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

Table I. Acylamidine Derivatives 3, $R'C(O)N{=}CRN(CH_3)_2$

compd	R′	R	yield, %	mp, °C	formula[b]
3a	$3,5\text{-}(CH_3O)_2C_6H_3$	H	94	108-110	$C_{12}H_{16}N_2O_3$
3b	$3,5\text{-}(CH_3O)_2C_6H_3$	CH_3	90	90-92	$C_{13}H_{18}N_2O_3$
3c	$p\text{-}O_2NC_6H_4$	H	91	141-143	$C_{10}H_{11}N_3O_3$
3d	4-pyridyl	H	80	92-94	$C_9H_{11}N_3O$
3e	3-pyridyl	H	81	64-66	$C_9H_{11}N_3O$
3f	$3,4,5\text{-}(CH_3O)_3C_6H_2$	H	91	152-154	$C_{13}H_{18}N_2O_4$
3g	$3,4,5\text{-}(CH_3O)_3C_6H_2$	CH_3	91	121-123	$C_{14}H_{20}N_2O_4$
3h	C_6H_5	H	80	73-75[a]	$C_{10}H_{12}N_2O$
3i	$p\text{-}BrC_6H_4$	CH_3	90	133-135	$C_{11}H_{13}BrN_2O$
3j	$m\text{-}CF_3C_6H_4$	CH_3	81	77-79	$C_{12}H_{13}F_3N_2O$
3k	$p\text{-}CF_3C_6H_4$	CH_3	86	112-114	$C_{12}H_{13}F_3N_2O$

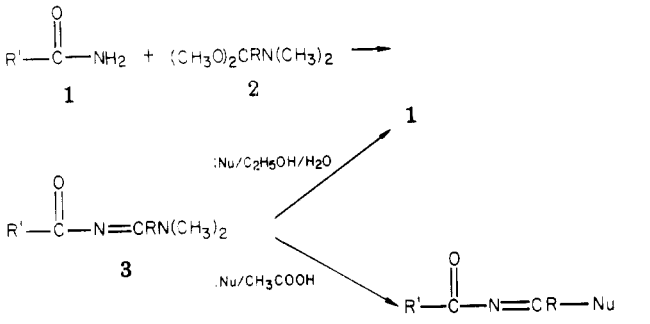
[a] Lit.[2] mp 67-69 °C. [b] Satisfactory analytical data (±0.3% for C, H, N, and X when present) were reported for all compounds in Tables I-IV except those for which literature melting point values are given.

amino)methylene moiety led to the discovery of a new synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles.

Results and Discussion

N′-Acyl-*N,N*-dimethylamidines **3** were prepared in excellent yields (80–94%) by reactions of amides **1** with *N,N*-dimethylformamide dimethyl acetal or *N,N*-dimethylacetamide dimethyl acetal.[2] The acylamidines **3** synthesized are tabulated in Table I.

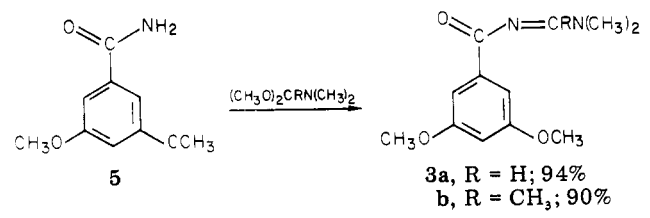
The acylamidines **3** reacted with nucleophiles in two different pathways, depending on the nature of reaction media. In aqueous ethanol, the acylamidines **3** were readily decomposed by hydrazine back to the starting amides **1**.



4a, Nu = OH
b, Nu = $NHNHCOOC_2H_5$
c, Nu = NHNHR″
d, Nu = NHOH

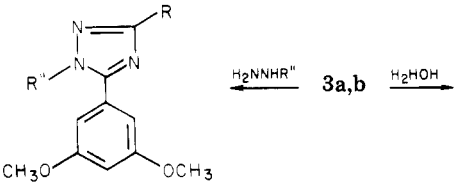
In acetic acid, however, the acylamidines **3** reacted readily at room temperature with nucleophiles such as water,[3] ethyl carbazate, hydroxylamine, and hydrazines to give the intermediates **4**. When heated, the intermediates **4c** and **4d** cyclized to give 1,2,4-triazoles and 1,2,4-oxadiazoles, respectively, in excellent yields, whereas the intermediate **4b** did not.

The efficiency of the new synthetic method is illustrated by the following examples. Reaction of 3,5-dimethoxybenzamide (**5**) with *N,N*-dimethylformamide dimethyl acetal or with *N,N*-dimethylacetamide dimethyl acetal at 120 °C gave the acylformamidine **3a** in 94% yield or the acylacetamidine **3b** in 90% yield. The acylformamidine **3a** then reacted with hydrazine hydrate in acetic acid at 90 °C to give the *s*-triazole **6a** in 92% yield or with methylhydrazine to give the 1,2,4-triazole **6b** in 70% yield. The acylformamidine **3a** also reacted with *p*-bromophenylhydrazine hydrochloride in a mixture of 5 N sodium hydroxide solution, 70% aqueous acetic acid, and *p*-dioxane at 90 °C to give the 1,2,4-triazole **6c** in 90% yield or with hydroxylamine hydrochloride to give the 1,2,4-oxadiazole **7a** in 71% yield. The acylacetamidine **3b** similarly

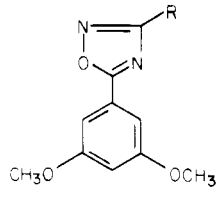


5

3a, R = H; 94%
b, R = CH_3; 90%



6a, R = H; R″ = H; 92%
b, R = H; R″ = CH_3; 70%
c, R = H; R″ = *p*-BrPh; 90%
d, R = CH_3; R″ = *p*-BrPh; 90%



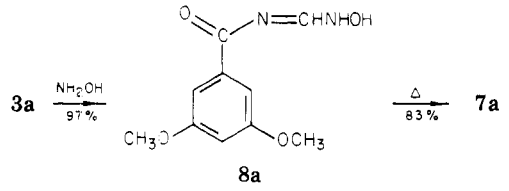
7a, R = H; 71%
b, R = CH_3; 95%

reacted with *p*-bromophenylhydrazine hydrochloride in a mixture of 5 N sodium hydroxide solution, 70% aqueous acetic acid, and *p*-dioxane at 90 °C to give the 1,2,4-triazole **6d** in 90% yield or reacted with hydroxylamine hydrochloride in 70% aqueous acetic acid at room temperature to give the 1,2,4-oxadiazole **7b** in 95% yield.

5-Monosubstituted 1,2,4-oxadiazoles are unstable and isomerize to acylcyanamides.[4] Therefore, an improved and stepwise procedure for the synthesis of 5-monosubstituted 1,2,4-oxadiazoles was developed. The acylformamidine **3a** reacted with hydroxylamine hydrochloride in a mixture of 5 N sodium hydroxide solution and 70% aqueous acetic acid at room temperature for 10 min to give the acylformamidine **8a** in 97% yield. The intermediate acylformamidine **8a**, when heated in a mixture of anhydrous acetic acid and *p*-dioxane at 90 °C, cyclized to give the 1,2,4-oxadiazole **7a** in 83% yield.

Twenty other 1,2,4-triazoles and 1,2,4-oxadiazoles were similarly prepared and are tabulated in Tables II and III,

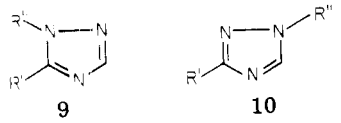
(1) Yang-i Lin and S. A. Lang, Jr., *J. Heterocycl. Chem.*, 14, 345 (1977).
(2) H. Weidinger and H. Eilingsfeld (Badische Anilin & Soda-Fabrik), Belgian Patent 629 972 (1963); M. Takeuchi and H. Tomioka (Chugai Pharmaceutical Co., Ltd.), Japan Kokai 77 125 141 (1977).
(3) Yang-i Lin and S. A. Lang, Jr., to be submitted for publication in *Synthesis*.
(4) G. Ponzio, *Gazz. Chim. Ital.*, 62, 415 (1932); C. Moussebois and F. Eloy, *Helv. Chim. Acta*, 47, 838 (1964).



8a

respectively. See Table IV for data on 8.

In theory, the reaction of the acylformamidine **3a** with a monosubstituted hydrazine (H_2NNHR'') can produce the two isomers **9** and **10**. Although the NMR analysis of the



9 10

crude product indicated the formation of a single disubstituted 1,2,4-triazole, the position of the substituent R'' could not be determined. Therefore, the structures of the 1,2,4-triazoles **6b** and **6c** were determined by single-crystal X-ray analyses.

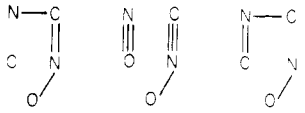
Crystallography. Crystals of **6b** and **6c** were obtained from benzene and ethanol, respectively. All intensity measurements were made on an Enraf-Nonius CAD-3 diffractometer (Ni-filtered Cu Kα radiation, $\theta/2\theta$ scans, pulse-height discrimination). The crystal data are given in Table V. Both structures were solved by using the MULTAN[5] direct-phase determination program. All refinement calculations were made with the XRAY72 system[6] using atomic tabulated scattering factors.[7]

The structures of the other 1,2,4-triazoles and 1,2,4-oxadiazoles synthesized in this report were all supported by NMR, IR, and elementary analyses.

As shown in Tables II and III, the 1,2,4-triazoles were synthesized in 70–95% yield and the 1,2,4-oxadiazoles in 81–95% yield. The success of this new synthetic reaction is attributed to the extremely fast and selective replacement of the dimethylamino moiety in acetic acid by a nucleophile such as $R''NHNH_2$ or NH_2OH, which is followed by the facile rate-determining intramolecular cyclization.

Numerous synthetic methods such as the Einhorn–Brunner reaction[8] (diacylimines and hydrazines), reaction of amidrazones and carboxylic acid derivatives,[9] and the Pellizzari reaction[9] (hydrazides and amides) can be utilized for the synthesis of the 1,2,4-triazoles shown in Table II. Of these intermolecular condensation reactions, the Einhorn–Brunner[8] reaction gives the best yields, ranging from 34 to 84%. In contrast, the rate-determining intramolecular cyclization reaction reported herein gives yields ranging from 70 to 95% and appears to be much more convenient. Nevertheless, the new 1,2,4-triazole synthesis may be termed "an improved Einhorn–Brunner reaction" if one considers the (dimethylamino)alkylidene moiety as a masked acyl function.

The chemistry of 1,2,4-oxadiazoles was reviewed recently by Clapp.[10] Two widely used general methods of synthesizing 1,2,4-oxadiazoles embrace 95% of the practical preparations of these compounds: the conversion of amidoximes by means of carboxylic acid derivatives to the cyclic structure (shown schematically in **11**) and the cycloaddition of nitrile oxides to nitriles in **12**. Evidently,



11 12 13

both methods (**11** and **12**) are applicable to the synthesis of the 3,5-disubstituted 1,2,4-oxadiazoles shown in Table III. However, only the acylformamidoxime method (**11**) is applicable to the synthesis of 5-monosubstituted 1,2,4-oxadiazoles, but in low yields.[11] Needless to say, our new method (**13**), which provides a new and general way for constructing the 1,2,4-oxadiazole ring system, is superior to the reported ones (**11** and **12**) in yield and convenience.

Experimental Section

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried at 78 °C (ethanol boiling point) under high vacuum for 5–24 h. IR spectra were measured on a Perkin-Elmer spectrophotometer (Model 21). NMR spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in ppm relative to internal tetramethylsilane.

General Preparation of Acylamidines. A solution of 10 g of amide in 20 mL of *N,N*-dimethylalkanamide dimethyl acetal (or diethyl acetal) was stirred at 120 °C for 1.5 h, during which time some methanol (or ethanol) was formed and collected through a reflux condenser. After the mixture was cooled, crystals were collected by filtration. In some cases, an appropriate amount of the corresponding *N,N*-dimethylalkanamide was added to the reaction mixture in order to dissolve the acylamine. Two examples are described as follows.

Example A: *N*-[(Dimethylamino)methylene]-3,5-dimethoxybenzamide (3a). A solution of 75.0 g of 3,5-dimethoxybenzamide in 150 mL of *N,N*-dimethylformamide dimethyl acetal was stirred at 120 °C for 1.5 h, during which time some methanol was formed and collected through a reflux condenser. After being cooled, the solution deposited 91.7 g (94%) of the desired product as colorless crystals: mp 108–110 °C; NMR ($CDCl_3$) δ 3.10 (s, NCH_3, 3), 3.14 (s, NCH_3, 3), 3.80 (s, OCH_3, 6), 6.58 (t, aromatic, 1), 7.42 (d, J = 1.5 Hz, aromatic, 2), 8.54 (s, =CH, 1).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.0; H, 6.83; N, 11.9. Found: C, 60.9; H, 6.87; N, 11.9.

Example B: *N*-[(Dimethylamino)ethylidene]-3,5-dimethoxybenzamide (3b). A solution of 75.0 g of 3,5-dimethoxybenzamide in 150 mL of *N,N*-dimethylacetamide dimethyl acetal (~85%) was stirred at 120 °C for 1.5 h, during which time some methanol was formed and collected through a reflux condenser. After being cooled, the solution deposited 93.1 g (90%) of the desired product as light tan crystals: mp 90–92 °C; NMR ($CDCl_3$) δ 2.29 (s, CH_3, 3), 3.11 (s, NCH_3, 6), 3.81 (s, OCH_3, 6), 6.57 (t, aromatic, 1), 7.31 (d, J = 1.5 Hz, aromatic, 2).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.4; H, 7.25; N, 11.2. Found: C, 62.2; H, 7.03; N, 11.2.

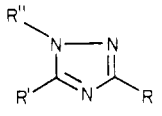
General Preparation of 3-Aryl-*s*-triazoles and 1-Alkyl-5-aryl-1*H*-1,2,4-triazoles. To a solution of hydrazine hydrate or alkylhydrazine (10% excess) in 100 mL of acetic acid was added 10.0 g of the acylamidine **3**. The reaction mixture was stirred at 90 °C for 1.5 h.

For 3-aryl-*s*-triazoles the mixture was concentrated under reduced pressure to ca. 15 mL. Upon addition of ether (ca. 50 mL), the solution deposited the product as colorless crystals.

For 1-alkyl-5-aryl-1*H*-1,2,4-triazoles the reaction mixture was evaporated under reduced pressure to an oil which was dissolved in chloroform. The chloroform solution was washed with saturated

(5) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(6) "X-Ray System", Technical Report TR-192, The Computer Science Center, University of Maryland, College Park, MD, 1972.
(7) "International Tables for X-Ray Crystallography", Vol. III, 2nd ed., Kynoch Press, Birmingham, England, 1968.
(8) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 3418 (1952); 141 (1954); 3319 (1954); Einhorn and Szelinsky, *Justus Liebigs Ann. Chem.*, **343**, 229 (1905).
(9) J. H. Boyer, *Heterocycl. Compd.*, **7**, 400, 436 (1961).
(10) L. B. Clapp, *Adv. Heterocycl. Chem.*, **20**, 65 (1976).
(11) R. Lenaers, C. Moussebois, and F. Eloy, *Helv. Chim. Acta*, **45**, 441 (1962).
(12) H. G. O. Becker, W. Riediger, L. Krahnert, and K. Wehner, East German Patent 67 130 (1969).
(13) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5914 (1951).

Table II. 1,2,4-Substituted Triazoles

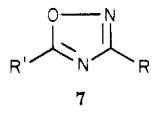


6

compd	R''	R	R'	yield, %	mp, °C	formula
6a	C_6H_5	H	3,5-$(CH_3O)_2C_6H_3$	90	110-112	$C_{16}H_{15}N_3O_2$
6b	CH_3	H	3,5-$(CH_3O)_2C_6H_3$	70	97-99	$C_{11}H_{13}N_3O_2$
6c	p-BrC_6H_4	H	3,5-$(CH_3O)_2C_6H_3$	90	141-143	$C_{16}H_{14}BrN_3O_2$
6d	p-BrC_6H_4	CH_3	3,5-$(CH_3O)_2C_6H_3$	90	125-127	$C_{17}H_{16}BrN_3O_2$
6e	p-FC_6H_4	H	3,5-$(CH_3O)_2C_6H_3$	82	113-115	$C_{16}H_{14}FN_3O_2$
6f	H	H	3,5-$(CH_3O)_2C_6H_3$	92	190-192	$C_{10}H_{11}N_3O_2$
6g	H	H	3,4,5-$(CH_3O)_3C_6H_2$	91	185-187	$C_{11}H_{13}N_3O_3$
6h	H	H	p-$O_2NC_6H_4$	81	228-229	$C_8H_6N_4O_2$
6i	H	H	3-pyridyl *N*-oxide	87	231-233	$C_7H_6N_4O$
6j	H	H	4-pyridyl	90	230-232[a]	$C_7H_6N_4$
6k	H	H	3-pyridyl	95	169-172[b]	$C_7H_6N_4$
6l	p-FC_6H_4	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	85	125-127	$C_{18}H_{18}FN_3O_3$
6m	CH_2CF_3	H	3,5-$(CH_3O)_2C_6H_3$	75	82-84	$C_{12}H_{12}F_3N_3O_2$
6n	C_6H_5	H	C_6H_5	87	85-87[c]	$C_{14}H_{11}N_3$

[a] Lit.[12] mp 202 °C. [b] Lit.[12] mp 174 °C. [c] Lit.[13] mp 90.5-91 °C.

Table III. 1,2,4-Substituted Oxadiazoles



7

compd	R	R'	yield, %	mp, °C	formula
7a	H	3,5-$(CH_3O)_2C_6H_3$	81, 71[a]	108-109	$C_{10}H_{10}N_2O_3$
7b	CH_3	3,5-$(CH_3O)_2C_6H_3$	95	90-91	$C_{11}H_{12}N_2O_3$
7c	H	p-$O_2NC_6H_4$	85	169-171	$C_8H_5N_3O_3$
7d	H	3,4,5-$(CH_3O)_3C_6H_2$	81	94-96	$C_{11}H_{12}N_2O_4$
7e	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	94	134-135	$C_{12}H_{14}N_2O_4$
7f	CH_3	p-BrC_6H_4	93	98-100	$C_9H_7N_2BrO$
7g	CH_3	m-$CF_3C_6H_4$	88	*b*	$C_{10}H_7F_3N_2O$
7h	CH_3	p-$CF_3C_6H_4$	92	66-68	$C_{10}H_7F_3N_2O$

[a] Obtained from procedure B for the preparation of 5-substituted 1,2,4-oxadiazoles in the Experimental Section. Others were obtained from procedure A. [b] Oil.

Table IV. Substituted *N*-(Hydroxyaminomethylene)benzamides 8, R'C(O)N=CHNHOH

compd	R'	yield, %	mp, °C	formula
8a	3,5-$(CH_3O)_2C_6H_3$	97	155-157	$C_{10}H_{12}N_2O_4$
8b	3,4,5-$(CH_3O)_3C_6H_2$	92	161-162	$C_{11}H_{14}N_2O_5$
8c	p-$O_2NC_6H_4$	97	165-167	$C_8H_7N_3O_4$

sodium bicarbonate solution and water, dried over sodium sulfate, and filtered. After removal of the chloroform, the residue was dissolved in ether. When cooled, the ether solution deposited the product as colorless crystals. Two examples are described as follows.

Example A: 3-(3,5-Dimethoxyphenyl)-*s*-triazole (6a). To a solution of 2.33 g (0.0466 mol) of hydrazine hydrate in 100 mL of acetic acid was added 10.0 g (0.0424 mol) of **3a**. The reaction mixture was then stirred at 90 °C for 1.5 h and concentrated under reduced pressure to ca. 10 mL. The addition of 50 mL of ether caused the deposition of 8.0 g (92%) of the product as colorless crystals: mp 190–192 °C; NMR (Me_2SO-d_6) δ 3.85 (s, OCH_3, 6), 6.61 (t, J = 2.5 Hz, aromatic, 1), 7.28 (d, J = 2.5 Hz, aromatic, 2), 8.40 (s, triazole, 1).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.40; N, 20.5. Found: C, 58.6; H, 5.44; N, 20.7.

Example B: 5-(3,5-Dimethoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (6b). To a solution of 2.16 g (0.0467 mol) of methylhydrazine in 100 mL of acetic acid was added 10.0 g (0.0424 mol) of **3a**. The reaction mixture was then stirred at 90 °C for 1.5 h and evaporated under reduced pressure to an oil which was dissolved in 250 mL of chloroform. The chloroform solution was washed with saturated sodium bicarbonate solution (60 mL) and water (60 mL), dried over sodium sulfate, and filtered. After removal of the chloroform, the residue was dissolved in 40 mL of ether. When cooled, the solution deposited 6.5 g (70%) of the

Table V. Summary of Crystal Data for Compounds 6b and 6c

	6b	6c
formula	$C_{11}H_{13}N_3O_2$	$C_{16}H_{14}N_3O_2Br$
fw	219.2	360.2
space group	$P\bar{1}$	$P2_1/c$
a	10.578 (3) Å	5.317 (3) Å
b	7.307 (2) Å	33.212 (13) Å
c	7.711 (2) Å	8.533 (4) Å
α	89.19 (2)°	90.0°
β	105.94 (2)°	93.31 (5)°
γ	107.91 (2)°	90.0°
cell vol	544 Å^3	1504 Å^3
Z	2	4
d_{calcd}	1.337 g cm^{-3}	1.590 g cm^{-3}
d_{obsd} (flotation in KI soln)	1.324 g cm^{-3}	1.614 g cm^{-3}
no. of rfletns measd	1635	2239
unobsd, $I < 2.0\sigma(I)$	271	496
crystal size	600 × 400 × 350 μm	500 × 350 × 300 μm
max θ	60°	60°
least-squares refinement	block diagonal	block diagonal
heavier atoms	anisotropic	anisotropic
hydrogens	isotropic	isotropic
final *R* (unweighted)	0.071	0.071

product as colorless crystals: mp 97–99 °C; NMR ($CDCl_3$) δ 3.83 (s, OCH_3, 6), 3.99 (s, CH_3, 3), 6.58 (t, J = 2.5 Hz, aromatic, 1), 6.81 (d, J = 2.5 Hz, aromatic, 2), 7.90 (s, triazole, 1).

Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.98; N, 19.2. Found: C, 60.1; H, 5.90; N, 19.1.

General Preparation of 1,5-Diaryl-1*H*-1,2,4-triazoles and 1,5-Diaryl-3-methyl-1*H*-1,2,4-triazoles. To a solution of phenylhydrazine hydrochloride (20% excess) in a mixture of 70% aqueous acetic acid (100 mL) and *p*-dioxane (50–100 mL) was added 10.0 g of the acylamidine **3**. The reaction mixture was stirred at 90 °C for 1.5–3 h.

For 1,5-diaryl-1*H*-1,2,4-triazoles the reaction mixture was then poured into water (200 mL). Crystals thus obtained were recrystallized from ethanol.

For 1,5-diaryl-3-methyl-1*H*-1,2,4-triazoles the reaction mixture was evaporated under reduced pressure to a residue. The residue was partitioned between chloroform and water. The chloroform layer was separated, washed with water, dried over sodium sulfate, and filtered. After removal of the chloroform, the residue was triturated with ether and recrystallized from ethanol/ether to give the product. Two examples are described as follows.

Example A: 1-(*p*-Bromophenyl)-5-(3,5-dimethoxyphenyl)-1*H*-1,2,4-triazole (6c). To a solution of 11.4 g (0.0510 mol) of 4-bromophenylhydrazine hydrochloride in a mixture of 10.2 mL (0.0510 mol) of 5 N sodium hydroxide solution, 100 mL of 70% aqueous acetic acid, and 50 mL of *p*-dioxane was added 10.0 g (0.0424 mol) of **3a**. The reaction mixture was then stirred at 90 °C for 1.5 h and poured into 120 mL of water. Yellow crystals (14.8 g) thus obtained were collected by filtration. Recrystallization from ethanol gave 13.8 g (90%) of the desired triazole as colorless crystals: mp 141–143 °C; NMR ($CDCl_3$) δ 3.70 (s, OCH_3, 6), 6.50 (t, J = 2.5 Hz, aromatic, 1), 6.60 (d, J = 2.5 Hz, aromatic, 2), 7.24 (d, J = 9 Hz, aromatic, 2), 7.54 (d, J = 9 Hz, aromatic, 2), 8.04 (s, triazole, 1).

Anal. Calcd for $C_{16}H_{14}BrN_3O_2$: C, 53.3; H, 3.92; N, 11.7; Br, 22.2. Found: C, 53.4; H, 3.95; N, 11.6; Br, 21.9.

Example B: 1-(*p*-Bromophenyl)-5-(3,5-dimethoxyphenyl)-3-methyl-1*H*-1,2,4-triazole (6d). To a solution of 10.7 g (0.0480 mol) of 4-bromophenylhydrazine hydrochloride in a mixture of 9.6 mL (0.048 mol) of 5 N sodium hydroxide solution, 100 mL of 70% aqueous acetic acid, and 100 mL of *p*-dioxane was added 10.0 g (0.0400 mol) of **3a**. The reaction mixture was stirred at 90 °C for 3 h and then evaporated under reduced pressure to a tan residue. The residue was partitioned between chloroform (250 mL) and water (50 mL). The chloroform layer was separated, washed with water (50 mL), dried over sodium sulfate, and filtered. After removal of the chloroform, the tan residue was triturated with ether to give 14.8 g of the crude product as slightly tan crystals, mp 123–125 °C. Recrystallization from ethanol/ether gave 13.5 g (90%) of the product as colorless crystals: mp 125–127 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 2.39 (s, CH_3, 3), 3.67 (s, OCH_3, 6), 6.55 (m, aromatic, 3), 7.27 (d, J = 8 Hz, aromatic, 2), 7.58 (d, J = 8 Hz, aromatic, 2).

Anal. Calcd for $C_{17}H_{16}BrN_3O_2$: C, 54.6; H, 4.31; N, 11.2; Br, 21.4. Found: C, 54.6; H, 4.44; N, 11.1; Br, 20.9.

Preparation of 5-Aryl-1,2,4-oxadiazoles. Two procedures, A and B, have been developed for the synthesis of 5-aryl-1,2,4-oxadiazoles. Procedure A involved the isolation of the intermediate, namely, *N*-[(hydroxyamino)methylene]benzamide, whereas procedure B did not. As is evident from Table III, procedure A gave better yields. Both procedures for the synthesis of 5-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole (**7a**) are described as follows.

5-(3,5-Dimethoxyphenyl)-1,2,4-oxadiazole (7a). Procedure A. To a solution of 3.54 g (0.0510 mol) of hydroxylamine hydrochloride in a mixture of 10.2 mL (0.0510 mol) of 5 N sodium hydroxide solution and 50 mL of 70% aqueous acetic acid was added 10.0 g (0.0424 mol) of **3a**. The reaction mixture was stirred at room temperature for 10 min and then diluted with 30 mL of water. After the mixture was cooled in an ice bath for 1 h, colorless crystals were collected by filtration, washed with water, and dried, leaving 9.2 g (97%) of **8a** as colorless crystals: mp 155–157 °C; NMR ($CDCl_3$/Me_2SO-d_6) δ 3.82 (s, OCH_3, 6), 6.65 (t, J = 2.5 Hz, aromatic, 1), 7.06 (d, J = 2.5 Hz, aromatic, 2), 7.66 (br peak, =CH, 1), 9.74 (br peak, NH, 1), 10.67 (br peak, OH, 1).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.39; N, 12.5. Found: C, 53.4; H, 5.14; N, 12.4.

N-[(Hydroxyamino)methylene]-3,5-dimethoxybenzamide (**8a**; 9.2 g) thus obtained was dissolved in a mixture of anhydrous acetic acid (70 mL) and *p*-dioxane (70 mL). The reaction mixture was stirred at 90 °C for 1.5 h, cooled down to room temperature, and diluted with water (140 mL). After the mixture was cooled in an ice bath for 2 h, colorless crystals were collected by filtration and dried, leaving 7.0 g (83%) of the product: mp 108–109 °C; NMR ($CDCl_3$) δ 3.85 (s, OCH_3, 6), 6.65 (t, J = 2.5 Hz, aromatic, 1), 7.25 (d, J = 2.5 Hz, aromatic, 2), 8.44 (s, oxadiazole, 1).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.2; H, 4.89; N, 13.6. Found: C, 58.4; H, 4.89; N, 13.5.

Procedure B. To a solution of 3.54 g (0.0510 mol) of hydroxylamine hydrochloride in a mixture of 10.2 mL (0.0510 mol) of 5 N sodium hydroxide solution, 50 mL of *p*-dioxane, and 100 mL of 70% aqueous acetic acid was added 10.0 g (0.0424 mol) of **3a**. The reaction mixture was then stirred at 90 °C for 1.5 h. When cooled, the solution deposited 6.20 g (71%) of the desired product as colorless crystals, mp 108–109 °C.

General Preparation of 5-Aryl-3-methyl-1,2,4-oxadiazoles. To a solution of hydroxylamine hydrochloride (20% excess) in a mixture of 5 N sodium hydroxide solution (20% excess) and 70% aqueous acetic acid (50–65 mL) was added 10.0 g of the acylamidine **3**. The reaction mixture was stirred at room temperature for 20 min–5 h, depending on the substituent of the phenyl in the acylamidine **3**. The reaction is slower with an electron-withdrawing substituent.

For 3-methyl-5-[*m*-(trifluoromethyl)phenyl]-1,2,4-oxadiazole (**7g**) the reaction mixture was evaporated under reduced pressure to a residue which was dissolved in chloroform. The chloroform solution was washed with water, dried over sodium sulfate, and filtered. After removal of the chloroform, the residue was distilled under reduced pressure to give the product.

For other 1,2,4-oxadiazoles the reaction mixture was diluted with 30 mL of water. After the mixture was cooled in an ice bath for 1 h, the product was collected by filtration, washed with water, and dried. An example is described as follows.

5-(3,5-Dimethoxyphenyl)-3-methyl-1,2,4-oxadiazole (7b). To a solution of 3.34 g (0.0480 mol) of hydroxylamine hydrochloride in a mixture of 9.6 mL (0.048 mol) of 5 N sodium hydroxide solution and 50 mL of 70% aqueous acetic acid was added 10.0 g (0.0400 mol) of **3b**. The reaction mixture was stirred at room temperature for 20 min and then diluted with 30 mL of water. After the mixture was cooled in an ice bath for 1 h, colorless crystals were collected by filtration, washed with water, and dried, leaving 8.4 g (95%) of the product: mp 90–91 °C; NMR ($CDCl_3$) δ 2.45 (s, CH_3, 3), 3.84 (s, OCH_3, 6), 6.63 (t, J = 2.5 Hz, aromatic, 1), 7.21 (d, J = 2.5 Hz, aromatic, 2).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.49; N, 12.7. Found: C, 59.8; H, 5.46; N, 12.7.

Acknowledgment. We wish to thank Mr. L. Brancone and staff for microanalyses and Dr. W. Gore and staff for spectral data.

Registry No. **1** (R^1 = 3,5-$(CH_3O)_2C_6H_3$, 17213-58-0; **1** (R^1 = *p*-$O_2NC_6H_4$), 619-80-7; **1** (R^1 = 4-pyridyl), 1453-82-3; **1** (R^1 = 3-pyridyl), 98-92-0; **1** (R^1 = 3,4,5-$(CH_3O)_3C_6H_2$), 3086-62-2; **1** (R^1 = C_6H_5), 55-21-0; **1** (R^1 = *p*-BrC_6H_4), 698-67-9; **1** (R^1 = *m*-$CF_3C_6H_4$), 1801-10-1; **1** (R^1 = *p*-$CF_3C_6H_4$), 1891-90-3; **2** (R = H), 4637-24-5; **2** (R = CH_3), 18871-66-4; **3a**, 71565-85-0; **3b**, 71565-86-1; **3c**, 65675-91-4; **3d**, 71565-87-2; **3e**, 71565-88-3; **3f**, 71565-89-4; **3g**, 71597-11-0; **3h**, 41876-75-9; **3i**, 71565-90-7; **3j**, 71565-91-8; **3k**, 71565-92-9; **6a**, 71565-93-0; **6b**, 71597-10-9; **6c**, 71565-94-1; **6d**, 71565-95-2; **6e**, 71565-96-3; **6f**, 71565-97-4; **6g**, 71565-98-5; **6h**, 6219-52-9; **6i**, 71565-99-6; **6j**, 14803-99-7; **6k**, 23195-63-3; **6l**, 71566-00-2; **6m**, 71566-01-3; **6n**, 24685-75-4; **7a**, 71566-02-4; **7b**, 71566-03-5; **7c**, 71566-04-6; **7d**, 71566-05-7; **7e**, 71566-06-8; **7f**, 71566-07-9; **7g**, 71566-08-0; **7h**, 71566-09-1; **8a**, 71566-10-4; **8b**, 71566-11-5; **8c**, 71566-12-6; hydrazine hydrate, 7803-57-8; methyl hydrazine, 60-34-4; 4-bromophenylhydrazine hydrochloride, 622-88-8; phenylhydrazine hydrochloride, 27140-08-5; 4-fluorophenylhydrazine hydrochloride, 823-85-8; trifluoroethylhydrazine hydrochloride, 5042-29-5; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available: Atomic coordinates, thermal parameters, and bond distances and angles for **6b** and **6c** (8 pages). Ordering information is given on any current masthead page.