THE SYNTHESIS OF NOVEL N-PYRIDYL-3,6-DIHYDRO-1,2-OXAZINES

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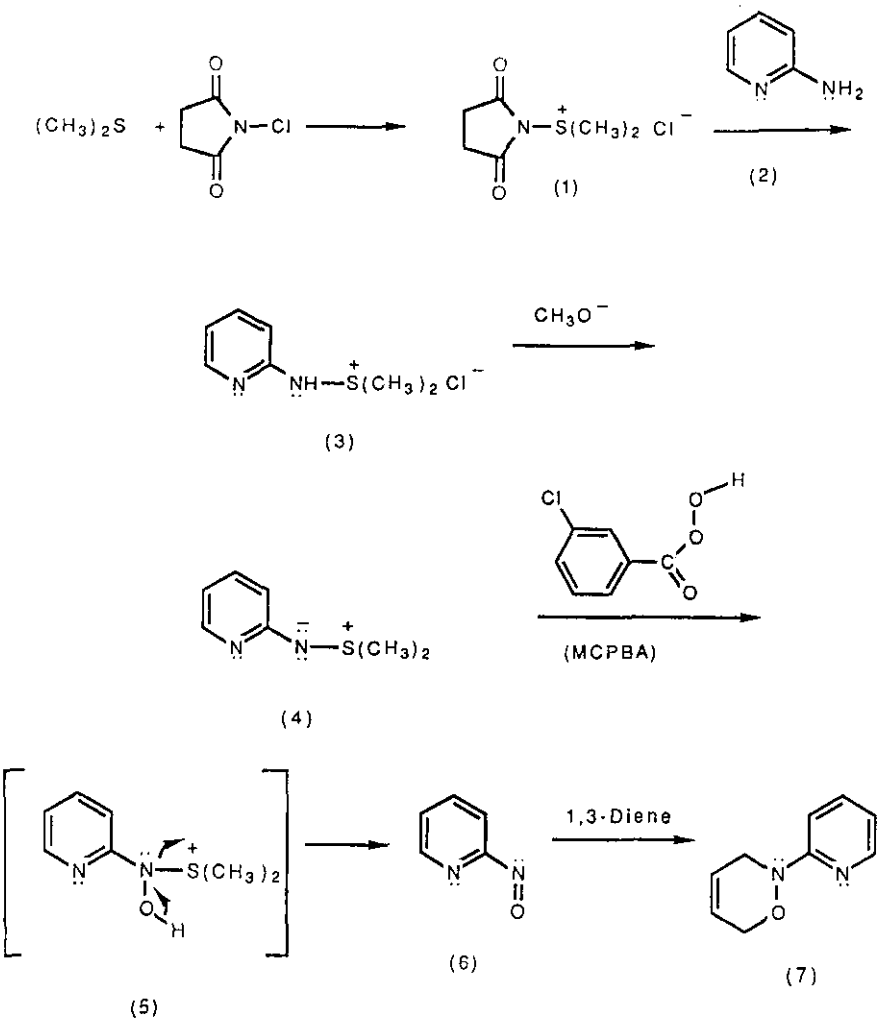
Abstract - A series of *fifteen new N-pyridyl-3,6-dihydro-1,2-oxazines* has been prepared from 1,3-butadienes and nitrosopyridines. 2-Aminopyridine, 2-amino-4-methylpyridine and 2-amino-6-methylpyridine were converted via nitroso compounds to 1,2-oxazines. The transformation was carried out sequentially in one vessel without isolation of either the intermediate sulfilimine or the nitroso compound.

INTRODUCTION

N-Unsubstituted[1,2] or N-arylsubstituted 3,6-dihydro-1,2-oxazines[1,3] can be easily prepared via Diels-Alder cycloaddition using 1-chloro-1-nitrosocyclohexane or aromatic nitroso compounds as dienophiles. However, only a few such reactions have been reported in which heterocyclic nitroso compounds were utilized as dienophiles.[4] This is because direct nitrosation of the heterocyclic ring, using nitrous acid or through nitration followed by reduction, both proceeding by electrophilic substitution, is possible only with π-electron rich systems.[5] The π-electron deficient nitrogen heterocycles, such as pyridine, react with electrophiles at nitrogen rather than at carbon. Pyridine has a low reactivity mainly because it is converted initially to a pyridinium ion by an electrophile. This makes electrophilic attack at the 4 or the 2 position especially unfavorable. An electrophilic substitution in the nucleus itself is possible only under forcing conditions and occurs preferentially at the 3-position.[6]

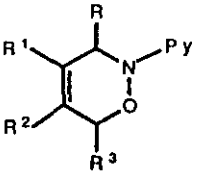
An amino group, when present on a π-electron deficient nitrogen heterocycle, is also not susceptible to electrophilic attack because of the delocalization of electron density to the π-system. Therefore, electrophilic reagents attack at the ring nitrogen atom rather than the exocyclic amino group. When the amino group, however, is converted into a sulfilimine (aminosulfurane) the reactivity of the exocyclic nitrogen is enhanced and consequently, it is easily oxidized to the nitroso group.[4,7,8]

The sulfilimines were found to be conveniently prepared from dimethyl sulfide, N-chlorosuccinimide (NCS) and amine. Dimethyl sulfide and NCS are assumed to form an intermediate complex (1) which is subsequently converted to an azasulfonium salt (3) by reaction with a heteroaromatic amine (2).[9,10] Deprotonation of the latter with sodium methoxide affords sulfilimine (4).[4,8] The conversion of sulfilimine to nitroso compound can be accomplished through oxidation with m-chloroperoxybenzoic acid (MCPBA). Since the ylide nitrogen is sufficiently nucleophilic, it reacts directly with MCPBA to form an intermediate (5) which is then transformed into nitroso compound (6) by deprotonation and simultaneous cleavage of the nitrogen-sulfur bond.[8] The nitroso compounds can be used, without isolation, for the reaction with diene to form N-substituted 1,2-oxazines[4] in which the substituent is a 2-pyridyl moiety. (Scheme I).



Since very few oxazines of this type have been prepared,[4] attention has been given to the synthesis of these systems. Several 1,3-butadienes, namely, isoprene, piperylene, 2-methyl-1-phenyl-1,3-butadiene, 2-ethyl-1-phenyl-1,3-butadiene, 2-methyl-1-(p-methoxyphenyl)-1,3-butadiene, and 2-ethyl-1-(p-methoxyphenyl)-1,3-butadiene, were allowed to react with 2-nitrosopyridine, 4-methyl-2-nitrosopyridine and 6-methyl-2-nitrosopyridine to form corresponding N-pyridyl-3,6-dihydro-1,2-oxazines. The preparation and structural features of all synthesized oxazines are discussed.

Py = (a) 2-pyridyl
(b) 4-methyl-2-pyridyl
(c) 6-methyl-2-pyridyl



I	a,b,c	R, R^2, R^3 = H; R^1 = CH_3
II	a,b,c	R = CH_3; R^1, R^2, R^3 = H
III	a,b,c	R, R^1, R^2 = H; R^3 = CH_3
IV	a,b,c	R, R^1 = H; R^2 = CH_3; R^3 = C_6H_5
V	a,b	R, R^1 = H; R^2 = C_2H_5; R^3 = C_6H_5
VI	a,b,c	R, R^1 = H; R^2 = CH_3; R^3 = p-$C_6H_4OCH_3$
VII	a,b	R, R^1 = H; R^2 = C_2H_5; R^3 = p-$C_6H_4OCH_3$

RESULTS AND DISCUSSION

The conversion of aminopyridines to the corresponding nitroso compounds and the Diels-Alder reaction were carried out sequentially in the same vessel without isolation of either the intermediate sulfilimine or the quite unstable nitroso compound.

The S,S-dimethyl-N-(2-pyridyl)sulfilimine, S,S-dimethyl-N-(4-methyl-2-pyridyl)sulfilimine, and S,S-dimethyl-N-(6-methyl-2-pyridyl)sulfilimine were prepared by treating aminopyridines with NCS and dimethyl sulfide in dry methylene chloride. Because the sulfonium salt intermediate is very unstable, the introduction of NCS was carried out at -20°C. The aminopyridines were transformed to their azasulfonium salts by stirring of the reaction mixtures at room temperature for 2 hours. Addition of freshly prepared sodium methoxide to these mixtures produced sulfilimines which were subsequently oxidized to nitrosopyridines with MCPBA. Upon addition of this reagent the characteristic colors of nitroso compounds, ranging from bright green to dark green, were observed. The oxidation process, which was assumed to proceed through unstable intermediate (5), was carried out at low temperature (0-5°C). The concentrated solutions of nitrosopyridines in methylene chloride were immediately subjected to treatment with an appropriate diene. Addition of the diene caused the color of the reaction mixture to change from green to dark red almost instantly. To ensure completion of the reaction, the mixtures were stirred for an additional three hours. In order to isolate adducts, the solvent was evaporated and the residues were chromatographed on alumina (activated 80-200 mesh, Fisher type F-20), with the solvent system chloroform-hexane (ranging from 5:95 to 50:50). Thin layer chromatography was used to monitor column chromatrography. In some cases, crude oxazines were rechromatographed on smaller columns. Solid products were purified by recrystallization from isopropanol while liquid oxazines were distilled at reduced pressure.

The reaction of isoprene with nitrosopyridines afforded the 4-methyl derivative of oxazine almost exclusively in each case (Ia, Ib, Ic), and this was established by proton nmr decoupling experiments. The proton spectra of the major isomers (Ia, Ic) which contain methyl resonances at δ1.81, also contain a singlet at δ1.69 of intensity approximately 10% of that at δ1.81. This resonance may be due to the presence of the 5-methyl isomer. In contrast, the spectrum of isomer Ib contains only one methyl resonance at δ1.82. In this case, however, there is no indication of the presence of a second isomer. The chemical shifts for the oxazine protons are similar for all three adducts. The CH_2N resonances are broad singlets at δ4.08 (Ia, Ic) and δ4.05 (Ib), respectively. The CH_2O resonances appear as quintets (Ia-δ4.46; Ib, Ic-δ4.48), and the resonance due to the olefinic protons appears as sextets (Ia-δ5.56; Ib-δ5.58; Ic-δ5.55). The predominant formation of the 4-methyl isomer seems to be characteristic for cycloaddition of aromatic nitroso compounds, since nitrosobenzene also affords 4-methyl adduct as the major product when condensed with isoprene.[3,11,12] This fact leads to the suggestion that steric effects are not decisive in determining the regioselectivity of the cycloaddition of isoprene with nitrosoaromatic or nitrosoheteroaromatic compounds. Conversely, the adduct formed from isoprene and 1-chloro-1-nitrosocyclohexane is a mixture of 4- and 5-methyl isomers, with the latter being the major product. The preferential formation of 5-methyl isomer in this case presumably proceeds via a less sterically hindered activated complex.

The reaction of piperylene with nitrosopyridines produced mixtures of both isomers, 3- and 6-methyl derivatives in almost equimolar quantities. Off resonance decoupled (ORD) ^{13}C nmr allowed clear assignment of the C-3 and C-6 methyl resonances in the oxazine spectrum. The methyl group assignments which are in accord with calculated chemical shifts were also supported by decoupling experiments. For the 3-methyl isomers (IIa, IIb, IIc) the methyl resonances appear at δ1.32 and the CH_2O AB patterns are centered at δ4.41 (δ_{AB} = 0.65 ppm, J=16.6Hz), while for the 6-methyl isomers (IIIa, IIIb, IIIc) the

methyl resonances are at δ1.22 and the CH_2N AB patterns appear at δ4.30 (δ_{AB} = 0.08 ppm, J=16.6Hz), respectively. The reaction of nitrosopyridine with piperylene can be compared to those of nitrosobenzene or substituted nitrosobenzenes with the same diene, where the formation of the mixture of two isomeric adducts is also observed.[3,13] The product from piperylene and 1-chloro-1-nitrosocyclohexane[2], however, is exclusively the 6-methyloxazine derivative. In this case, the structural orientation is probably determined by the steric factors.

The reaction of 1,2-disubstituted 1,3-butadienes, namely, 2-methyl-1-phenyl, 2-ethyl-1-phenyl, 2-methyl-1-(p-methoxyphenyl), and 2-ethyl-1-(p-methoxyphenyl), with nitrosopyridines afforded in each case only one isomer in which substituents were located in the positions 5 and 6 of the oxazine ring (IVa, IVb, IVc, Va, Vb, VIa, VIb, VIc, VIIa, VIIb), respectively. Both nmr integration and decoupling experiments confirm that these are the only isomers formed. ^1H Nmr spectra contain the expected resonances. The methyl resonances for adducts IV (a, b, c) and VI (a, b, c) are singlets with fine splittings from long range couplings (δ1.54-1.56), while the CH_2N (δ4.22-4.26) and the olefinic (δ5.85-5.89) resonances are 7-line multiplets. The CHO resonances (δ5.25-5.33) are broad singlets and the phenyl proton resonances which appear as multiplets (δ7.35-7.39) are partly obscured by the pyridine signals. The spectra of compounds V (a,b) and VII (a,b) also contain expected signals due to oxazine protons: CH_2N (δ4.25-4.28), CHO (δ5.34-5.38), and olefinic (δ5.85-5.88). The ethyl groups appear as triplets (δ0.98-1.00) and quartets (δ1.80-1.85). The structural orientation which is observed in the diene synthesis of nitrosopyridines with 1,2-disubstituted 1,3-butadienes is also observed in cases when either nitrosobenzene or 1-chloro-1-nitroso-cyclohexane is used as dienophiles.[2,3] The products formed from these reactions have substituents in the positions 5 and 6 of the oxazine ring. This could be due to the dominating steric influence of the 1-substituent in the diene.

In view of the above, it seems that the regioselectivity of the cycloaddition reactions of 1,3-butadienes and nitrosoaromatic or nitrosoheteroaromatic compounds is determined by the same factors.

EXPERIMENTAL

Ir Spectra. Ir spectra were obtained using a Perkin-Elmer model 597 spectrophotometer. Solid samples were run as 10% solutions in chloroform.

^1H Nmr Spectra. The ^1H nmr spectra were recorded using ca. 10% w/v solution in $CDCl_3$ and either IBM NR80 (80 MHz), or Brucker WM360 (360 MHz) spectrometers. Spectra were obtained in the Department of Chemistry, Central Michigan University (CMU), Mount Pleasant, Michigan, or at the Michigan Molecular Institute (MMI), Midland, Michigan. Chemical shifts are given downfield in ppm (δ) with respect to tetramethylsilane as internal reference.

^{13}C Nmr Spectra. The ^{13}C nmr spectra were recorded using $CDCl_3$ solutions (ca. 20% w/v) and the IBM NR80 spectrometer. Chemical shifts are given downfield in ppm (δ) with respect to tetramethylsilane as internal reference.

A. S,S-Dimethyl-N-(2-pyridyl)sulfilimine. 2-Aminopyridine (11.6 g; 0.123 mol) and dimethyl sulfide (9.4 g; 11.1 ml; 0.151 mol) were dissolved in dry methylene chloride (100 ml) and the solution was cooled to -20°C. To this solution, N-chlorosuccinimide (16.4 g; 0.123 mol) in methylene chloride (350 ml) was added dropwise, over a period of 1.5 h. The mixture was stirred for 1 h at room temperature. A solution of sodium methoxide in methanol (5.2 g of sodium in 100 ml of methanol) was then added, the reaction mixture was stirred for 15 min, 200 ml of water was added and stirring was continued for 4 h. The organic layer was removed, and the aqueous layer was extracted twice with 100-ml portions of methylene chloride. The organic extracts were combined, washed with water, dried (Na_2SO_4), and concentrated to about 250 ml. The sulfilimine was not isolated; the solution was used directly for conversion to 2-nitrosopyridine.

B. 2-Nitrosopyridine. To a solution of m-chloroperoxybenzoic acid (21.2 g; 0.123 mol) in dry methylene chloride (400 ml) cooled to -5°C, was added all at once, the concentrated solution of sulfilimine (A). The mixture was stirred for about 1.5 h at 0°C, then dimethyl sulfide was added (6.0 ml), and stirring was continued for 0.6 h. Subsequently the reaction mixture was shaken with saturated aqueous sodium carbonate solution, the bright green organic layer separated, washed with water and dried (Na_2SO_4). The solution containing nitrosopyridine was concentrated at reduced pressure to about 250 ml and at once used for reaction with the appropriate diene.

C. 4-Methyl-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (Ia). To a concentrated solution of nitrosopyridine there was added isoprene (16.8 g; 0.246 mol). The reaction mixture, which immediately turned bright red, was stirred for about 3 h, then methylene chloride was removed at reduced pressure. The residue, a dark red oil, was chromatographed on alumina using a mixture of chloroform/hexane (50:50) as eluent. The yellowish oil collected was distilled at reduced pressure; yield 32.6%; bp 107-109/1 torr; ir (film) 3050, 3000, 2960, 2910, 1895, 1870, 1820, 1800, 1600, 1565, 1470, 1440, 850, 780, 740, 700 cm^{-1}; ^1H nmr ($CDCl_3$)δ 1.81 (br s, 3H, CH_3), 4.08 (br s, 2H, CH_2N), 4.46 (m, 2H, CH_2O), 5.56 (m, 1H, C=CH), 6.77 (dd, 1H, H(5), J=4.8 and 7.4 Hz), 7.16 (d, 1H, H(3), J=8.4 Hz), 7.55 (dd, 1H, H(4), J=7.4 and 8.4 Hz), 8.23 (d, 1H, H(6), J=4.8 Hz); ^{13}C nmr ($CDCl_3$) δ 51.7 (C3), 131.3 (C4), 118.8 (C5), 68.3 (C6), 20.1 ($4CH_3$), 161.2 (Py2), 110.2 (Py3), 137.6 (Py4), 116.5 (Py5), 147.6 (Py6).

Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.89. Found: C, 68.08; H, 6.91; N, 15.97.

The following N-pyridyl-3,6-dihydro-1,2-oxazines were prepared in an analogous manner, except that appropriate 2-aminopyridines and 1,3-butadienes were used.

4-Methyl-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (Ib). Prepared from 2-amino-4-methylpyridine (0.091 mol) and isoprene (0.279 mol). White solid; yield 36.6%; mp 95-96°C; ir ($CHCl_3$) 3050, 2970, 2930, 2875, 2830, 1600, 1550, 1470, 1430, 870, 810 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.81 (br s, 3H, CH_3), 2.31 (s, 3H, $PyCH_3$), 4.05 (br s, 2H, CH_2N), 4.48 (m, 2H, CH_2O), 5.58 (m, 1H, C=CH), 6.64 (d, 1H, H(5), J=5.1 Hz), 7.03 (br s, 1H, H(3)), 8.09 (d, 1H, H(6), J=5.2 Hz); ^{13}C nmr ($CDCl_3$) δ 52.0 (C3), 131.5 (C4), 118.9 (C5), 68.5 (C6), 20.8 ($4CH_3$), 161.4 (Py2), 110.6 (Py3), 148.9 (Py4), 118.1 (Py5), 147.3 (Py6), 21.3 ($4PyCH_3$).

Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.41; N, 14.72. Found: C, 69.37; H, 7.40; N, 14.68.

4-Methyl-N-(6-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (Ic). Prepared from 2-amino-6-methylpyridine (0.063 mol) and isoprene (0.189 mol). Oil; yield 43.7%; bp 112-114°/1 torr; ir (film) 3050, 3000, 2950, 2900, 2875, 2825, 2800, 1580, 1440, 820, 780, 740, 720, 680 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.81 (br s, 3H, CH_3), 2.42 (s, 3H, $PyCH_3$), 4.08 (br s, 2H, CH_2N), 4.48 (m, 2H, CH_2O), 5.55 (m, 1H, C=CH), 6.64 (d, 1H, H(5), J=7.3 Hz), 6.96 (d, 1H, H(3), J=8.1 Hz), 7.46 (dd, 1H, H(4), J=7.3 and 8.1 Hz); ^{13}C nmr ($CDCl_3$) δ 51.9 (C3), 131.4 (C4), 118.7 (C5), 68.1 (C6), 20.1 ($4CH_3$), 160.8 (Py2), 106.6 (Py3), 137.7 (Py4), 115.7 (Py5), 156.4 (Py6), 24.3 ($6PyCH_3$).

Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.41; N, 14.72. Found: C, 69.46; H, 7.52; N, 14.53.

(3-Methyl)- and (6-methyl)-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (IIa, IIIa). Prepared from 2-aminopyridine (0.161 mol) and piperylene (0.161 mol). Oil; yield 35.8%; bp 100-102°C/1 torr; ir (film) 3050, 3025, 2995, 2960, 2910, 2850, 2825, 1600, 1570, 1470, 1430, 820, 780, 740, 720, 700, 680 cm^{-1}; ^1H nmr ($CDCl_3$) IIa δ 1.32 (d, 3H, CH_3, J=7.3 Hz), 4.41 (AB, 2H, CH_2O, δ_{AB} = 0.65, J=16.6 Hz), 4.70 (br s, 1H, CHN), 5.78 (br s, 2H, CH=CH), 6.72 (br s, 1H, H(5)), 7.13 (br s, 1H, H(3)), 7.54 (br s, 1H, H(4)), 8.21 (br s, 1H, H(6)). IIIa δ 1.22 (d, 3H, CH_3, J=7.3 Hz), 4.30 (AB, 2H, CH_2N, δ = 0.08, J=16.6 Hz), 4.91 (br s, 1H, CHO), 5.94 (br s, 2H, CH=CH), 6.72 (br m, 1H, H(5)), 7.13 (br m, 1H, H(3)), 7.54 (br m, 1H, H(4)), 8.21 (br m, 1H, H(6)); ^{13}C nmr ($CDCl_3$) IIa δ 51.4 (C3), 129.5 (C4), 123.6 (C5), 68.1 (C6), 18.8 ($3CH_3$), 159.9 (Py2), 109.5 (Py3), 137.5 (Py4), 115.4 (Py5), 147.4 (Py6). IIIa δ 47.4 (C3), 123.1 (C4), 130.1 (C5), 73.7 (C6), 15.3 ($6CH_3$), 161.2 (Py2), 109.9 (Py3), 137.3 (Py4), 116.1 (Py5), 147.7 (Py6).

Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.89. Found: C, 67.95; H, 6.85; N, 16.02.

(3-Methyl)- and (6-methyl)-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (IIb, IIIb). Prepared from 2-amino-4-methylpyridine (0.164 mol) and piperylene (0.164 mol). Oil; yield 40.6%; bp 68-70°C/1 torr; ir (film) 3050, 3000, 2960, 2910, 2850, 2830, 1600, 1560, 1470, 1430, 860, 800, 730, 700 cm^{-1}; ^1H nmr ($CDCl_3$). IIb δ 1.32 (d, 3H, CH_3, J=7.3 Hz), 2.34 (s, 3H, $PyCH_3$), 4.41 (AB, 2H, CH_2O, δ_{AB} = 0.64, J=16.6 Hz), 4.71 (br s, 1H, CHN), 5.78 (br s, 2H, CH=CH), 6.57 (d, 1H, H(5), J=5.1 Hz), 7.02 (s, 1H, H(3)), 8.09 (d, 1H, H(6), J=5.1 Hz). IIIb δ 1.22 (d, 3H, CH_3, J=7.3 Hz), 2.34 (s, 3H, $PyCH_3$), 4.30 (AB, 2H, CH_2N, δ_{AB} = 0.08, J=16.6 Hz), 4.91 (br s, 1H, CHO), 5.93 (br s, 2H, CH=CH), 6.60 (br s, 1H, H(5)), 7.02 (br d, 1H, H(3), J=7.0 Hz), 8.12 (br d, 1H, H(6), J=6.0 Hz); ^{13}C nmr ($CDCl_3$) IIb δ 51.7 (C3), 130.1 (C4), 123.2 (C5), 68.3 (C6), 18.9 ($3CH_3$), 160.2 (Py2), 110.0 (Py3), 148.5 (Py4), 117.8 (Py5), 147.2 (Py6), 21.2 ($4PyCH_3$). IIIb δ 47.7 (C3), 123.7 (C4), 129.7 (C5), 73.8 (C6), 15.3 ($6CH_3$), 161.5 (Py2), 110.3 (Py3), 148.7 (Py4), 117.0 (Py5), 147.5 (Py6), 21.2 ($4PyCH_3$).

Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.41; N, 14.72. Found: C, 69.29; H, 7.46; N, 14.66.

(3-Methyl)- and (6-methyl)-N-(6-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (IIc, IIIc). Prepared from 2-amino-6-methylpyridine (0.123 mol) and piperylene (0.123 mol). Oil; yield 38.0%; bp 102-103°/1 torr; ir (film) 3050, 3025, 2960, 2910, 2850, 2825, 1600, 1465, 880, 850, 780, 740, 700, 680 cm^{-1}; ^1H nmr ($CDCl_3$) IIc δ 1.31 (d, 3H, CH_3, J=7.3 Hz), 2.41 (s, 3H, $PyCH_3$), 4.41 (AB, 2H, CH_2O, δ_{AB} = 0.65, J=16.6 Hz), 4.70 (br s, 1H, CHN), 5.78 (br s, 2H, CH=CH), 6.60 (m, 1H, H(5)), 6.94 (br t, 1H, H(3), J=7.0 Hz), 7.47 (br t, 1H, H(4), J=7.0 Hz). IIIc δ 1.22 (d, 3H, CH_3, J=7.3 Hz), 2.41 (s, 3H, $PyCH_3$), 4.31 (AB, 2H, CH_2N, δ_{AB} = 0.08, J=16.6 Hz), 4.90 (br s, 1H, CHO), 5.94 (br s, 2H, CH=CH), 6.60 (m, 1H, H(5)), 6.94 (br m, 1H, H(3), J=7.0 Hz), 7.47 (br m, 1H, H(4), J=7.0 Hz); ^{13}C nmr ($CDCl_3$) IIc δ 51.7 (C3), 129.8 (C4), 123.8 (C5), 68.2 (C6), 19.0 ($3CH_3$), 161.1 (Py2), 106.5 (Py3), 137.9 (Py4), 115.0 (Py5), 156.8 (Py6), 24.4 ($6PyCH_3$). IIIc δ 48.0 (C3), 123.4 (C4), 130.2 (C5), 73.8 (C6), 15.4 ($6CH_3$), 159.8 (Py2), 106.5 (Py3), 137.8 (Py4), 115.6 (Py5), 156.5 (Py6), 24.4 ($6PyCH_3$).

Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.41; N, 14.72. Found: C, 69.25; H, 7.36; N, 14.66.

5-Methyl-6-phenyl-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (IVa). Prepared from 2-aminopyridine (0.123 mol) and 2-methyl-1-phenyl-1,3-butadiene (0.072 mol). White crystalline solid; yield 51.0%; mp 72.0-74.0°C; ir ($CHCl_3$) 3050, 2960, 2920, 2870, 2825, 1595, 1575, 1460, 1430, 850, 700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.56 (b s, 3H, CH_3), 4.25 (m, 2H, CH_2N), 5.23 (br s, 1H, CHO), 5.89 (br m, 1H, C=CH), 6.71 (dd, 1H, H(5), J=4.8 and 7.5 Hz), 6.95 (d, 1H, H(3), J=8.8 Hz), 7.38 (br m, 6H, Ph, H(4)), 8.18 (d, 1H, H(6), J=4.8 Hz); ^{13}C nmr ($CDCl_3$) δ 47.7 (C3), 119.8 (C4), 134.2 (C5), 83.5 (C6), 19.1 ($5CH_3$), (138.1, 128.5, 129.3, 128.7)(6Ph), 161.1 (Py2), 110.5 (Py3), 137.4(Py4), 116.4 (Py5), 147.4 (Py6).

Calcd for $C_{16}H_{16}N_2O$: C, 76.16, H, 6.39; N, 11.10. Found: C, 75.99; H, 6.44; N, 11.17.

5-Methyl-6-phenyl-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (IVb). Prepared from 2-amino-4-methylpyridine (0.119 mol) and 2-methyl-1-phenyl-1,3-butadiene (0.068 mol). White crystalline solid; yield 40.0%; mp 86-87°C; ir ($CHCl_3$) 3050, 2960, 2910, 2860, 2820, 1600, 1560, 1475, 1430, 850, 810, 700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.55 (m, 3H, CH_3), 2.20 (s, 3H, $PyCH_3$), 4.25 (m, 2H, CH_2N), 5.33 (br s, 1H, CHO), 5.88 (m, 1H, C=CH), 6.58 (d, 1H, H(5), J=5.6 Hz), 6.82 (br s, 1H, H(3)), 7.39 (br m, 5H, Ph), 8.06 (d, 1H, H(6), J=4.8 Hz); ^{13}C nmr ($CDCl_3$) δ 48.0 (C3), 119.8 (C4), 134.2 (C5), 83.6 (C6), 19.0 ($5CH_3$), (138.1, 128.5, 129.3, 128.7)(6Ph), 161.4 (Py2), 110.8 (Py3), 148.7 (Py4), 118.0 (Py5), 147.1 (Py6), 21.2 ($4PyCH_3$).

Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.71; H, 6.86; N, 10.58.

5-Methyl-6-phenyl-N-(6-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (IVc). Prepared from 2-amino-6-methylpyridine (0.119 mol) and 2-methyl-1-phenyl-1,3-butadiene (0.068 mol). Pale yellow crystals; yield 47.0%; mp 65-66°C; ir ($CHCl_3$) 3050, 2970, 2900, 2850, 2810, 1590, 1570, 1440, 845, 690 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.55 (m, 3H, CH_3), 2.40 (s, 3H, $PyCH_3$), 4.23 (m, 2H, CH_2N), 5.30 (br s, 1H, CHO), 5.88 (m, 1H, C=CH), 6.58 (d, 1H, H(5), J=6.4 Hz), 6.76 (d, 1H, H(3), J=8.2 Hz), 7.37 (br m, 6H, Ph, H(4)); ^{13}C nmr ($CDCl_3$) δ 48.1 (C3), 120.0 (C4), 134.1 (C5), 83.4 (C6), 19.1 ($5CH_3$), (138.3, 128.4, 129.3, 128.6)(6Ph), 160.9 (Py2), 107.0 (Py3), 137.7 (Py4), 115.6 (Py5), 156.3 (Py6), 24.4 ($6PyCH_3$).

Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.61, H, 6.76; N, 10.69.

5-Ethyl-6-phenyl-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (Va). Prepared from 2-aminopyridine (0.104 mol) and 2-ethyl-1-phenyl-1,3-butadiene (0.059 mol). Pale yellow solid; yield 49.8%; mp 78-79°C; ir ($CHCl_3$) 3050, 2970, 2930, 2860, 2820, 1595, 1570, 1465, 1430, 845, 690, 620 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.00 (t, 3H, CH_3, J=7.3 Hz), 1.85 (q, 2H, CH_2, J=7.3 Hz), 4.28 (m, 2H, CH_2N), 5.38 (br s, 1H, CHO), 5.88 (m, 1H, C=CH), 6.71 (dd, 1H, H(5), J=4.5 and 7.4 Hz), 7.40 (br m, 7H, PH, H(3), H(4)), 8.17 (d, 1H, H(6), J=4.5 Hz); ^{13}C nmr ($CDCl_3$) δ 47.8 (C3), 117.7 (C4), 139.8 (C5), 82.9 (C6), 11.7 ($5\underline{C}H_3CH_2$), 25.4 ($5CH_3\underline{C}H_2$), (138.3, 128.4, 129.4, 128.7)(6Ph), 161.2 (Py2), 110.5 (Py3), 137.4 (Py4), 116.3 (Py5), 147.3 (Py6).

Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.48; H, 6.88; N, 10.54.

5-Ethyl-6-phenyl-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (Vb). Prepared from 2-amino-4-methylpyridine (0.104 mol) and 2-ethyl-1-phenyl-1,3-butadiene (0.080 mol). White crystals; yield 33.0%; mp 61-62°C; ir ($CHCl_3$) 3050, 2960, 2910, 2860, 2810, 1600, 1580, 1480, 1430, 850, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.98 (t, 3H, CH_3, J=7.3 Hz), 1.80 (q, 2H, CH_2, J=7.3 Hz), 2.17 (s, 3H, $PyCH_3$), 4.26 (m, 2H, CH_2N), 5.39 (br s, 1H, CHO), 5.87 (m, 1H, C=CH), 6.54 (d, 1H, H(5), J=5.1 Hz), 6.79 (br s, 1H, H(3)), 7.40 (br m, 5H, Ph), 8.04 (d, 1H, H(6), J=5.1 Hz); ^{13}C nmr ($CDCl_3$) δ 48.1 (C3), 117.7 (C4), 139.8 (C5), 82.9 (C6), 11.7 ($5\underline{C}H_3CH_2$), 25.3 ($5CH_3\underline{C}H_2$), (138.3, 128.4, 129.3, 128.6)(6Ph), 161.4 (Py2), 110.7 (Py3), 148.5 (Py4), 117.9 (Py5), 147.0 (Py6), 21.1 ($4Py\underline{C}H_3$).

Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.04; H, 7.22; N, 9.89.

5-Methyl-6-(p-methoxyphenyl)-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (VIa). Prepared from 2-aminopyridine (0.119 mol) and 2-methyl-1-(p-methoxyphenyl)-1,3-butadiene (0.117 mol). Pale yellowish solid; yield 31.0%, mp 43-45°C; ir ($CHCl_3$) 3050, 2960, 2900, 2860, 2820, 1595, 1580, 1510, 1465, 1430, 850, 830, 730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.56 (m, 3H, CH_3), 3.79 (s, 3H, CH_3O), 4.24 (m, 2H, CH_2N), 5.26 (br s, 1H, CHO), 5.88 (m, 1H, C=CH), 6.80 (br m, 4H, Ph(2,6), H(5), H(3)), 7.4 (br m, 3H, Ph(3,5), CH(4)), 8.17 (d, 1H, H(6), J=5.1 Hz); ^{13}C nmr ($CDCl_3$) δ 47.7 (C3), 119.7 (C4), 134.4 (C5), 83.0 (C6), 19.1 ($5CH_3$), (130.3, 130.6, 113.9, 160.1)(6Ph), 55.3 ($PhO\underline{C}H_3$), 161.2 (Py2), 110.5 (Py3), 137.4 (Py4), 116.3 (Py5), 147.4 (Py6).

Calcd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.92. Found: C, 72.28; H, 6.52; N, 9.76.

5-Methyl-6-(p-methoxyphenyl)-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (VIb). Prepared from 2-amino-4-methylpyridine (0.119 mol) and 2-methyl-1-(p-methoxyphenyl)-1,3-butadiene (0.113 mol). Pale yellow solid; yield 38.0%; mp 82-83°C; ir ($CHCl_3$) 3050, 2985, 2965, 2900, 2810, 1600, 1560, 1510, 1425, 810, 720, 660 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.55 (m, 3H, CH_3), 2.21 (s, 3H, $PyCH_3$), 3.80 (s, 3H, CH_3O), 4.22 (m, 2H, CH_2N), 5.28 (br s, 1H, CHO), 5.87 (m, 1H, C=CH), 6.58 (d, 1H, H(5), J=5.3 Hz), 6.80 (br s, 1H, H(3)), 6.88 (d, 2H, Ph(2,6), J=8.8 Hz), 7.37 (d, 2H, Ph(3,5), J=8.8 Hz), 8.04 (d, 1H, H(6), J=4.8 Hz); ^{13}C nmr ($CDCl_3$) δ 48.0 (C3), 119.7 (C4), 134.5 (C5), 83.1 (C6), 19.1 ($5CH_3$), (130.3, 130.5, 113.9, 160.0)(6Ph), 55.3 ($PhO\underline{C}H_3$), 161.4 (Py2), 110.7 (Py3), 148.6 (Py4), 117.9 (Py5), 147.1 (Py6), 21.2 ($4Py\underline{C}H_3$).

Calcd for $C_{18}H_{20}N_2O$: C, 72.94; H, 6.80; N, 9.45. Found: C, 72.88; H, 6.97; N, 9.44.

5-Ethyl-6-(p-methoxyphenyl)-N-(2-pyridyl)-3,6-dihydro-1,2-oxazine (VIIa). Prepared from 2-aminopyridine (0.185 mol) and 2-ethyl-1-(p-methoxyphenyl)-1,3-butadiene (0.050 mol). Pale yellow solid; yield 43.5%; mp 40-41°C; ir ($CHCl_3$) 3050, 2995, 2950, 2910, 2860, 2810, 1600, 1590, 1560, 1510, 1460, 1430, 820, 720, 660 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.00 (t, 3H, CH_3, J=7.4 Hz), 1.80 (q, 2H, CH_2, J=7.4 Hz), 3.78 (s, 3H, CH_3O), 4.26 (m, 2H, CH_2N), 5.34 (br s, 1H, CHO), 5.87 (m, 1H, C=CH), 6.80 (br m, 2H, H(3), H(5)), 6.86 (d, 2H, Ph(2,6), J=8.8 Hz), 7.36 (d, 3H, Ph(3,5), H(4), J=8.8 Hz), 8.17 (d, 1H, H(6), J=5.1 Hz); ^{13}C nmr ($CDCl_3$) δ 47.8 (C3), 117.6 (C4), 140.0 (C5), 82.3 (C6), 11.7 ($5\underline{C}H_3CH_2$), 25.4 ($5CH_3\underline{C}H_2$), (130.5, 130.6, 113.8, 160.0)(6Ph), 55.3 ($PhO\underline{C}H_3$), 161.2 (Py2), 110.5 (Py3), 137.4 (Py4), 116.2 (Py5), 147.3 (Py6).

Calcd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45. Found: C, 73.08; H, 6.84; N, 9.35.

5-Ethyl-6-(p-methoxyphenyl)-N-(4-methyl-2-pyridyl)-3,6-dihydro-1,2-oxazine (VIIb). Prepared from 2-amino-4-methylpyridine (0.185 mol) and 2-ethyl-1-(p-methoxyphenyl)-1,3-butadiene (0.050 mol). Pale yellow solid; yield 40.5%; mp 44-46°C; ir ($CHCl_3$) 3050, 2960, 2920, 2860, 2820, 1620, 1560, 1500, 1440, 820, 750 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.98 (t, 3H, CH_3, J=7.3 Hz), 1.84 (q, 2H, CH_2, J=7.3 Hz), 2.17 (s, 3H, $PyCH_3$), 3.73 (s, 3H, CH_3O), 4.25 (m, 2H, CH_2N), 5.35 (br s, 1H, CHO), 5.85 (m, 1H, C=CH), 6.54 (d, 1H, H(5), J=4.8 Hz), 6.80 (m, 1H, H(3)), 6.86 (d, 2H, Ph(2,6), J=8.8 Hz), 7.36 (d, 2H, Ph(3,5), J=8.8 Hz), 8.04 (d, 1H, H(6), J=5.1 Hz); ^{13}C nmr ($CDCl_3$) δ 48.1 (C3), 117.6 (C4), 140.1 (C5), 82.4 (C6), 11.7 ($5\underline{C}H_3CH_2$), 25.3 ($5CH_3\underline{C}H_2$), (130.5, 130.6, 113.8, 160.0)(6Ph), 55.2 ($PhO\underline{C}H_3$), 161.5 (Py2), 110.7 (Py3), 148.5 (Py4), 117.8 (Py5), 147.0 (Py6), 21.1 ($4Py\underline{C}H_3$).
Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.71; H, 7.28; N, 9.07.

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