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Synthesis of Five-membered Heterocycles containing a Nitrogen-Oxygen Bond *via* O-Acylation of Aliphatic Nitro Compounds[1)]

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O-Acylation of primary aliphatic nitro compounds with acid chlorides in N,N-dimethylacetamide led to the formation of nitrile oxides, which cyclized *in situ* with olefinic dipolarophiles in a 1,3-dipolar cycloaddition mode to afford 2-isoxazoline derivatives. Optimum reaction conditions were investigated, and the use of several types of dipolarophiles, such as acetylenes, Schiff bases, aromatic nitriles, and ketones, in this cycloaddition resulted in the formation of the corresponding cycloadducts, namely isoxazoles, 1,2,4-oxadiazolines, 1,2,4-oxadiazoles, and 1,4,2-dioxazoles, respectively, in reasonable yields.

Keywords——O-acylation; 1,3-dipolar cycloaddition; aliphatic nitro compounds; nitrile oxide; 2-isoxazoline; isoxazole; 1,2,4-oxadiazoline; 1,2,4-oxadiazole; 1,4,2-dioxazole

Of the several methods available for the synthesis of five-membered heterocycles containing a nitrogen-oxygen bond in the ring, 1,3-dipolar cycloaddition of nitrile oxide with dipolarophiles has been most extensively used.[3)] The nitrile oxides are commonly generated *in situ* from hydroxamoyl chlorides by dehydrochlorination with triethylamine,[3,4)] or from primary nitroalkanes by treatment with isocyanate in the presence of amines,[5)] and some applications of the latter method have been reported.[6)] In addition, the thermolysis of 1,3,2,4-dioxathiazole 2-oxide,[7)] potassium salts of dinitroalkanes,[8)] or furoxanes[9)] was recently described.

In our previous communication,[10)] a novel route generating nitrile oxides was developed by O-acylation of aliphatic nitro compounds with acyl chlorides in N,N-dimethylacetamide (DMA). A facile one-pot synthesis of isoxazole derivatives was presented to illustrate the usefulness of this method. Here we wish to give a full account of this reaction, and applications to the synthesis of other five-membered heterocycles, *i.e.*, 2-isoxazolines, 1,2,4-oxadiazolines, 1,2,4-oxadiazoles, and 1,4,2-dioxazoles.

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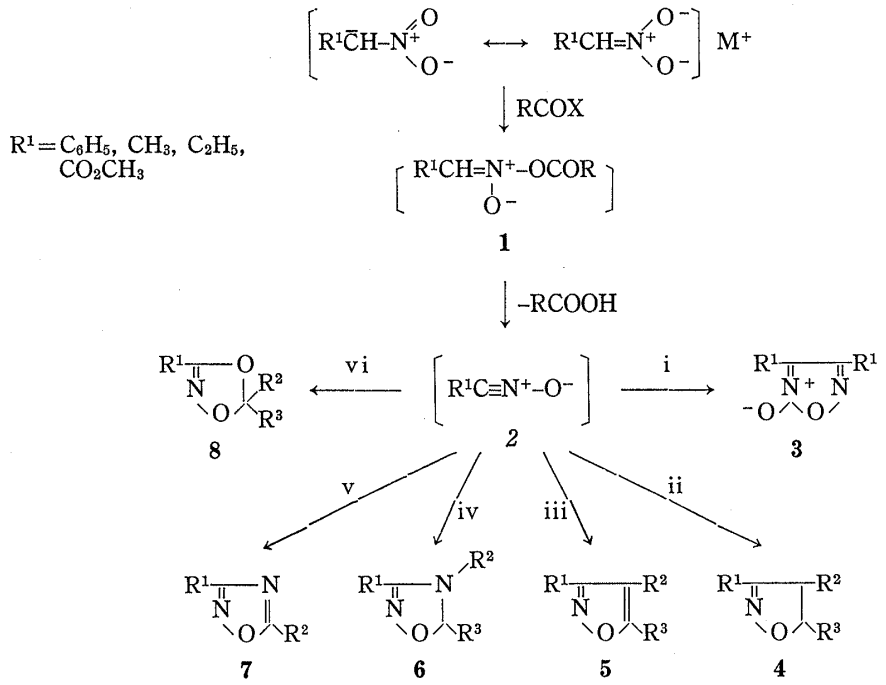
O-Acylation of Aliphatic Nitro Compounds

O-Acylation of aliphatic nitro compounds has been reviewed thoroughly[11,12] as regards the chemistry of the products; stable nitronic carboxylic anhydrides (mixed anhydrides) were formed from secondary nitroalkanes, whereas rearrangement of the corresponding anhydrides formed from primary nitroalkanes into hydroxamic acid esters has been observed. Nevertheless, our current interest[13] in the alkylation of aliphatic nitro compounds has led us to develop a novel method for generating nitrile oxides by the fragmentation of mixed anhydrides in a dipolar aprotic solvent such as DMA.

The reactions of nitroethane, phenylnitromethane, and methyl nitroacetate with acetyl chloride in DMA at room temperature gave 3,4-disubstituted furoxanes,[14] *i.e.*, **3** (R^1=CH_3, C_6H_5, and $COOCH_3$), in 14, 12, and 28% yields, respectively; these products appear to be formed by dimerization of nitrile oxides (**2**) generated by fragmentation of the initially formed mixed anhydrides (**1**), as shown in Chart 1. Attempts to trap the nitrile oxides with dimethyl fumarate gave the expected 3,4,5-trisubstituted isoxazolines (**4a**, **4e**, and **4f**; see Table II). We further examined the O-acylation of nitroethane with several kinds of acylating agents and bases in the presence of dimethyl fumarate in order to identify the optimum reaction conditions. Table I summarizes the effects of various conditions on the synthesis of the isoxazoline (**4a**); Method A employed alkali metal salts of nitroethane, while Method B employed free nitroethane and one equivalent of base, with provision of Na^+ by adding 1 N sodium methoxide in methanol to the mixture of starting materials.



i) dimerization, ii) $R^2CH{=}CHR^3$, iii) $R^2C{\equiv}CR^3$, iv) $R^2N{=}CHR^3$, v) $R^2C{\equiv}N$, vi) R^2–COR^3

Chart 1

It should be noted that Method B gave higher yields of **4a** than Method A, and the acetyl chloride–sodium methoxide system is convenient as regards handling. Aroyl chlorides, although

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Table I. Effects of Various Acylating Agents and Bases on the Synthesis of Isoxazoline (**4a**)[a]

RCOX	Base or alkali metal cation	Yield of **4a** (%)	
		Method A	Method B
CH_3COCl	Na	29	44
CH_3COCl	K	15	—
CH_3COCl	Li	31	—
CH_3COCl	$(C_2H_5)_2NH$	—	0
CH_3COCl	DBU[b]	—	4
CH_3COBr	Na	30	47
$(CH_3)_3CCOCl$	Na	—	49
Cl_3CCOCl	Na	—	4
C_6H_5COCl	Na	32	50
C_6H_5COBr	Na	34	53
p-$NO_2C_6H_4COCl$	Na	23	—
p-$CH_3C_6H_4COCl$	Na	23	51
p-ClC_6H_4COCl	Na	—	55
p-$ClOC$–C_6H_4COCl[c]	Na	—	32
$(COCl)_2$[c]	Na	—	6.5
$(CH_2COCl)_2$[c]	Na	—	18
$C_6H_5CH_2OCOCl$	Na	35	—

a) All experiments were carried out in DMA at room temperature for 15 hr.
b) 1,8-Diazabicyclo[5,4,0]undec-7-ene.
c) A half-molar amount of acid chloride relative to nitroalkane was employed.

they gave a slightly higher yield of **4a** than acetyl chloride, should be avoided because of the resulting contamination by aromatic carboxylic acids in the crude products. Furthermore, the use of a phase transfer catalyst, *e.g.* 18-crown-6 in benzene or triethylbenzylammonium chloride in benzene–water, resulted in 11% and 14% yields of **4a**, respectively.

On the other hand, O-acylation of methyl nitroacetate with benzoyl chloride or *p*-toluoyl chloride in the absence of a dipolarophile resulted in the formation of a by-product which was characterized as methyl 2-chloro-2-aroyloxyiminoacetate (**9a** and **9b**), accompanied by a major product, furoxane (**3a**). These compounds (**9**) might be formed by 1,3-addition of aroyl chloride to the nitrile oxide.[15]

Table II. Isoxazoline Derivatives (**4**)

Compd.	R^1	R^2	R^3	Yield (%) (Method B)	mp (°C) bp (°C/Torr)	$J_{4,5}$ (Hz)	Ref. No.[a]
4a	CH_3	$COOCH_3$	$COOCH_3$	44	74—74.5	5.0	—
4b	CH_3	H	$COOCH_3$	15	45—55/0.2	8.5	16)
4c	CH_3	$COOCH_3$	C_6H_5	36	70—80/0.2	8.0	—
4d	CH_3	C_6H_5	$COOCH_3$	9	70—80/0.2	6.0	—
4e	C_2H_5	$COOCH_3$	$COOCH_3$	58	75—83/0.3	6.0	—
4f	C_6H_5	$COOCH_3$	$COOCH_3$	76	100—105/0.3	5.0	8)
4g	C_6H_5	H	$COOCH_3$	73	71.5—72.5	8.5	17)
4h	C_6H_5	$COOCH_3$	C_6H_5	49	107—108	6.0	17)
4i	C_6H_5	C_6H_5	$COOCH_3$	10	82.0—84.5	4.0	17)
4j	C_6H_5	COC_6H_5	COC_6H_5	73	122—123	6.0	18)
4k	C_6H_5	$-(CH_2)_2-O-$		85	106—107	6.0	19)
4l	C_6H_5	$-(CH_2)_3-O-$		35	88—90	6.0	19)

a) All known compounds gave analytical data consistent with the reported data.

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Synthesis of 2-Isoxazoline, Isoxazole, 1,2,4-Oxadiazoline, 1,2,4-Oxadiazole, and 1,4,2-Dioxazole Derivatives

First, application of our method to the synthesis of 2-isoxazoline derivatives was examined. Nitroethane, 1-nitropropane and phenylnitromethane were O-acylated by Method B with acetyl chloride in the presence of a number of olefinic dipolarophiles, to afford 2-isoxazoline derivatives (**4a**—**l**) in reasonable yields. The results are summarized in Table II. All the isoxazolines other than **4b** and **4g** have the 4,5-*trans* configuration, since their $J_{4,5}$ values were in the range of 5.0—8.5 Hz.[8] Acylation of nitroethane in the presence of dimethyl maleate gave rise to a *trans*-isoxazoline (**4a**), which was identical with the product from dimethyl fumarate, in 25% yield (Method A). An analogous result was reported by Rahman *et al.*[8]

When methyl cinnamate was used with nitroethane or phenylnitromethane, a regioisomeric mixture of **4c** and **4d**, or of **4h** and **4i**, respectively, was obtained. On the basis of Huisgen's report[17] on the melting points and the proton magnetic resonance (PMR) spectra of **4h** and **4i**, they could be assigned as shown in Table II. The assignment of **4c** and **4d**, which could not be isolated, was inferred by PMR spectroscopy in comparison with the results for **4h** and **4i**. Thus, the major isomer was deduced to be **4c**, the ratio of which was determined by PMR integration. The use of ethyl β-nitrocrotonate with nitroethane led to the expected cycloadduct (**10**; 29% yield) identified by spectroscopic studies, but this lost nitrous acid on standing at room temperature to give the corresponding isoxazole (**11**).

Table III. Isoxazole Derivatives (**5**)

Compd.	R^1	R^2	R^3	Yield (%) (Method B)	mp (°C) bp (°C/Torr)	Ref. No.[a]
5a	CH_3	$COOCH_3$	$COOCH_3$	75	31—32	12)
5b	CH_3	H	CH_2OAc	39	65—73/2	—
5c	CH_3	H	$COOC_2H_5$	54	27—28	20)
5d	CH_3	H	C_6H_5	36	65—66	21)
5e	C_6H_5	$COOCH_3$	$COOCH_3$	76	63.5—64.5	12)
5f	C_6H_5	H	CH_2OAc	57	37—38	22)
5g	C_6H_5	H	$COOC_2H_5$	63	45—46	7)
5h	C_6H_5	H	C_6H_5	47	141—143	23)
5i	$COOCH_3$	$COOCH_3$	$COOCH_3$	20	101—102	—

a) All known compounds gave analytical data consistent with the reported data.

On the other hand, isoxazole derivatives were synthesized directly by O-acylation of aliphatic nitro compounds with acetyl chloride in the presence of several acetylenic dipolarophiles. The results are shown in Table III. In view of the results in Tables II and III, the reactivity of the dipolarophiles towards nitrile oxides in 1,3-cycloaddition appears to be consistent with Huisgen's proposal.[24]

The use of dipolarophiles containing a C=X (X=N or O) or C≡N bond was also examined. Cycloaddition of benzylidenealkylamine or its heterocyclic analogs with nitrile oxides derived from primary nitro compounds other than methyl nitroacetate readily gave the desired 1,2,4-oxadiazolines (**6**) in good yields (see Table IV), while the reaction of benzylideneaniline with methyl nitroacetate, or of propylidenebutylamine with phenylnitromethane gave rise to an

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Table IV. 1,2,4-Oxadiazoline Derivatives (**6**)

Compd.	R^1	R^2	R^3	Yield (%) (Method B)	mp (°C) bp (°C/Torr)[a]	n_D^{20}	Ref. No.[c]
6a	CH_3	n-C_3H_7	C_6H_5	42	90—100/0.15	1.5342	—
6b	CH_3	n-C_4H_9	C_6H_5	56	95—105/0.1	1.5288	—
6c	CH_3	$CH_2C_6H_5$	C_6H_5	48	135—148/0.35	*b*)	—
6d	C_2H_5	n-C_3H_7	C_6H_5	36	100—110/0.3	*b*)	—
6e	C_2H_5	n-C_4H_9	C_6H_5	56	110—115/0.6	*b*)	—
6f	C_2H_5	n-C_6H_{13}	C_6H_5	43	120—125/0.6	1.5152	—
6g	C_2H_5	$CH_2C_6H_5$	C_6H_5	50	140—150/0.3	1.5061	—
6h	C_6H_5	n-C_3H_7	C_6H_5	71	150—160/0.4	1.5633	—
6i	C_6H_5	n-C_6H_{13}	C_6H_5	79	140—150/0.2	1.5429	—
6j	C_6H_5	$CH_2C_6H_5$	C_6H_5	80	150—160/0.2	1.5174	25)
6k	C_6H_5	*sec*-C_4H_9	C_6H_5	43	79.5—80.5	—	—
6l	C_6H_5	C_6H_5	C_6H_5	39	75—76	—	26)
6m	C_6H_5	n-C_4H_9	2-Furyl	63	140—150/0.4	1.5569	—
6n	C_6H_5	$CH_2C_6H_5$	2-Pyridyl	73	170—180/0.2	1.5662	—
6o	C_6H_5	n-C_4H_9	2-Thienyl	86	150—160/0.15	1.5828	—
6p	p-Cl-C_6H_4	C_6H_5	C_6H_5	88	146.5—147	—	26)

a) Bath temperature is given.
b) Refractive index could not be measured because of the lability of these compounds.
c) All known compounds gave analytical data consistent with the reported data.

isoxazoline N-oxide (**12a**[27] or **12b**). Formation of isoxazoline N-oxides may be due to the conversion of incipient Michael adducts into 1,3-dinitroalkanes, followed by cyclization[27] to **12**. In the reaction of benzylideneaniline with nitroethane, however, fair amounts of the starting materials were recovered together with a Michael adduct (**13**[28]; 9.5%).

Table V. 1,2,4-Oxadiazole Derivatives (**7**) and 1,4,2-Dioxazole Derivatives (**8**)

Compd.	R^1	R^2	R^3	Yield (%)[a] (Method B)	mp (°C) bp (°C/Torr)[b]	Ref. No.[c]
7a	C_6H_5	C_6H_5	—	45	108—109	24)
7b	C_6H_5	p-Cl-C_6H_4	—	16.5	121.5—122	30)
7c	C_6H_5	p-Me-C_6H_4	—	41	115—116	30)
7d	C_6H_5	1-Naphthyl	—	38	100—101	25)
7e	C_6H_5	3-Pyridyl	—	35	117—118	29)
8a	C_6H_5	CH_3	$COOCH_3$	44	85—90/0.2	—
8b	C_6H_5	CH_3	$COOC_2H_5$	58	100—105/0.2	32)
8c	C_6H_5	CH_3	$COCH_3$	60	65—73/0.09	32)
8d	C_6H_5	CH_2Cl	C_6H_5	32	125—130/0.15	—

a) Data obtained in the presence of a 2-fold molar excess of boron trifluoride etherate.
b) Bath temperature is given.
c) All known compounds gave analytical data consistent with the reported data.
d) *p*-Chlorobenzoyl chloride was used as an acylating agent.

When benzaldoxime was used as a dipolarophile, 1,2,4-oxadiazole (**7a**: 10% yield), which can be regarded as a dehydrated product of an initial cycloadduct, was obtained with concomitant formation of dibenzamide (39%). Another synthesis of **7** was achieved by the use of aromatic nitriles to give **7a**—**e**, as shown in Table V. These reactions were accelerated by adding a two-fold molar excess of boron trifluoride etherate, as suggested elsewhere.[31]

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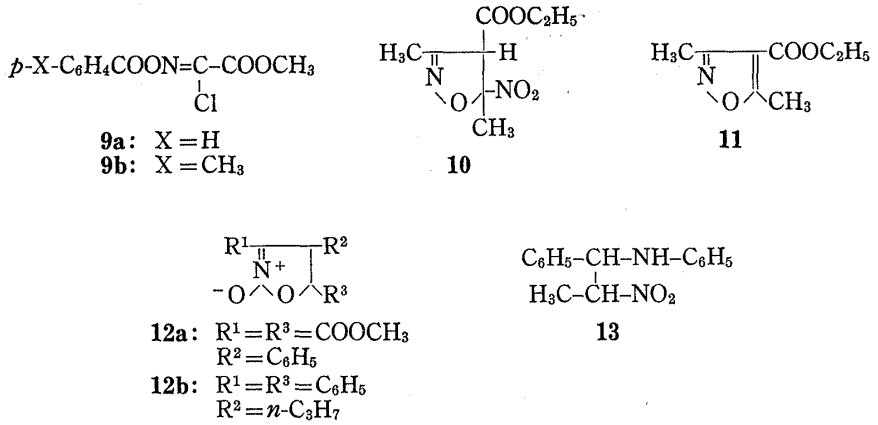

Chart 2

We attempted to obtain 1,4,2-dioxazole by using ketones possessing an electron-withdrawing group in the presence of boron trifluoride etharate, and obtained the expected dioxazoles (**8**). The results are shown in Table V.

In view of these results, our method appears to be widely applicable to the synthesis of five-membered heterocycles containing a nitrogen-oxygen bond. Further studies are in progress.

Experimental

Melting points are uncorrected. NMR spectra were recorded with Varian T-60 (60 MHz) and JEOL PS-100 (100 MHz) spectrometers using tetramethylsilane as an internal standard in chloroform-*d*. IR, UV, and mass spectra were measured with Jasco IRA-1, Hitachi 340, and JMS D-100 spectrometers, respectively. TLC was carried out on Kiesel gel G (Merck), spots being detected with iodine vapor and 10% sulfuric acid on a hot plate. Silica gel (Kanto Kagaku, up to 100 mesh) was used for column chromatography. In this section, detailed spectral and analytical data are given only for previously unknown compounds. Yields and physical constants are given in the tables.

4,5-Bis(methoxycarbonyl)-3-methyl-2-isoxazoline (4a): A General Procedure for Method A——Acetyl chloride (0.37 ml, 5.15 mmol) and dimethyl fumarate (740 mg, 5.15 mmol) were added to a stirred mixture of sodium ethanenitronate (500 mg, 5.15 mmol) and anhydrous DMA (20 ml). After stirring at room temperature for 16 hr, the mixture was partitioned between ice-water (75 ml) and benzene (25 ml). The aqueous phase was extracted with benzene (3×25 ml), dried (Na_2SO_4) and concentrated to furnish colorless crystals (602 mg), which were chromatographed on silica gel with ethyl acetate–hexane (1: 1), to give 250 mg (34% recovery) of dimethyl fumarate and 296 mg (29% yield) of **4a** as colorless crystals: mp 74—74.5° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester C=O), 1630 (C=N). PMR ($CDCl_3$) δ: 2.08 (3H, s, CH_3), 3.80 (6H, s, 2×$COOCH_3$), 4.30 (1H, d, H-4), 5.35 (1H, d, H-5). MS *m/e*: 201 (M^+). *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.47; N, 6.97. Found: C, 47.27; H, 5.22; N, 7.01.

Method B——Methanolic 1 N sodium methoxide (4 ml) was added to a stirred solution of nitroethane (300 mg, 4.0 mmol) in anhydrous DMA (20 ml). The mixture was cooled to 5° in an ice-bath, then acetyl chloride (0.29 ml, 4.1 mmol) and dimethyl fumarate (580 mg, 4.0 mmol) were added. After being stirred at room temperature for 16 hr, the reaction mixture was worked up in the manner described for Method A to furnish 135 mg (24% recovery) of dimethyl fumarate and 354 mg (44% yield) of **4a**.

4-Methoxycarbonyl-3-methyl-5-phenyl-2-isoxazoline (4c) and 5-Methoxycarbonyl-3-methyl-4-phenyl-2-isoxazoline (4d)——Nitroethane (375 mg, 5.0 mmol), acetyl chloride (0.36 ml, 5.1 mmol), and *trans*-methyl cinnamate (810 mg, 5.0 mmol) were reacted by Method B. General work-up gave 475 mg (59% recovery) of methyl cinnamate and 492 mg of a syrupy mixture of **4c** and **4d** in a *ca.* 4: 1 ratio as determined by PMR spectroscopy. Yields, bp, and $J_{4,5}$ data are summarized in Table II. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1740 (ester C=O), 1630 (C=N). PMR ($CDCl_3$) δ for **4c**: 2.05 (3H, s, CH_3), 3.83 (3H, s, $COOCH_3$), 3.93 (1H, d, H-4), 5.88 (1H, d, H-5), 7.37 (5H, s, C_6H_5); δ for **4d**: 1.80 (3H, s, CH_3), 3.83 (3H, s, $COOCH_3$), 4.45 (1H, d, H-4), 4.83 (1H, d, H-5), 7.37 (5H, s, C_6H_5). MS *m/e*: 219 (M^+). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 6.14; N, 6.59.

3-Ethyl-4,5-bis(methoxycarbonyl)-2-isoxazoline (4e)——1-Nitropropane, acetyl chloride, and dimethyl fumarate were reacted by Method B. **4e**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1740 (ester C=O), 1630 (C=N). PMR ($CDCl_3$) δ: 1.20 (3H, t, $CH_2\underline{CH_3}$), 2.47 (2H, q, $\underline{CH_2}CH_3$), 3.83 (6H, s, 2×$COOCH_3$), 4.35 (1H, d, H-4), 5.35

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(1H, d, H-5). MS *m/e*: 215 (M^+). *Anal.* Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.11; H, 6.02; N, 6.45.

5-Acetoxymethyl-3-methylisoxazole (5b)——Nitroethane, acetyl chloride, and O-acetylpropagyl alcohol[33] were reacted by Method B. **5b**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1750 (ester C=O), 1619 (C=N). PMR ($CDCl_3$) δ: 2.12 (3H, s, $COCH_3$), 2.30 (3H, s, CH_3), 5.11 (2H, s, CH_2O), 6.11 (1H, s, H-4). UV λ_{max}^{MeOH} nm (log ε): 211 (3.78), 252 (2.60). MS *m/e*: 155 (M^+). *Anal.* Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.54; H, 5.49; N, 9.25.

3,4,5-Tris(methoxycarbonyl)isoxazole (5i)——Methyl nitroacetate, acetyl chloride, and dimethyl acetylene dicarboxylate were reacted by Method B. **5i**; IR ν_{max}^{KBr} cm^{-1}: 1750 (ester C=O), 1635 (C=N). PMR ($CDCl_3$) δ: 3.94 (3H, s, 3-$COOCH_3$), 3.97 (6H, s, 4,5-$COOCH_3$). UV λ_{max}^{MeOH} nm (log ε): 236 (3.66), 209 (3.83). MS *m/e*: 243 (M^+). *Anal.* Calcd for $C_9H_9NO_7$: C, 44.45; H, 3.73; N, 5.76. Found: C, 44.42; H, 3.66; N, 5.60.

3-Methyl-5-phenyl-4-propyl-1,2,4-oxadiazoline (6a)——Nitroethane, acetyl chloride, and benzylidenepropylamine were reacted by Method B. **6a**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1610 (C=N). PMR ($CDCl_3$) δ: 0.80 (3H, t, $CH_2CH_2\underline{CH_3}$), 1.30 (2H, m, $CH_2\underline{CH_2}CH_3$), 2.00 (3H, s, 3-CH_3), 2.90 (2H, t, NCH_2), 6.10 (1H, s, H-5), 7.46 (5H, s, C_6H_5). MS *m/e*: 204 (M^+). *Anal.* Calcd for $C_{12}H_{17}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.31; H, 7.72; N, 13.58.

4-Butyl-3-methyl-5-phenyl-1,2,4-oxadiazoline (6b)——Nitroethane, acetyl chloride, and benzylidenebutylamine were reacted by Method B. **6b**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1615 (C=N). PMR ($CDCl_3$) δ: 0.70—1.30 (7H, m, *n*-C_3H_7), 1.90 (3H, s, 3-CH_3), 2.85 (2H, t, NCH_2), 5.99 (1H, s, H-5), 7.35 (5H, s, C_6H_5). MS *m/e*: 218 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.26; H, 8.23; N, 12.94.

4-Benzyl-3-methyl-5-phenyl-1,2,4-oxadiazoline (6c)——Nitroethane, acetyl chloride, and benzylidenebenzylamine were reacted by Method B. **6c**: IR $\nu_{max}^{liq.film}$ cm^{-1}: 1610 (C=N). PMR ($CDCl_3$) δ: 2.05 (3H, s, CH_3), 3.90 and 4.35 (each 1H, d, J=16 Hz, $\underline{CH_2}C_6H_5$), 6.05 (1H, s, H-5), 7.0—7.35 (5H, m, $CH_2C_6\underline{H_5}$), 7.40 (5H, s, C_6H_5). MS *m/e*: 252 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.50; H, 6.37; N, 10.89.

3-Ethyl-5-phenyl-4-propyl-1,2,4-oxadiazoline (6d)——1-Nitropropane, acetyl chloride, and benzylidenepropylamine were reacted by Method B. **6d**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1603 (C=N). PMR ($CDCl_3$) δ: 0.6—1.35 (8H, m, $CH_2\underline{CH_2}\underline{CH_3}$ and 3-$CH_2\underline{CH_2}CH_3$), 2.30 (2H, q, 3-$\underline{CH_2}CH_3$), 2.90 (2H, t, NCH_2), 6.08 (1H, s, H-5), 7.43 (5H, s, C_6H_5). MS *m/e*: 218 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.05; H, 8.19, N, 12.73.

4-Butyl-3-ethyl-5-phenyl-1,2,4-oxadiazoline (6e)——1-Nitropropane, acetyl chloride, and benzylidenebutylamine were reacted by Method B. **6e**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 0.7—1.5 (10H, m, $CH_2\underline{C_3H_7}$ and 3-$CH_2\underline{CH_2}CH_3$), 2.37 (2H, q, 3-$\underline{CH_2}CH_3$), 2.99 (2H, t, NCH_2), 6.11 (1H, s, H-5), 7.47 (5H, s, C_6H_5). MS *m/e*: 232 (M^+). *Anal.* Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.02. Found: C, 71.72; H, 8.55; N, 12.11.

3-Ethyl-4-hexyl-5-phenyl-1,2,4-oxadiazoline (6f)——1-Nitropropane, acetyl chloride, and benzylidenehexylamine were reacted by Method B. **6f**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1610 (C=N). PMR ($CDCl_3$) δ: 0.8—1.32 (14H, m, $CH_2\underline{C_5H_{11}}$ and 3-$CH_2\underline{CH_2}CH_3$), 2.30 (2H, q, 3-$\underline{CH_2}CH_3$), 2.90 (2H, t, NCH_2), 6.03 (1H, s, H-5), 7.39 (5H, s, C_6H_5). MS *m/e*: 260 (M^+). *Anal.* Calcd for $C_{16}H_{23}N_2O$: C, 73.80; H, 9.29, N, 10.76. Found: C, 74.27; H, 9.39; N, 10.70.

4-Benzyl-3-ethyl-5-phenyl-1,2,4-oxadiazoline (6g)——1-Nitropropane, acetyl chloride, and benzylidenebenzylamine were reacted by Method B. **6g**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1605 (C=N). PMR ($CDCl_3$) δ: 1.28 (3H, t, $CH_2\underline{CH_3}$), 2.40 (2H, q, $\underline{CH_2}CH_3$), 3.90 and 4.35 (each 1H, d, J=16 Hz, $\underline{CH_2}C_6H_5$), 6.06 (1H, s, H-5), 7.0—7.3 (5H, m, $CH_2\underline{C_6H_5}$), 7.38 (5H, s, C_6H_5). MS *m/e*: 266 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.87; H, 6.87; N, 10.65.

3,5-Diphenyl-4-propyl-1,2,4-oxadiazoline (6h)——Phenylnitromethane, acetyl chloride, and benzylidenepropylamine were reacted by Method B. **6h**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1599 (C=N). PMR ($CDCl_3$) δ: 0.60—1.60 (5H, m, $CH_2\underline{C_2H_5}$), 3.05 (2H, t, NCH_2), 6.33 (1H, s, H-5), 7.3—7.7 (10H, m, 2×C_6H_5). MS *m/e*: 266 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.85; H, 6.88; N, 10.85.

4-Hexyl-3,5-diphenyl-1,2,4-oxadiazoline (6i)——Phenylnitromethane, acetyl chloride, and benzylidenehexylamine were reacted by Method B. **6i**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 0.7—1.4 (11H, m, $CH_2\underline{C_5H_{11}}$), 3.06 (2H, t, NCH_2), 6.30 (1H, s, H-5), 7.3—7.6 (10H, m, C_6H_5). MS *m/e*: 308 (M^+). *Anal.* Calcd for $C_{19}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.48; H, 7.48; N, 8.81.

4-*sec*-Butyl-3,5-diphenyl-1,2,4-oxadiazoline (6k)——Phenylnitromethane, acetyl chloride, and benzylidene-*sec*-butylamine were reacted by Method B. **6k**; IR ν_{max}^{KBr} cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 0.6—1.8 (8H, m, $CH(\underline{CH_3})\underline{C_2H_5}$), 3.47 (1H, m, NCH), 6.45 (1H, s, H-5), 7.2—7.8 (10H, m, 2×C_6H_5). MS *m/e*: 280 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.24; H, 7.08; N, 9.93.

4-Butyl-5-(2-furyl)-3-phenyl-1,2,4-oxadiazoline (6m)——Phenylnitromethane, acetyl chloride, and furfurylidenebutylamine were reacted by Method B. **6m**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 0.6—1.7 (7H, m, $CH_2\underline{C_3H_7}$), 3.08 (2H, t, NCH_2), 6.38 (1H, s, H-5), 6.40 and 6.55 (each 1H, d, $J_{3',4'}$=3 Hz,

33) O. Schlichting and K. Klager, U.S. Patent 2340701 [*C.A.*, **38**, 4269 (1944)].

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H-3′,4′), 7.2—7.6 (6H, m, C_6H_5 and H-5′). MS *m/e*: 270 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.90; H, 6.73; N, 10.36.

4-Benzyl-3-phenyl-5-(2-pyridyl)-1,2,4-oxadiazoline (6n)——Phenylnitromethane, acetyl chloride, and pyridylidenebenzylamine were reacted by Method B. **6n**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 4.05 and 4.45 (each 1H, d, $J=16$ Hz, $\underline{CH_2}C_6H_5$), 6.25 (1H, s, H-5), 6.9—7.7 (14H, m, $2\times C_6H_5$ and C_5H_4N). MS *m/e*: 315 (M^+). *Anal.* Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.33. Found: C, 75.62; H, 5.22; N, 12.91.

4-Butyl-3-phenyl-5-(2-thienyl)-1,2,4-oxadiazoline (6o)——Phenylnitromethane, acetyl chloride, and thienylidenebutylamine were reacted by Method B. **6o**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1600 (C=N). PMR ($CDCl_3$) δ: 0.6—1.5 (7H, m, $CH_2\underline{C_3H_7}$), 3.12 (2H, t, NCH_2), 6.60 (1H, s, H-5), 6.9—7.7 (8H, m, C_6H_5 and C_4H_3S). MS *m/e*: 286 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2OS$: C, 67.17; H, 6.29; N, 9.79. Found: C, 66.79; H, 6.01; N, 9.54.

5-Methoxycarbonyl-5-methyl-3-phenyl-1,4,2-dioxazole (8a)——Phenylnitromethane, *p*-chlorobenzoyl chloride, and methyl pyruvate were reacted by Method B in the presence of a 2-fold molar excess of boron trifluoride etherate. General work-up followed by column chromatography on silica gel with benzene gave 3,4-diphenylfuroxane[14] (25% yield) and **8a**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1750 (ester C=O), 1620 (C=N). PMR ($CDCl_3$) δ: 1.96 (3H, s, CH_3), 3.87 (3H, s, $COOCH_3$), 7.4—7.9 (5H, m, C_6H_5). MS *m/e*: 221 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.23; H, 4.95; N, 6.14.

5-Chloromethyl-3,5-diphenyl-1,4,2-dioxazole (8d)——Phenylnitromethane, *p*-chlorobenzoyl chloride, and α-chloroacetophenone were reacted by Method B in the manner described for **8a**. Work-up gave a mixture of diphenylfuroxane and α-chloroacetophenone along with **8d**; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1615 (C=N). PMR ($CDCl_3$) δ: 4.03 (2H, s, CH_2Cl), 7.2—7.4 (10H, m, $2\times C_6H_5$). MS *m/e*: 273 (M^+), 275 (M^++2). *Anal.* Calcd for $C_{15}H_{12}ClNO_2$: C, 65.81; H, 4.39; N, 5.12. Found: C, 65.70; H, 4.41; N, 5.19.

Methyl 2-Benzoyloxyimino-2-chloroacetate (9a)——A mixture of sodium methoxycarbonylmethanenitronate (282 mg, 2.0 mmol) and benzoyl chloride (0.23 ml, 2.0 mmol) in anhydrous DMA (15 ml) was stirred at room temperature for 16 hr. General work-up followed by column chromatography on silica gel with chloroform–hexane (2: 1) gave 137 mg (56% yield) of benzoic acid and 160 mg (33% yield) of **9a** as colorless needles: mp 125.5—126.3° (MeOH–H_2O). IR ν_{max}^{KBr} cm^{-1}: 1770 and 1740 (ester C=O), 1585 (C=N). PMR ($CDCl_3$) δ: 4.00 (3H, s, $COOCH_3$), 7.50—8.22 (5H, m, C_6H_5). UV λ_{max}^{MeOH} nm (log ε): 240 (4.16). MS *m/e*: 210 (M^+-OCH_3), 212 ($M^++2-OCH_3$). *Anal.* Calcd for $C_{10}H_8ClNO_2$: C, 49.69; H, 3.31; N, 5.80. Found: C, 49.28; H, 3.32; N, 5.74.

Methyl 2-(*p*-Tolyloxyimino)-2-chloroacetate (9b)——Sodium methoxycarbonylmethanenitronate and *p*-tolyl chloride were employed in the manner described for **9a**. General work-up followed by column chromatography on silica gel with chloroform–hexane (3: 1) gave *p*-toluic acid (40% yield) and **9b** (14% yield) as colorless needles: mp 133.5—134.5° (MeOH–H_2O). IR ν_{max}^{KBr} cm^{-1}: 1780 and 1740 (ester C=O), 1580 (C=N). PMR ($CDCl_3$) δ: 2.35 (3H, s, CH_3), 4.01 (3H, s, $COOCH_3$), 7.3—8.1 (4H, m, C_6H_5). UV λ_{max}^{MeOH} nm (log ε): 251 (4.26). MS *m/e*: 255.5 (M^+), 257.5 (M^++2). *Anal.* Calcd for $C_{11}H_{10}ClNO_4$: C, 51.66; H, 3.91; N, 5.48. Found: C, 51.49; H, 3.92; N, 5.76.

4-Ethoxycarbonyl-3,5-dimethyl-5-nitro-2-isoxazoline (10) and 4-Ethoxycarbonyl-3,5-dimethylisoxazole (11)——Acetyl chloride (0.32 ml, 4.55 mmol) and ethyl β-nitrocrotonate (0.32 ml, 4.55 mmol) were added to a stirred mixture of sodium ethanenitronate (437 mg, 4.55 mmol) in anhydrous DMA (25 ml) under ice-cooling. After being stirred at room temperature for 16 hr, the mixture was worked up as usual, followed by chromatography on silica gel with benzene to give 136 mg (19% recovery) of ethyl β-nitrocrotonate and 213 mg (29% yield) of **10** as a yellow syrup: bp 30—35°/0.15 Torr. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1720 (ester C=O), 1610 (C=N), 1540 and 1380 (C–NO_2). PMR ($CDCl_3$) δ: 1.40 (3H, t, $CH_2\underline{CH_3}$), 2.47 (3H, s, 3-CH_3), 2.70 (3H, s, 5-CH_3), 3.83 (1H, s, H-4), 4.35 (2H, q, $\underline{CH_2}CH_3$). MS *m/e*: 170 (M^+-NO_2), 169 (M^+-HNO_2).

On standing at room temperature for about 1 week, **10** was converted into an isoxazole (**11**) in 75% yield, which was isolated by chromatography on a column of silica gel with benzene to give a brownish syrup; IR $\nu_{max}^{liq.film}$ cm^{-1}: 1740 (ester C=O), 1610 (C=N). PMR ($CDCl_3$) δ: 1.30 (3H, t, $CH_2\underline{CH_3}$), 2.37 (3H, s, 3-CH_3), 2.55 (3H, s, 4-CH_3), 4.26 (2H, q, $\underline{CH_2}CH_3$). MS *m/e*: 169 (M^+). *Anal.* Calcd for $C_8H_{11}NO_3$: N, 8.23. Found: N, 7.76.

3,5-Diphenyl-4-propylisoxazoline N-Oxide (12b)——Methanolic 1 N sodium methoxide (5 ml), acetyl chloride (0.36 ml, 5.1 mmol) and propylidenebutylamine (570 mg, 5.0 mmol) were added to a stirred solution of phenylnitromethane (685 mg, 5.0 mmol) in anhydrous DMA (20 ml) under ice cooling. After being stirred at room temperature for 16 hr, the mixture was worked up as usual and chromatographed on silica gel with ethyl acetate–hexane (1: 5) to give 110 mg (32% recovery) of butylaldehyde and 475 mg (68% yield) of **12b** as colorless needles: mp 113.5—114.5° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1610 (C=N). PMR ($CDCl_3$) δ: 0.9—2.0 (7H, m, *n*-C_3H_7), 3.73 (1H, m, H-4), 5.38 (1H, d, $J_{4,5}=2.0$ Hz, H-5), 7.3—8.0 (10H, m, $2\times C_6H_5$). MS *m/e*: 281 (M^+). *Anal.* Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.63; H, 6.70; N, 5.05.

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