (2,3) followed by cyclization. The intermediate then could lose the formyl residue to excess formyl hydrazine or transfer it to the more basic amine. The intermediate aminopyrazole or its formylated counterpart then reacts further with formyl hydrazine to give the product. Steric factors could explain the lack of bicyclic product when acetylhydrazine is employed. The reaction of **1** with 1 equivalent of acetylhydrazine in ethanol gives the acetylated aminopyrazole, **8d**.

EXPERIMENTAL

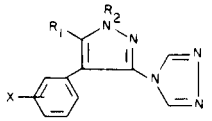
All melting points were observed on a Mel-Temp®, ir spectra were recorded with a Perkin Elmer 137, and unless noted were recorded as a potassium bromide pellet. Nmr spectra were recorded on a Varian HA 100 and uv on a Cary 15 spectrophotometer. The α-phenyl-α-cyanoacetaldehydes and ethyl α-phenyl-α-cyanoacetales were prepared by literature procedures (5).

Table I

Pyrazolyltriazoles Prepared

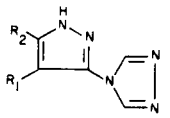


	Formula	X	R	M.p., °C	*Anal.* Calcd. Found	% Yield
3a	$C_{11}H_9N_5$	H	H	271-274	C, 62.5; H, 4.29; N, 33.2 C, 62.3; H, 4.32; N, 33.3	27
3b	$C_{11}H_8ClN_5$	*p*-Cl	H	257-260	C, 53.8; H, 3.28; N, 28.5; Cl, 14.4 C, 53.6; H, 3.38; N, 28.7; Cl, 14.5	32
3c	$C_{12}H_{11}N_5$	H	CH_3	330-333	C, 63.9; H, 4.92; N, 31.1 C, 63.8; H, 4.86; N, 31.1	85
3d	$C_{17}H_{13}N_5$	H	C_6H_5	318-321	C, 71.1; H, 4.56; N, 24.4 C, 69.9; H, 4.58; N, 24.6	75
3e	$C_{12}H_{10}ClN_5$	*p*-Cl	CH_3	281-284	C, 55.4; H, 3.88; N, 27.0; Cl, 13.7 C, 55.2; H, 4.00; N, 26.7; Cl, 13.6	62
3f	$C_{12}H_{10}BrN_5$	*p*-Br	CH_3	295-298	C, 47.4; H, 3.31; N, 23.0; Br, 26.3 C, 47.2; H, 3.26; N, 23.2; Br, 26.0	52
3g	$C_{11}H_8FN_5$ (a)	*p*-F	H	206-209	C, 57.5; H, 3.52; N, 30.6; F, 8.29 C, 57.7; H, 3.61; N, 31.0; F, 8.29	25
3h	$C_{12}H_{11}N_5$	*o*-CH_3	H	202-205	C, 63.9; H, 4.92; N, 31.1 C, 63.6; H, 4.95; N, 31.1	32
3i	$C_{12}H_{11}N_5$	*m*-CH_3	H	198-201	C, 63.9; H, 4.92; N, 31.1 C, 63.8; H, 4.78; N, 31.1	35
5a	$C_{11}H_9N_5O$	H	OH	296-299	C, 58.1; H, 3.99; N, 30.8 C, 58.0; H, 4.05; N, 31.1	36
5b	$C_{11}H_8ClN_5O$	*p*-Cl	OH	241-244	C, 50.5; H, 3.08; N, 26.8; Cl, 13.6 C, 50.8; H, 3.17; N, 27.0; Cl, 13.6	16
5c	$C_{11}H_8FN_5O$	*p*-F	OH	261-263	C, 53.8; H, 3.29; N, 28.6; F, 7.75 C, 53.5; H, 3.39; N, 28.7; F, 7.46	25



		X	R_1	R_2			
6a	$C_{11}H_9N_5 \cdot HCl$	H	H	H	210-216	C, 53.3; H, 4.07; N, 28.3; Cl, 14.3 C, 52.8; H, 4.10; N, 28.4; Cl, 14.2	90
6b	$C_{12}H_{11}N_5 \cdot HCl$	H	CH_3	H	212-214	C, 55.0; H, 4.62; N, 26.8; Cl, 13.5 C, 54.9; H, 4.57; N, 27.0; Cl, 13.3	85
6c	$C_{13}H_{11}N_5O$	H	H	CH_3CO	165-168	C, 61.7; H, 4.38; N, 27.7 C, 61.8; H, 4.36; N, 27.7	65
6d	$C_{13}H_{11}N_5O \cdot HCl$	H	H	CH_3CO	212-214	C, 53.9; H, 4.18; N, 24.2; Cl, 12.3 C, 54.0; H, 4.12; N, 24.1; Cl, 12.4	90
6e	$C_{14}H_{12}FN_5O$	*p*-F	CH_3	CH_3CO	172-174	C, 58.9; H, 4.24; N, 24.6; F, 6.66 C, 58.7; H, 4.29; N, 24.3; F, 6.83	55
6f	$C_{12}H_{11}N_5 \cdot HCl$	*m*-CH_3	H	H	215-220	C, 55.1; H, 4.62; N, 26.8; Cl, 13.6 C, 55.0; H, 4.67; N, 26.8; Cl, 13.4	20

Table I (continued)

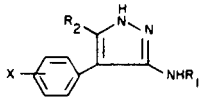


	Formula	R_1	R_2	M.p., °C	*Anal.*	Calcd. Found	% Yield
4a	$C_{11}H_9N_5$	H	C_6H_5	182-185 (b)			
4b	$C_{12}H_{11}N_5$	CH_3	C_6H_5	235-238	C, 63.9; H, 4.92; N, 31.1 C, 63.5; H, 4.61; N, 31.3		
4c	$C_{12}H_{11}N_5 \cdot HCl$	CH_3	C_6H_5	255-260	C, 55.1; H, 4.02; N, 26.7; Cl, 13.4 C, 54.8; H, 4.65; N, 26.7; Cl, 13.2		
4d	$C_{11}H_9N_5 \cdot HCl$	H	C_6H_5	230-235	C, 53.3; H, 4.07; N, 28.3; Cl, 14.3 C, 53.6; H, 4.20; N, 28.2; Cl, 14.4		

(a) N; Calcd.: 30.6; Found: 31.0. (b) Lit. m.p. 192° (16) reference (4).

Table II

3-Amino-4-phenylpyrazoles Prepared



	Formula	X	M.p., °C (a)	R_1	R_2
8a	$C_9H_9N_3$	H	179-183 (b)	H	H
8b	$C_9H_8ClN_3$	*p*-Cl	145-147 (c)	H	H
8c	$C_{10}H_9N_3O$	H	168-171 (a)	CHO	H
8d	$C_{11}H_{11}N_3O$	H	114-117 (d)	CH_3CO	H
8e	$C_{10}H_{10}FN_3$	*p*-F	139-142 (a)	H	CH_3
8f	$C_{10}H_{11}N_3$	*m*-CH_3	108-111 (e)	H	H
8g	$C_9H_9N_3O$	H	252-255 (a)	H	OH
8h	$C_{10}H_{10}ClN_3$	*m*-Cl	128-131 (a)	H	CH_3
8i	$C_9H_8ClN_3O$	*p*-Cl	245-247 (a)	H	OH
8j	$C_9H_8FN_3O$	*p*-F	245-248 (a)	H	OH

(a) All new compounds have correct analyses and supportative spectral data. (b) Lit. m.p. 176-177°, reference (2). (c) Lit. m.p. 141-143°, reference (2). (d) Lit. m.p. 155-157°, reference (2). (e) Lit. m.p. 120-121°, reference (2).

General Procedure for the Preparation of 4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole.

A solid mixture of 5 g. of α-phenyl-α-cyanoacetaldehyde and 10 g. of formylhydrazine were placed in an oil bath at 160-180°. After melting, the homogeneous liquid was maintained at 160°. After 3-5 hours, the mixture was cooled and the viscous oil or solid was triturated with water and chloroform. The residual solid was collected and recrystallized from methanol, methanol-DMSO, or DMSO.

4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole (**3a**).

An integral mixture of 5 g. of α-phenyl-α-cyanoacetaldehyde and 10 g. of formylhydrazine were heated in an oil bath at 170-180° and the homogeneous mixture was stirred and heated for 3 hours. After cooling the residual material was stirred with 50 ml. of water and 50 ml. of chloroform. The solid was collected by filtration and recrystallized from methanol-DMSO, m.p. 271-274° dec.; ir: 3125, 2900, 1600, 1625; nmr (DMSO-d_6): 7.2 (m, 5), 8.2 (s, 1), 8.7 (s, 2), 13.4 (NH); MS: M/e 211 (m^+) 100%. High resolution conditions 211.0836 observed, 211.0858 calcd.; uv (methanol): 238, (methanolic hydrogen chloride): 232, (sodium hydroxide-methanol): 255 mμ and this corresponds to uv adsorption of pyrazoles at 240 mμ (6).

4-[4-(*p*-Chlorophenyl)-3-pyrazolyl]-4*H*-1,2,4-triazole (**3b**).

An integral mixture of 5 g. of α-(4-chlorophenyl)-α-cyanoacetaldehyde and 10 g. of formylhydrazine were heated at 170° and treated as above, yield 2.8 g. (32%), m.p. 257-260°; nmr (DMSO-d_6): 7.2 (2, d), 7.4 (2, d, J = 14 Hz), 7.3 (s, 1), 7.8 (s, 2); MS: M/e 247, 246, 245 (m^+, 100%), 244.

4-(4-Phenyl-5-methyl-3-pyrazolyl)-4*H*-1,2,4-triazole (**3c**).

A mixture of 5 g. of cyanoketone and 10 g. of formylhydrazine were stirred and heated at 160° for 3 hours. After cooling, the residue was stirred with water and chloroform and the solid was collected and recrystallized from DMSO, yield 6.3 g. (80%), m.p. 330-333°; nmr (TFA-d): 2.5 (s, 3), 7.3 (m, 2), 7.5 (m, 3), 8.3 (s, 3); MS: M/e 225 (m^+, 100%), 224, 197.

4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole Hydrochloride.

A suspension of 1.75 g. of 4-phenyl-3-pyrazolyl-4*H*-1,2,4-triazole in 25 ml. of methanol and 25 ml. of water was stirred and concentrated hydrochloric acid was added dropwise until a clear solution was obtained. The solvent was removed and the residue recrystallized from methanol-ether at -10°, yield 1.7 g. (90%), m.p. 210-216° dec.

4-(5-Methyl-4-phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole Hydrochloride.

A suspension of 2 g. of 5-methyl-4-phenyl-3-pyrazolyl-4*H*-1,2,4-triazole in 25 ml. of methanol and 25 ml. of water was stirred and concentrated hydrochloric acid was added dropwise until a clear solution was obtained. The solvent was removed *in vacuo* and the residue recrystallized from methanol-ether (-10°), yield 1.85 g. (85%), m.p. 212-214°.

4-(1-Acetyl-4-phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole (**6c**).

A suspension of 1 g. of 4-(4-phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole in 10 ml. of acetic anhydride was refluxed until a clear solution was obtained (~ 1 hour). The clear solution was poured into ice water and stirred for 0.5 hour. The yellowish solid was collected and recrystallized from chloroform-hexane (charcoal) giving a white powder, m.p. 165-168° (65%); nmr (deuteriochloroform): 2.79 (s, 3), 7.2 (m, 2), 7.3 (m, 3), 8.4 (s, 3); MS: M/e m^+ (100%), 253, 295.

Treatment of a small sample in refluxing 1 *N* sodium hydroxide yielded starting pyrazolyltriazole.

3-Amino-4-phenylpyrazole (**8a**).

A mixture of 10 g. of α-phenyl-α-cyanoacetaldehyde and 20 g. of acetylhydrazine was heated at 160° for 3 hours. The sludge was partitioned between water and chloroform. The solid was collected and recrystallized from methanol, giving white cubes, m.p. 179-182°; nmr (deuteriochloroform-DMSO-d_6): 4.7 (e exch), 7.1-7.7 (m, 6); MS: m^+ 159, 160, (158 m^+ - 1, 9% of m^+), 143, 142, 104.

3-Amino-4-(*p*-chlorophenyl)pyrazole (**8b**).

An integral mixture of 5 g. of α-(4-chlorophenyl)-α-cyanoacetaldehyde and 10 g. of acetylhydrazine was heated at 165-170° for 3 hours. The clear melt was cooled to about 90° and ice-water and then chloroform was added and the mixture stirred for 20 minutes. The solid was collected by filtration and recrystallized from chloroform (charcoal), giving white plates, m.p. 145-147° (4.1 g., 72%); nmr (deuteriochloroform-DMSO-d_6): 6.0 (2, exch), 7.4 (m, 5); Lit. m.p. 141-143° (2).

3-*N*-Formylamide-4-phenylpyrazole (**8c**).

A suspension of 5 g. of α-phenyl-α-cyanoacetaldehyde and formylhydrazine (2.04 g., 1 eq.) in 15 ml. of diphenylether was was heated at 160°. After 3 hours, the dark reaction mixture was cooled and poured into hexane. The resultant solid was collected and recrystallized from chloroform-hexane (charcoal), m.p. 169-171°; Lit. m.p. 167-168° (2).

This material could also be obtained by refluxing 2 g. of 3-amino-4-phenylpyrazole in 10 ml. of ethyl formate until a clear solution was obtained. The mixture was cooled, filtered and recrystallized from chloroform-hexane, giving a white powder, m.p. 168-171°; ir: 3250, 1675; nmr (deuteriochloroform•DMSO-d_6): 7.1-7.5 (m, 5), 7.8 (s, 1), 8.3 (d, CHO, 1), 9.7 (NHC(=O), d, 1), 12.4 (NH, 1); MS: M/e m^+ 187, 158, 131, 104.

3-(*N*-Acetylamido)-4-phenylpyrazole (**8d**).

A suspension of 3-amino-4-phenylpyrazole (5 g., 0.03125 mole) in 15 ml. of pyridine was treated with stirring with acetic anhydride 3.19 g. (3 ml., 1 eq.). After stirring for 1 hour, the solution was poured into ice-water. The solid was collected and recrystallized from chloroform-hexane, giving white plates, m.p. 112-117°; Lit. m.p. 155-157° (2).

A mixture of α-phenyl-α-cyanoacetaldehyde (5 g.) and acetylhydrazine (2.6 g., 1 eq.) in 15 ml. of diphenyl ether was heated to 160° for 3 hours. After cooling, hexane was added and the solid collected and recrystallized from chloroform-hexane, giving slightly off white crystals, m.p. 108-113°.

4-(5-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole (**4a**).

A mixture of 5 g. of benzoylacetonitrile (Eastman) and 10 g. of formylhydrazine were heated at 160°. The cooled mixture was stirred with water and chloroform and the solid was collected and recrystallized from chloroform-methanol giving 8.4 g., 75% of a white powder 180-184°; nmr (deuteriochloroform•DMSO-d_6): 7.0 (s, 1), 7.4 (m, 2), 7.6 (m, 3), 8.9 (s, 2), 13.4 (NH); MS: M/e m^+ 211, 187, 159, 102; Lit. m.p. 192° (4).

4-(4-Phenyl-3-pyrazolyl)-4*H*-1,2,4-triazole (**3a**).

A mixture of 3-(*N*-formamido)-4-phenylpyrazole (4.5 g.) and formylhydrazine (9 g.) was heated at 160° for 2 hours. Workup gave triazole (3.2 g.), identical to that reported earlier.

Reaction of 3-(*N*-Formylamido)-4-phenylpyrazole with Acetylhydrazine.

Reaction of 2 g. of 3-(*N*-formamido)-4-phenylpyrazole and 4 g. of acetylhydrazine gave deformylated pyrazole.

4-Phenyl-5-(4*H*-1,2,4-triazol-4-yl)-3-pyrazolol (**5a**).

A mixture of 10 g. of ethyl phenylcyanoacetate (Aldrich) and 18 g. of formylhydrazine was heated at 165° for 3 hours. After cooling, the residue was stirred with water and chloroform. The solid was filtered and recrystallized from DMSO, yield 3.2 g. (36%), m.p. 296-299° giving a dark green ferric chloride test; nmr (DMSO): 7.1-7.3 (m, 5), 8.62 (s, 2), 10.5 (NH, exchangeable); MS: M/e 227 (m^+), 175, 118.

3-Amino-4-phenyl-3-pyrazolol.

A mixture of cyanoester (10 g.) and acetylhydrazine (20 g.) was heated at 160° for 3 hours. After cooling, the residue was stirred with chloroform and water and the resulting solid was collected and recrystallized from methanol•DMSO, yield 3.6 g. (13%), m.p. 252-255° of white material giving a dark brown color with ferric chloride; nmr (TFA): 7.4 (aryl); MS: M/e (m^+), 118.

Acknowledgments.

We wish to thank Mr. L. Brancone and staff for microanalysis, Mr. W. Fulmor, Mr. G. Morton and staff for spectral analysis, and Dr. R. E. Diehl (American Cyanamid Co., Princeton, New Jersey) for the data on the two step synthesis of 4-(4-phenyl-3-pyrazolyl)-4*H*-1,2,4-triazoles.

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