crystallized from ethanol–water solutions with decolorizing carbon.

Kinetic Runs in 80% Me_2SO and CH_3CN. Stock solutions of TNB, BA, NEt_3, and the salts were prepared in either of the solvents and thermostated at the experimental temperature, and the quantities for each run were pipetted into volumetric flasks and diluted to the required volume. The decrease in absorbance as a function of time was then recorded at 570 nm against solvent blank by employing a nonrecording Carl-Zeiss VSU2-P spectrophotometer.

Kinetic Runs in Me_2SO. Kinetics of the cyclization process catalyzed by Me_2SO were followed by mixing the appropriate solutions (preequilibrated to required temperature) and transferring the reaction mixture to a thermostated cell in a Carl-Zeiss VSU2-P spectrophotometer. The increase in absorbance as a function of time was then recorded at 510 nm against solvent blank. Figures 1 and 5 were obtained on a Carl-Zeiss UV–vis specord.

Acknowledgment. We are very grateful to the Department of Science and Technology, Government of India, for a research grant.

Registry No. 1:1 TNB–(*p*-OCH_3)BA complex, 95346-53-5; 1:1 TNB–(*p*-$NHCOCH_3$)BA complex, 95346-54-6; 1:1 TNB–(*p*-CH_3)BA complex, 95346-55-7; 1:1 TNB–BA complex, 95346-56-8; 1:1 TNB–(*p*-Cl)BA complex, 95346-57-9; 1:1 TNB–(*p*-Br)BA complex, 95346-58-0; 1:1 TNB–(*m*-Cl)BA complex, 95346-59-1; 1:1 TNB–(*m*-Br)BA complex, 95346-60-4; 1:1 TNB–(*m*-NO_2)BA complex, 95346-61-5; 1:1 TNB–(*p*-NO_2)BA complex, 95346-62-6; NEt_3, 121-44-8.

Direct Synthesis of 5-Methyl-3-aryl-1,2,4-oxadiazoles from Aryl Aldehydes, Nitroethane, and Ammonium Acetate

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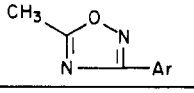
The condensation of 2,5-dimethoxybenzaldehyde (**1b**) with nitroethane and ammonium acetate in glacial acetic acid has been found to give three different products, depending on reactant ratio and reaction time. At an aldehyde:nitroethane:ammonium acetate ratio of 1:1.5:0.8 a normal Knoevenagel condensation occurred, yielding 1-(2,5-dimethoxyphenyl)-2-nitropropene. At a reactant ratio of 1:3:2 (same reactant sequence), the primary product was 2,5-dimethoxybenzonitrile, and at a reactant ratio of 1:40:8, with extended reflux time, the major product was 3-(2,5-dimethoxyphenyl)-5-methyl-1,2,4-oxadiazole (**8b**). This last reaction served as a prototype for a new oxadiazole synthesis which was then extended to include six additional 5-methyl-3-aryl-1,2,4-oxadiazoles (**8a,c–g**; where aryl = Ph, 2,5-dimethoxyphenyl, 2,4-dichlorophenyl, *m*-chlorophenyl, *p*-tolyl, 3,5-dimethoxyphenyl, and *p*-carboxyphenyl), whose structures were assigned on the basis of ^{13}C NMR characteristics of known reference compounds. Benzonitrile also reacted with excess nitroethane and ammonium acetate to yield 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**). The overall mechanism of oxadiazole formation is shown to be dependent on a preliminary reaction wherein the nitroalkane, in the presence of ammonium acetate and acetic acid, is first transformed into the corresponding alkanoic acid and hydroxylamine. Hydroxylamine then converts the aromatic aldehyde, via the intermediary nitrile, to the oxadiazoles following reactions of established precedent.

Major synthetic routes to the 1,2,4-oxadiazoles have been recently reviewed by Clapp,[1] who pointed out that 95% of the practical preparations are encompassed by two general methods; viz., (a) the condensation of amidoximes with carboxylic acid derivatives, and (b) the dipolar cycloaddition of nitrile oxides to nitriles. Subsequently, Lin and co-workers[2] reported a new general method in which *N'*-acyl-*N,N*-dimethylamides react with hydroxylamine to form 3,5-disubstituted or 5-monosubstituted 1,2,4-oxadiazoles in high yields.

We have now observed a new and unusual formation of 5-methyl-3-aryl-1,2,4-oxadiazoles (**8a–g**, Table I) from the reaction of aromatic aldehydes with nitroethane in the presence of ammonium acetate and report here several examples of the synthesis along with evidence concerning the mechanism of the transformation (Scheme I).

The Henry (Knoevenagel) condensation of aromatic aldehydes with nitroalkanes is by now a classical route to β-nitrostyrenes.[3] In a particular application of this process we had prepared 1-(2,5-dimethoxyphenyl)-2-nitropropene (**2b**) from 2,5-dimethoxybenzaldehyde (**1b**), nitroethane, and ammonium acetate (ratio 1:1.5:0.8) via a 3-h reflux in acetic acid essentially as described in the literature.[4] While the yield was quite adequate (70%), an attempt was made to improve it by altering the proportions of **1b**:

Table I. ^1H and ^{13}C NMR Resonance Assignments[a] for the 5-Methyl-3-aryl-1,2,4-oxadiazoles 8a–g



		δ (^1H)	δ (^{13}C)		
8	Ar	5-Me	5-Me	C-3	C-5
a	phenyl	2.54	11.8	168.0	176.1
b	2,5-dimethoxyphenyl	2.65	12.2	166.8	175.4
c	2,4-dichlorophenyl	2.68	12.0	166.2	176.0
d	*m*-chlorophenyl	2.64	12.3	167.4	176.8
e	*p*-tolyl	2.38	12.2	168.3	176.2
f	3,5-dimethoxyphenyl	2.46	12.4	168.4	176.5
g	*p*-carboxyphenyl	2.70	12.0	167.0	177.7

[a] δ values are ppm with respect to Me_4Si.

(1) Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *20*, 65.
(2) Lin, Y.; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
(3) (a) Jones, G. "Organic Reactions"; Wiley New York, 1967; Vol. 15, Chapter 2. (b) Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
(4) Coutts, R. T.; Malicky, J. L. *Can. J. Chem.* **1973**, *51*, 1402.

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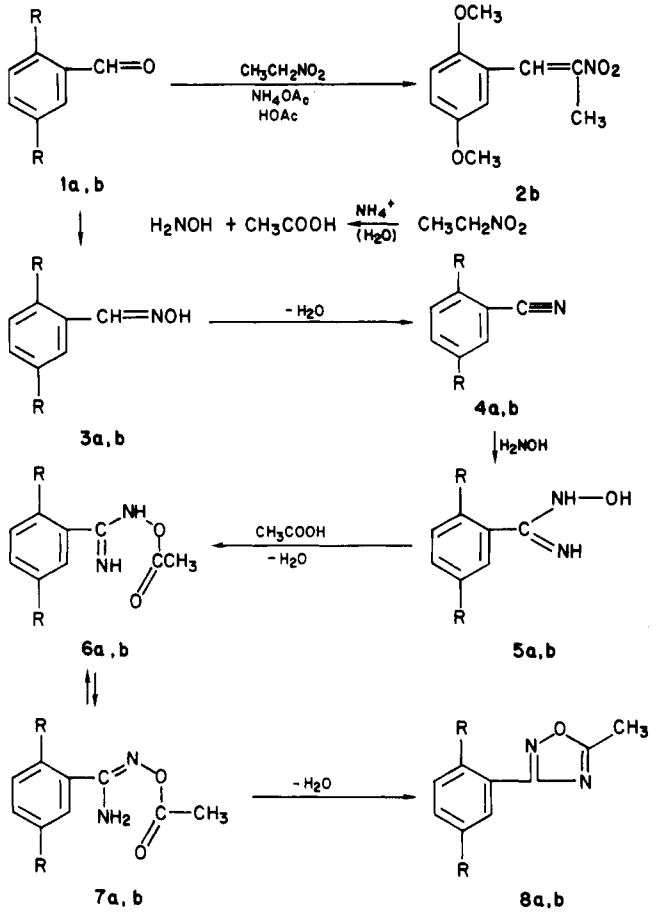
Scheme I[a]



[a] Series a, R = H, series b, R = OCH_3.

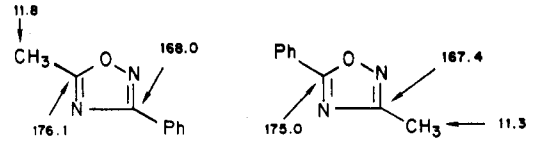
$EtNO_2$:NH_4OAc to 1:3:2, and refluxing under nitrogen for several hours. This time there resulted (62% yield) a new product, 2,5-dimethoxybenzonitrile (**4b**), which was identified by NMR, IR, and mass spectroscopy.

A literature survey revealed that a similar conversion of aromatic aldehydes to nitriles had already been reported[5] using nitropropane and ammonium monohydrogen phosphate. Since the literature study was of limited scope, the reaction of **1b** as described above was repeated with further variation of reactant ratios and with the intent of further increasing the efficiency of the aldehyde to nitrile conversion. Surprisingly, at an aldehyde(**1b**):nitroethane:ammonium acetate ratio of 1:40:8 and a 72-h reflux in glacial acetic acid, only a trace of the nitrile was obtained by preparative TLC. The major product isolated under these conditions was 3-(2,5-dimethoxyphenyl)-5-methyl-1,2,4-oxadiazole (**8b**), whose structure was subsequently assigned on the basis of proton and ^{13}C NMR spectroscopy and mass spectrometry as described below.

The convenience of this one-pot synthesis of 1,2,4-oxadiazoles seemed worthy of extension and the reaction was elaborated to include six additional examples, including four of known structure (**8a,c,e,g**), all summarized in Table I, along with ^{13}C NMR assignments for the methyl substituent and the C-3 and C-5 of the oxadiazole ring.

The carbon atoms of the 1,2,4-oxadiazole ring were characterized unequivocally by the ^{13}C NMR spectra (Scheme II) of authentic 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**)[6] and its isomer 3-methyl-5-phenyl-1,2,4-oxadiazole

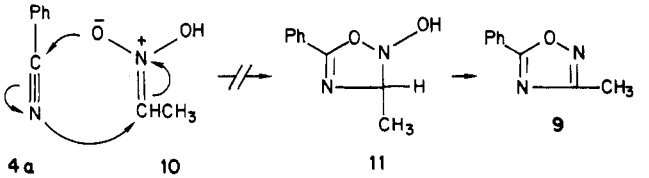
Scheme II. ^{13}C Resonance Assignments (ppm) for Isomeric Methylphenyl-1,2,4-oxadiazoles



(**9**),[7] each of which was synthesized unambiguously from the corresponding amidoxime (benzamidoxime and acetamidoxime, respectively). All of the oxadiazoles showed a ^{13}C resonance near 175 ppm and another near 167 ppm in the completely decoupled spectra. The nondecoupled spectra showed some long-range coupling between the methyl protons and the carbon (C-3 or C-5) of the oxadiazole ring bearing the methyl group. Selective irradiation of the protons of the methyl group caused this splitting to collapse to an NOE-enhanced singlet for both the methyl carbon and the adjoining ring carbon. In this way the carbon resonance at lower field could be clearly correlated with C-5 of the heterocyclic ring of 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**). Similar decoupling experiments on the remaining oxadiazoles **8b–g** of Table I showed that in each case the carbon resonating at lower field (175.4–177.7 ppm) was attached to the ring-methyl substituent. In contrast, selective irradiation of the methyl protons of authentic 3-methyl-5-phenyl-1,2,4-oxadiazole (**9**) showed that the methyl group was on the higher field (167.4 ppm) carbon (C-3) of the oxadiazole ring (cf. Scheme II).

Since the conversion of aromatic aldehydes to the corresponding nitriles under similar reaction conditions had already been demonstrated, it seemed possible that the nitriles were intermediates on the pathway to the 1,2,4-oxadiazoles. Accordingly, we subjected benzonitrile to reaction with excess nitroethane and ammonium acetate and again observed formation of 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**), identical in all respects with an authentic sample.[6] Indeed, intermittent monitoring of the reaction mixtures by TLC showed that oxadiazole formation from benzonitrile was faster than when benzaldehyde was the starting material.

A priori it is easy to rationalize the formation of a 1,2,4-oxadiazole ring from benzonitrile and the aci-nitro form (**10**) of nitroethane via a dipolar cycloaddition reaction (cf. the reaction sequence **4a** + **10** → **11** → **9**).

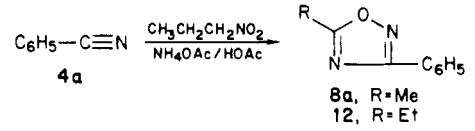


However, the normal polarities of the reactants **4a** and **10** would be expected to yield intermediate **11**, which on dehydration would afford the wrong isomer, 3-methyl-5-phenyl-1,2,4-oxadiazole (**9**), which is not an observed product. Hence, the conversion of aromatic aldehydes (or the corresponding carbonitriles) to 3-aryl-5-methyl-1,2,4-oxadiazoles (**8**) must take a different course.

In order to determine whether the two-carbon moiety comprising carbon-5 of the oxadiazole ring and the substituent methyl group did indeed arise from the nitroethane or alternately from the acetic acid, we carried out a simple crossover experiment as follows: benzonitrile was

(5) Blatter, H. M.; Lukaszewski, H.; De Stevens, G. *J. Am. Chem. Soc.* **1961**, *83*, 2203.
(6) Ooi, N. S.; Wilson, D. A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1792.
(7) Eloy, F. *Fortschr. Chem. Forsch.* **1965**, *4*, 807.

allowed to react with 1-nitropropane in the presence of ammonium acetate and acetic acid. Surprisingly, the



products, separated by column chromatography and quantitatively analyzed by both GC and NMR, included both 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**, 41% yield) and 5-ethyl-3-phenyl-1,2,4-oxadiazole (**12**, 32% yield). In an analogous experiment involving benzonitrile, nitroethane, ammonium propionate, and propionic acid, again both the 5-methyl (**8a**) and 5-ethyl (**12**) derivatives were obtained, indicating that the R-C-5 unit of the oxadiazoles arose from both the carboxylic acid and from the nitroalkane.

The mineral acid catalyzed rearrangement of nitroalkanes to hydroxamic acids, with subsequent hydrolysis to the corresponding carboxylic acids and hydroxylamine, has long been known[8,9] and has been most efficiently accomplished (yields in the 90% range) with 85% sulfuric acid.[9] Since it appeared possible that the same kind of process was occurring as a preliminary step in the oxadiazole syntheses under consideration, we subjected 1-nitropropane to 72-h reflux with ammonium acetate and acetic acid, conditions approximating those of the reaction with aromatic aldehydes or nitriles. The reaction occurred

$$CH_3CH_2CH_2NO_2 \xrightarrow[H_2O]{NH_4OAc/HOAc} CH_3CH_2COOH + H_2NOH$$

to give propionic acid in 26% yield, as shown by GC analysis of the products. In a separate and comparable experiment, the hydroxylamine was trapped with benzophenone to form benzophenone oxime (cf. Experimental Section) in good yield.

Although no water was deliberately introduced into the above reaction mixtures, there was enough present in the acetic acid, as well as in the hygroscopic ammonium acetate, to initiate formation of propionic acid and hydroxylamine. Once hydroxylamine has been formed the remaining steps in the oxadiazole synthesis follow normal literature precedent as summarized in Scheme I, which shows nitrile **4** formation by dehydration of the aldoximes **3**. Further addition of hydroxylamine to the nitriles **4** would then give the amidoximes **5**, which are acylated by the carboxylic acids present to yield *O*-acylamidoximes (**6** $\rightleftharpoons$ **7**), known precursors of 1,2,4-oxadiazoles **8**.[6,7] Since additional water is produced in these later condensation steps, the further conversion of nitroalkane to carboxylic acid plus hydroxylamine is sustained.

Overall, the reaction of aromatic aldehydes with excess nitroethane and ammonium acetate in glacial acetic acid leads to well-defined 3-aryl-5-methyl-1,2,4-oxadiazoles in low to moderate yields (12–57%) of analytically pure products. While no attempts were made to optimize these isolated product yields, the crossover experiments, wherein the oxadiazoles produced were quantitatively analyzed by GC, showed that higher yields (54% and 73% observed) were possible. The convenience of this synthesis directly from readily available aromatic aldehydes makes the reaction an attractive route to substituted 1,2,4-oxadiazoles, and the process is an interesting divergent pathway from the usual Knoevenagel condensation of aromatic aldehydes with nitroalkanes.

(8) Nenitsescu, C. D.; Isacescu, D. A., *Bull. Soc. Chim., Roumania* **1932**, *14*, 53.
(9) Lippincott, S. B.; Hass, H. B. *Ind. Eng. Chem.* **1939**, *31*, 118.

Experimental Section

General Methods. Proton and carbon-13 NMR Spectra were recorded on a JOEL FX90Q multinuclear spectrometer with proton chemical shifts referenced to Me_4Si and carbon resonances referenced to the solvent. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer, and mass spectra were obtained by using a Finnegan Model 4021 automated gas chromatograph–mass spectrometer system. Melting points (uncorrected) were determined on a Mel-Temp apparatus.

Column chromatography was performed by using flash chromatographic methods in which the elution solvent is forced by nitrogen pressure through a glass column, which had been dry-packed with silica gel (Merck silica gel 60, 230–400 mesh), such that the solvent moved through the column at a rate of about 2 in. per min. Preparative TLC was carried out on Analtech silica gel GF plates (20 × 20 cm) of 500- or 1000-μm thickness. Whenever possible, reaction progress was followed by analytical TLC which employed Merck pre-coated sheets (silica gel 60 F_{254}, 200-μm thickness).

Gas chromatography was performed on a Hewlett-Packard Model 5880A instrument equipped with a 12-m capillary column packed with cross-linked methyl silicone.

5-Methyl-3-phenyl-1,2,4-oxadiazole (8a). Method A: From Benzaldehyde. A solution of benzaldehyde (2.0 mL, 19.7 mmol), ammonium acetate (12 g, 150 mmol), and nitroethane (50 mL, 700 mmol) in acetic acid (25 mL) was refluxed under N_2 for 72 h. The mixture was then cooled to room temperature, basified with 25% NaOH, and extracted with three 100-mL portions of ether. The combined extracts were dried ($MgSO_4$) and the solvent was removed, leaving a yellow oil which was treated by column chromatography ($CHCl_3$). The major fraction (1.69 g) formed large, transparent, waxy prisms when kept at 0 °C overnight. However, the TLC still showed some trace of impurities so column chromatography (ether/petroleum ether, 1:15) was repeated and three fractions were isolated. Fraction A was a white solid (7 mg) which exhibited two aromtic multiplets in the proton spectrum but no methyl signal; Fraction B was a colorless oil (70 mg) which had the following spectral characteristics: ^1H NMR ($CDCl_3$) δ 2.56 (s, 3 H), 7.51 (m, 3 H), 7.72 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 9.60, 126.0, 127.9, 129.1, 130.4, 149.5, 153.8; IR (neat) 1448, 1435, 1382, 1257, 1009, 972, 886, 763, 685 cm^{-1}. Fraction C was a colorless oil (1.58 g, 50%) which formed waxy prisms of 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**) at 0 °C: R_f 0.47 ($CHCl_3$); mp 34–38 °C (lit.[10] mp 41 °C); ^1H NMR ($CDCl_3$) δ 2.54 (s, 3 H), 7.43 (m, 3 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.8, 126.6, 126.9, 128.5, 130.7, 168.0, 176.1; IR (neat) 3040, 2920, 1592, 1571, 1525, 1472, 1442, 1353, 1260, 896, 712, 682 cm^{-1}.

Method B: From Benzonitrile. A mixture of benzonitrile (2.00 g, 19 mmol), ammonium acetate (12.0 g, 156 mmol), nitroethane (52.25 g, 700 mmol), and glacial acetic acid (25 mL) was refluxed under N_2 for 48 h. The resulting solution was cooled in ice and basified to pH 8 with 10% NaOH. The solution was extracted with 2 × 50 mL portionsof ether, and the extracts were washed once with water and dried (Na_2SO_4). Evaporation of the ether left 1.96 g of yellow oil which was taken up in hexane and chromatographed on 50 g of silica gel 60 (30–70 mesh) in a 2 × 30 cm column using 1:1 (v:v) hexane benzene as eluent. There was obtained 0.85 g (28%) of 3-phenyl-5-methyl-1,2,4-oxadiazole as white crystals, mp 38–39 °C. The ^1H and ^{13}C NMR and IR spectra were identical with those obtained when benzaldehyde was the starting material.

Method C: From Benzamidoxime. Authentic 5-methyl-3-phenyl-1,2,4-oxadiazole was obtained from benzamidoxime[6] and refluxing acetic anhdride essentially as described by Tiemann and Krüger.[10] The ^1H and ^{13}C NMR spectra and the infrared spectrum of this compound were identical with those obtained above when benzaldehyde or benzonitrile were the starting materials.

3-Methyl-5-phenyl-1,2,4-oxadiazole (9). This compound was obtained by reacting acetamidoxime[6] with benzoyl chloride. The

(10) Tiemann, F.; Krüger, P. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1696.

resulting *O*-benzoyl acetamidoxime was cyclized to 3-methyl-5-phenyl-1,2,4-oxadiazole by heating at 170 °C (50° above the melting point) for 3 h: mp 57.5–59.5 °C (lit[7] mp 57 °C); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3 H), 7.47 (m, 3 H), 8.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.3, 123.9, 127.6, 128.7, 132.2, 167.4, 175.0; IR (KBr) 3060, 2900, 2920, 1600, 1560, 1443, 1425, 1390, 1337, 780, 712, 678 cm^{-1}.

As expected, the heterocyclic carbons have resonances similar to those found with the 5-methyl 3-phenyl isomer, and it can be shown by selective decoupling that the methyl group is now attached to the carbon at higher field (δ 167.4).

2,5-Dimethoxybenzonitrile (4b). A solution of 2,5-dimethoxybenzaldehyde (11.25 g, 68 mmol), ammonium acetate (10.45 g, 136 mmol), and nitroethane (15.20 g, 202 mmol) in glacial acetic acid (50 mL) was refluxed under N_2 for 10 h. The solution was diluted to the cloud point with 60 mL of water followed by 10 mL of 95% ethanol to give a homogeneous soltuion which was refrigerated overnight to yield 6.85 g (62%) of crude nitrile, mp 77–79 °C. Recrystallization from methanol gave beige needles: mp 80–81 °C (lit.[11] mp 81–83 °C); ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H), 3.88 (s, 3 H), 6.84 to 7.18 (m, 3 H); IR (KBr) 3020 (w), 2980, 2847, 2225, 1582, 1505, 1290, 1240, 1038, 1016, 812 cm^{-1}.

5-Methyl-3-(2,5-dimethoxyphenyl)-1,2,4-oxadiazole (8b). A mixture of 2,5-dimethoxybenzaldehyde (2.0 g, 12 mmol), ammonium acetate (7.4 g, 96 mmol), and nitroethane (36.0 g, 480 mmol) in glacial acetic acid (15 mL) was refluxed for 3 days. The solution was then concentrated by rotary evaporation and diluted with an equal volume of EtOH and enough water added to the almost black mixture to precipitate 1.4 g of a brown solid. Regular flash chromatography (ether) afforded 0.69 g (26%) of **8b** after drying at room temperature (0.01 mmHg): mp 87–89 °C; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 3.83 (s, 3 H), 3.92 (s, 3 H), 7.00 (m, 2 H), 7.51 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.2, 55.8, 56.6, 113.2, 115.5, 116.3, 118.1, 152.3, 153.4, 166.8, 175.4; IR (KBr) 1580, 1500, 1258, 1222, 1040, 1030 cm^{-1}; mass spectrum; *m/e* 220.1 (M^+), 205.1, 175.1, 160.1, 149.1 (base), 134.1, 106.0, 92.9, 76.9, 62.8, 50.8, 42.8, 29.9.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.23; H, 5.73; N, 12.46.

5-Methyl-3-(2,4-dichlorophenyl)-1,2,4-oxadiazole (8c). A mixture of 2,4-dichlorobenzaldehyde (2.01 g, 11.4 mmol), ammonium acetate (7.0 g, 90 mmol), and nitroethane (30 mL, 420 mmol) was refluxed (N_2) with glacial acetic acid for 6 days. The cooled solution was then poured into 200 mL of cold water and neutralized with bicarbonate. A brown paste was filtered, dissolved into warm $CHCl_3$, and purified with silica gel furnishing a partially crystalline pumpkin-colored residue. The crude product was recrystallized from $EtOH/H_2O$, yielding pale yellow material (0.468 g) which was further purified by column chromatography (ether/petroleum ether, 1:5) leaving 0.392 g (15%) of **8c** as a white powder: mp 97.5–99 °C lit.[12] mp 100–102 °C); ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3 H), 7.32 dd, *J* = 2 and 9 Hz, 1 H), 7.56 (d, *J* = 2 Hz, 1 H), 7.87 (d, *J* = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 124.5, 127.1, 130.6, 132.1, 133.9, 136.9, 166.2, 176.0.

Anal. Calcd for $C_9H_6Cl_2N_2O$: C, 47.19; H, 2.64; N, 12.23. Found: C, 47.42; H, 2.78; N, 11.96.

5-Methyl-3-(3-chlorophenyl)-1,2,4-oxadiazole (8d). A solution of 3-chlorobenzaldehyde (2.58 g, 17.7 mmol), ammonium acetate (11.0 g, 143 mmol), nitroethane (50 mL, 700 mmol), and glacial acetic acid (25 mL) was refluxed for 4 days (N_2) and then cooled to room temperature, and a fourfold excess of water added, after removing volatile components by rotary evaporation. The yellow paste which formed was recrystallized twice from $EtOH/H_2O$ to give 1.05 g of colorless prisms which were about 80% pure by NMR. Adjusted yield is then 0.84 g (24%). An analytical sample of **8d** was prepared by preparative TLC ($CHCl_3$/petroleum ether, 2:1) and sublimation at 70 °C (1 mmHg): mp 70–72 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (s, 3 H), 7.40 (m, 2 H), 7.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.3, 125.4, 127.4, 128.4, 130.1, 131.1, 134.9, 167.4, 176.8.

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39. Found: C, 55.59; H, 3.76; N, 14.22.

5-Methyl-3-(4-methylphenyl)-1,2,4-oxadiazole (8e). A solution of 4-methylbenzaldehyde (1.0 mL, 8.5 mmol), nitroethane (29 mL, 400 mmol), ammonium acetate (6.2 g, 80 mmol), and acetic acid (15 mL) was refluxed under N_2. After 7 days the volatile components in the crude mixture were removed by rotary evaporation. The resulting dark-red viscous liquid was diluted with ethanol (20 mL) and water was added to the cloud point. Cooling at 0 °C overnight afforded long, beige needless which weighed 0.722 g (49%) after air-drying. Filtration of a chloroform solution through a bed of silica gel gave white flakes of **8e**: mp 76–78 °C (lit.[13] mp 80 °C); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.61 (s, 3 H), 7.26 (d, 2 H), 7.94 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.2, 21.4, 124.0, 127.2, 129.4, 141.3, 168.3, 176.2.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H 5.79; N, 16.08. Found: C, 68.70; H, 5.72; N, 15.96.

5-Methyl-3-(3,5-dimethoxyphenyl)-1,2,4-oxadiazole (8f). A solution of 3,5-dimethoxybenzaldehyde (0.99 g, 6.0 mmol), ammonium acetate (5.7 g, 74 mmol), nitroethane (20 mL, 280 mmol), and glacial acetic acid (10 mL) was refluxed under N_2. After 90 h the mixture was cooled in an ice bath and 100 mL of water was added, precipitating a brown powder which weighed 0.75 g after air-drying. The residue was purified by column chromatography furnishing 0.289 g (21%) of analytically pure **8f** as white flakes: mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 3.84 (s, 6 H), 6.58 (t, *J* = 2.4 Hz, 1 H), 7.21 (d, *J* = 2.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.4, 55.5, 104.0, 105.0, 128.5, 161.1, 168.4, 176.5.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.48; N, 12.48.

5-Methyl-3-(4-carboxyphenyl)-1,2,4-oxadiazole (8g). A mixture of 4-carboxybenzaldehyde (2.0 g 13 mmol), ammonium acetate (8.2 g, 106 mmol), nitroethane (40 mL, 560 mmol), and glacial acetic acid (20 mL) was heated at reflux (N_2) for 2 days. An additional 10 mL of nitroethane and 5 mL of acetic acid were added, and the whole was refluxed for 2 more days. Then, after reducing the volume by rotary evaporation, a fourfold excess of water was added, precipitating a pasty, brown solid which was filtered. The filtrate was made strongly acidic with concentrated HCl and another crop of brown, amorphous solid was produced. The two crops (nearly the same by TLC) were combined, dissolved in hot CH_3OH, and recrystallized with water which gave material of similar purity. Next, the crude product was dissolved in 80 mL of hot water which was made strongly alkaline with 15% NaOH. The insoluble material was filtered, and, after cooling to 0 °C, 6 N HCl was added, affording a white gelatinous precipitate which was extracted with ether (4 × 50 mL). The combined extracts were washed with an equal volume of saturated NaCl and dried ($MgSO_4$) for 0.5 h, and the solvent was removed, leaving 0.31 (12%) of **8g** as a white powder: mp 259–262 °C (lit.[14] mp 218 °C); ^{1}H NMR (Me_2SO-d_6) δ 2.70 (s, 3 H), 8.11 (s, 4 H); ^{13}C NMR (Me_2SO-d_6) δ 12.0, 127.0, 130.0, 133.2, 166.5, 167.0, 177.7.

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.62; H, 4.08; N, 13.53.

Crossover Experiments. A. Reaction of Benzonitrile, 1-Nitropropane, Ammonium Acetate, and Acetic Acid. A solution of 2.00 g (19 mmol) of benzonitrile, 12.0 g (156 mmol) of ammonium acetate, 62.4 g (700 mmol) of 1-nitropropane, and 25 mL (437 mmol) of acetic acid was refluxed (N_2) for 72 h. The pale yellow solution was cooled, rendered alkaline (pH 8) with 10% NaOH, and extracted with 2 × 50 mL portions of ether. The dried (Na_2SO_4) extract was evaported to leave 2.30 g of pale yellow oil, which on TLC ($CHCl_3$ development) showed a minor spot of R_f 0.02 and major spots at R_f 0.39 and 0.47, the latter two corresponding to 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**) and 5-ethyl-3-phenyl-1,2,4-oxadiazole (**12**), respectively. The oil was extracted with 2 × 10 ml portions of hexane, and this solution was chromatographed on a 2 × 38 cm column containing 50 g of Merck silica gel 60 (30–70 mesh) with the following sequence of eluents: 5 × 75 mL portions of hexane, 5 × 75 mL portions of 1:1 hexane–benzene, and 5 × 75 mL portions of benzene. Only compounds **8a** and **12** appeared in the eluates and were distributed in fractions 7–12. These fractions were analyzed by both GC and by NMR, the latter on the basis of the well-separated methyl signals of **8a** and **12**. The GC results, corroborated within 1%

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by the NMR analysis, were as follows:

fraction	wt, g	mol % 8a	mol % 12
7	0.25	0	100
8	0.62	5	95
9	0.41	62	38
10	0.29	93	7
11	0.25	100	0
12	0.21	100	0

Fraction 7, a liquid, was pure 5-ethyl-3-phenyl-1,2,4-oxadiazole (**12**):[15] *m/e* 174.2, calcd M^+ = 174.1; ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.6 Hz, 3 H, CH_3), 2.88 (q, J = 7.6, 2 H, CH_2), 7.42 (m, 3 H, Ar H), 8.10 (m, 2 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 10.5 (CH_3), 20.0 (CH_2), 126.8, 127.1, 128.5, 130.7, 168.0 (C-3), 180.4 (C-5); IR (neat) 3060, 3015, 2980, 2935, 2875, (all C-H), 1591, 1570, 1475, 1445, 1360, 1342, 1305, 902, 780, 714, 690 cm^{-1}.

Fractions 11 and 12 both formed white crystals of 5-methyl-3-phenyl-1,2,4-oxadiazole (**8a**) identical in mp, mmp, ^1H and ^{13}C NMR, and IR with an authentic sample.[10]

Fractions 7–12, comprising 88% recovery by weight of the original crude product, represented a 41% yield of **8a** and a 32% yield of **12**, for a total yield of 73% of combined oxadiazoles.

B. Reaction of Benzonitrile, Nitroethane, Ammonium Propionate, and Propionic Acid. In a parallel experiment employing 2.00 g (19 mmol) of benzonitrile, 14.2 g (156 mmol) of ammonium propionate, 52.3 g (700 mmol) of nitroethane, and 24.8 g (335 mmol) of propionic acid, refluxed (N_2) 72 h, there was obtained a 20% yield of **8a** and a 34% yield of **12**; total yield 54% of oxadiazoles.

Reaction of 1-Nitropropane with Ammonium Acetate in Acetic Acid. A. Formation of Propionic Acid. A solution of 14.2 g (184 mmol) of ammonium acetate in 62.5 g (702 mmol) of 1-nitropropane and 25 mL (436 mmol) of acetic acid was refluxed under N_2 for 72 h. The initially colorless solution gradually turned to a deep amber-yellow. Gas chromatographic analysis of the crude reaction mixture run isothermally at 30 °C on the HP 5880A capillary column showed the following fractions [retention time, (compound) relative area]: 0.75 min (HOAc) 1.09; 1.32 min (1-nitropropane) 3.97; 1.67 min (propionic acid) 1.39; 2.49 min (unknown) 0.74; 3.27 min (unknown) 0.86. Since all of the propionic acid must have originated from the 1-nitropropane, the yield of propionic acid was 26%.

B. Trapping of Hydroxylamine. A mixture of 11.11 g (61 mmol) of benzophenone, 10.45 g (136 mmol) of ammonium acetate, 17.8 g (200 mmol) of 1-nitropropane, and 26.2 g (436 mmol) of acetic acid was refluxed under N_2 for 10 h. The resulting pale yellow solution was cooled and then diluted with 150 mL of water to yield a white precipitate, which was thoroughly washed with H_2O and air-dried. One recrystallization from 95% ethanol gives 7.17 g (60% yield) of benzophenone oxime, mp 137–139 °C. One more crystallization gave pure oxime, mp 139.5–141 °C, identical (mp, mmp, and IR) with an authentic sample[16]

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Registry No. **1a**, 100-52-7; **1b**, 93-02-7; **4a**, 100-47-0; **4b**, 5312-97-0; **8a**, 1198-98-7; **8b**, 95124-65-5; **8c**, 69792-78-5; **8d**, 95124-66-6; **8e**, 81386-30-3; **8f**, 95124-67-7; **8g**, 95124-68-8; **9**, 1199-00-4; **12**, 10364-68-8; benzamidoxime, 613-92-3; acetamidoxime, 22059-22-9; *O*-benzoylacetamidoxine, 22046-72-6; 4-methylbenzaldehyde, 104-87-0; ammonium propionate, 17496-08-1; ammonium acetate, 631-61-8; nitroethane, 79-24-3; benzoyl chloride, 98-88-4; 2,4-dichlorobenzaldehyde, 874-42-0; 3-chlorobenzaldehyde, 587-04-2; 3,5-dimethoxybenzaldehyde, 7311-34-4; 4-formylbenzoic acid, 619-66-9; 1-nitropropane, 108-03-2; benzophenone, 119-61-9; benzophenone oxime, 574-66-3.

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2,4-Dinitrophenylhydrazones: A Modified Method for the Preparation of These Derivatives and an Explanation of Previous Conflicting Results

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Conventional methods for forming 2,4-dinitrophenylhydrazones (2,4-DNPH's) usually leave traces of acids complexed with the derivatives and cause variable melting points. A bicarbonate wash of the 2,4-DNPH crystals removes the acid and reproducibly gives derivatives with previously reported or higher melting ranges. 2,4-DNPH's of hydroxy ketones previously unattainable by the standard methods were prepared by this method. NMR studies showed that traces of acids catalyze the syn–anti isomerization or the dehydration of the products and thus cause the melting point anomalies.

Characterization of aldehydes and ketones through their 2,4-dinitrophenylhydrazone (2,4-DNPH) derivatives, one of the most important qualitative methods in organic analyses, was first introduced by Allen[2] and Brady.[3] Although some minor modifications[4-6] have been reported, Allen and Brady's procedures are still the standard methods used for the preparation of these derivatives.[7-10] Brady's method has been used more widely because of the greater solubility of 2,4-dinitrophenylhydrazine in sulfuric acid. However, this method often gives derivatives with low and ambiguous melting ranges and several recrystal-

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