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DIRECT PHENYLATION OF ISOXAZOLES USING PALLADIUM CATALYSTS
SYNTHESIS OF 4-PHENYLMUSCIMOL

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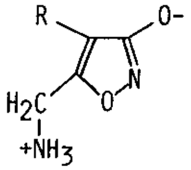
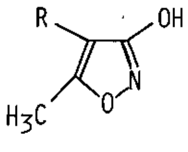
Abstract - Several 4-phenylisoxazoles were synthesized by the palladium-catalyzed coupling of the isoxazole ring with benzene or iodobenzene. Compound 4, thus obtained, was converted to 4-phenylmuscimol (2), according to the newly developed route to muscimol (1) from 3.

Muscimol (1), a natural product isolated from *Amanitae* fungi[1], is a potent receptor agonist of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Unlike GABA, 1 penetrates the blood-brain barrier after systemic administration. This property has made 1 an important neuropharmacological tool[2], and a variety of its derivatives have been synthesized to develop new therapeutic agents[3]. We planned the synthesis of 4-phenylmuscimol (2) with greater lipophilicity.



1 R=H
2 R=Ph

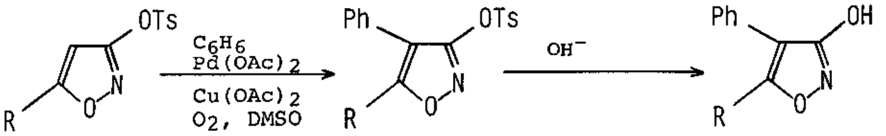


3 R=H
4 R=Ph

As an efficient synthesis of 1 was accomplished (*vide infra*) by modifying 3-hydroxy-5-methylisoxazole[4] (3), an agricultural chemical, 3-hydroxy-5-methyl-4-phenylisoxazole (4) would be the starting material for 2. In view of the poor yield of the reported synthesis of 4[5], it was desirable to prepare 4 from abundantly available 3. In the present paper we describe the palladium-catalyzed, direct phenylation at the 4-position of isoxazoles including the tosylate of 3[6].

Palladium-catalyzed cross-coupling reactions of aromatic hydrocarbons[7] or aryl halides[8,9] with olefins have been intensively investigated, and also applied to the formation of new heterocyclic rings.[10] To our knowledge, however, any intermolecular coupling of heterocyclic compounds with a benzene ring has not been realized by means of palladium catalysts, although the intramolecular oxidative coupling reaction of aroylindoles[11] suggests the possibility.

First, we examined the oxidative coupling of the tosylates 5a,b with benzene. The reaction of 5a with benzene in dimethylsulphoxide at 90° in the presence of palladium(II) acetate (1 eq.), cupric acetate (10 eq.) and oxygen afforded the phenylated product 6a in 66% yield. The structure of 6a was evidenced by its ^{1}H- and ^{13}C-NMR spectra : no proton absorption at 6.0 - 7.0 ppm; a singlet carbon absorption due to C_4 at 110.7 ppm. Further, alkaline hydrolysis of 6a yielded known 4[5] quantitatively. Similar reaction of 5b gave 6b in 62% yield. In other solvents such as acetic acid, acetonitrile, dimethylformamide or hexamethylphosphoric triamide, the phenylation was less successful. Without reoxidizing agents or with less amount of palladium(II) acetate (0.1 - o.2 eq.), the yields were reduced to 10 - 15%. The mesylate and the benzoate of 3 were not good substrates for this reaction.



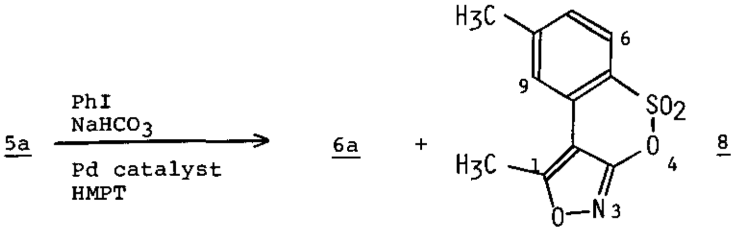
5a R=CH_3
5b R=Ph

6a 66%
6b 62%

4 R=CH_3
7 R=Ph

scheme 1

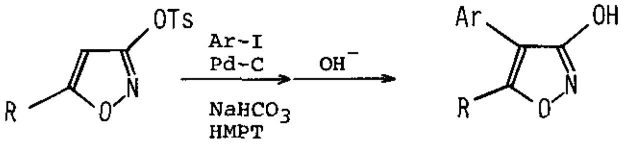
In order to economize the catalyst, phenylation of 5a with iodobenzene was investigated. When 5a was heated with iodobenzene (1.5 eq.) in hexamethylphosphoric triamide at 100° in the presence of palladium(II) acetate (0.1 eq.) and sodium bicarbonate, 6a (23%) and an intramolecular coupling product 8 (12%) were formed in addition to biphenyl.[12] The spectral data of 8 were consistent with the structure shown in scheme 2 : MS (*m/e*) , 251 (M^+); ^{13}C-NMR (in acetone-d_6), 100.8 ppm (singlet, C_{9b}). Addition of triphenylphosphine was not effective to improve the yield of 6a. A similar reaction using 10% palladium on charcoal (0.1 eq.) gave 6a in 44% yield together with less amount of 8 (3%). The latter result indicates the possibility that 8 was formed through palladation of the *p*-toluenesulphonyl group by the phenylpalladium complex derived from iodobenzene. This assumption was



scheme 2

supported by the fact that a similar reaction with palladium(II) acetate (0.1 eq.) excluding iodobenzene gave neither 6a nor 8.

Similarly, p-chloro- and o-carboxyphenyl groups were introduced into the 3-hydroxyisoxazole ring by arylation with p-chloroiodobenzene and the intramolecular reaction of the o-benzoate 10, as shown in scheme 3.



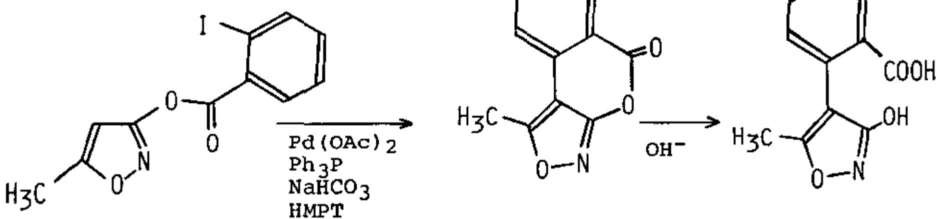
5a $R=CH_3$

5b R=Ph

7 R=Ph, Ar=Ph

9 $R=CH_3$, Ar=p-Cl-C_6H_4

scheme 3



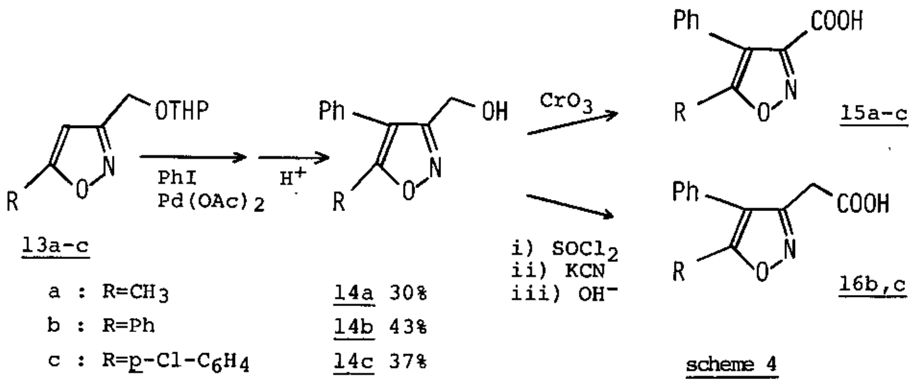
10

11 45%

12

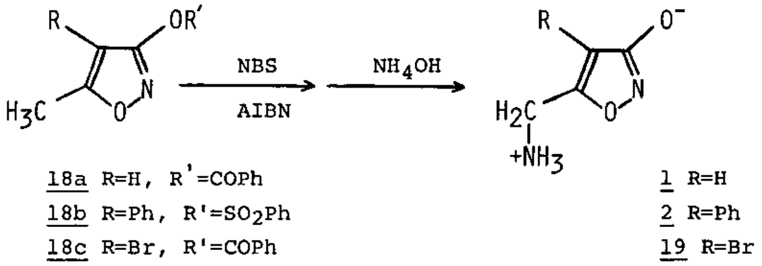
Isoxazoles other than 3-hydroxy derivatives can be phenylated, too. Phenylation of 3-(2-tetrahydropyranyloxymethyl)isoxazoles (13a-c) with the iodobenzene-palladium(II) acetate system gave the alcohols 14a-c after acidic hydrolysis. Palladium on charcoal was not effective in these coupling reactions. Several 4-phenylisoxazole-3-carboxylic and acetic acids (15a-c and 16b,c) were synthesized by conventional reactions[13] of 13a-c (scheme 4).

Finally, 1 and its 4-substituted derivatives were synthesized. The benzoate 18a[14] was brominated with N-bromosuccinimide, and then treated with ammonium hydro-



scheme 4

xide to afford 1 in 32% overall yield from 3. Similar sequence of reactions with 4 and 4-bromo-3-hydroxy-5-methylisoxazole[4b] (17) yielded 2 and 4-bromomuscimol (19), respectively, which showed no muscimol-like biological activities.



scheme 5

Experimental

Melting points were not corrected. Infrared (IR) spectra were taken with a JASCO A-2 spectrometer, and mass spectra with a JEOL-01SG mass spectrometer. Nuclear magnetic resonance (NMR) spectra were measured in deuteriochloroform, if not otherwise specified, on a Varian T-60 or XL-100A spectrometer.

5-Methyl-3-(p-toluenesulphonyloxy)isoxazole (5a) ---- To a solution of 3-hydroxy-5-methylisoxazole(3) (7.13 g, 72 mmol) and p-toluenesulphonyl chloride (13.72 g, 72 mmol) in 60 ml of benzene was added dropwise a solution of Et_3N (11 ml) in benzene (20 ml) during 15 min at5-6°. After stirred at the room temperature (r. t.) for 30 min, the mixture was washed with water, dried and evaporated. The residue was chromatographed over silica gel (160 g) column. Elution with 1-2% AcOEt in n-hexane gave pure 5a (13.95 g, 77%) of bp 148-150°/0.1 mmHg (bath temp.). ^{1}H-NMR δ : 2.38 (3H, s, CH_3), 2.45 (3H, s, CH_3), 6.09 (1H, br.s, H-C_4), 7.3-8.1 (4H, q-like m, aromatic H). ^{13}C-NMR (acetone-d_6) ppm : 12.9(q), 21.6 (q) (2 x CH_3), 96.4 (d, C_4), 129.4 (2 x d), 131.1 (2 x d) ($C_{2'}$, $C_{3'}$, $C_{5'}$ and $C_{6'}$), 132.6 (s, $C_{4'}$), 147.6 (s), 165.9 (s), 173.9 (s) (C_3, C_5 and $C_{1'}$). Anal. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.17; H, 4.38; N, 5.53; S, 12.65. Found : C, 52.09; H, 4.26; N, 5.53; S, 12.83.

5-Phenyl-3-(p-toluenesulphonyloxy)isoxazole (5b)---- 3-Hydroxy-5-phenylisoxazole (15.0 g) was tosylated as described above, using benzene-DMF (10:1) as the solvent. The crude product was recrystallized from Et_2O-n-hexane to give 5b of mp 69-70°. Yield, 22.9 g (78%). NMR δ : 2.43 (3H, s, CH_3), 6.58 (1H, s, H-C_4), 7.2-8.1 (9H, m, aromatic H). Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.95; H, 4.16; N, 4.44; S, 10.15. Found : C, 61.19; H, 4.07; N, 4.88; S, 10.26.

5-Methyl-4-phenyl-3-(p-toluenesulphonyloxy)isoxazole (6a)---- To a mixture of $Pd(OAc)_2$ (225 mg, 1mmol), $Cu(OAc)_2$ (1.81 g, 10 mmol) and DMSO (10 ml) was added a solution of 5a (253 mg, 1 mmol) in benzene (10 ml). The mixture was stirred at 90° for 7 hr, cooled, diluted with benzene (20 ml), filtered through celite, washed twice with water, dried and evaporated. The oily residue (311 mg) was chromatographed over silica gel (6 g). Elution with benzene gave 198 mg (58%) of 6a, mp 85-86° (cyclohexane-benzene). IR ν_{max}^{nujol} cm^{-1} : 1640, 1600, 1430, 1380, 1190, 1175. ^1H- NMR δ : 2.40 (3H, s), 2.42 (3H, s), 7.1-8.0 (9H, m). ^{13}C-NMR (acetone-d_6) ppm : 12.50 (q), 21.6 (q), 110.7 (s, C_4), 127.8 (s), 128.7 (d), 129.3 (4 x d), 129.5 (2 x d), 130.6 (2 x d), 132.9 (s) (11 aromatic C), 147.2 (s), 163.8 (s), 169.5 (s)(C_3, C_5 and 1 aromatic C). MS (m/e) : 329 (M^+), 265 (M^+-SO_2). Anal. Calcd. for $C_{17}H_{15}NO_4S$: C, 62.00; H, 4.59; N, 4.25; S, 9.72 Found : C, 62.17; H, 4.50; N, 4.28; S, 9.79. By further elution with benzene 5a (36 mg, 14%) was recovered.

Similar procedure under O_2 afforded 218 mg (66%) of 6a, in addition to recovered 5a (36 mg, 14%).

4,5-Diphenyl-3-(p-toluenesulphonyloxy)isoxazole (6b)---- Similarly 5b (631 mg, 2 mmol) was phenylated as described above under O_2, to yield 6b (462 mg, 61%) of mp 111-112° (Et_2O). NMR δ : 2.41 (3H, s), 7.1-8.0 (14H, m). MS (m/e): 391 (M^+), 327 (M^+-SO_2). Anal. Calcd. for $C_{22}H_{17}NO_4S$: C, 67.51; H, 4.38; N, 3.58. Found : C, 67.32; H, 4.34; N, 3.66.

3-Hydroxy-5-methyl-4-phenylisoxazole (4)---- To a solution of 6a (1.841 g) in dioxane (25 ml) was added 10 ml of 10% aq. NaOH. After stirred at r. t. for 1 hr, the mixture was acidified with 7% aq. HCl and extracted twice with AcOEt. The combined organic solution was washed with water, dried and evaporated, yielding 986 mg (100%) of 4. Recrystallization from Et_2O gave an analytical sample of mp 125-126° (lit[5] mp 127-128°). NMR δ : 2.41 (3H, s), 7.2-7.7 (5H, m), 11.70 (1H, s, OH). MS (m/e) : 175 (M^+). Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found : C, 68.26; H, 5.09; N, 7.62.

4,5-Diphenyl-3-hydroxyisoxazole (7)---- Similar hydrolysis of 6b (241 mg) as described above yielded 7 (147 mg, 100%) of mp 197-199° (acetone-n-hexane), NMR (DMSO-d_6) δ : 7.0-8.0 (10H, m), 8.0-8.6 (1H, br., OH). MS (m/e) : 237 (M^+). Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found : C, 75.62; H, 4.61; N, 5.96.

Phenylation of 5a with iodobenzene ---- A mixture of 5a (30.39 g, 0.12 mol), iodobenzene (36.72 g, 0.18 mol), $NaHCO_3$ (15.12 g, 0.18 mol), 10% Pd-C (12.77 g, 0.012 mol) and HMPT (250 ml) was heated at 100° for 9 hr under Ar. After cooled, the mixture was diluted with AcOEt (500 ml), filtered through celite and poured into water (1 l). The aq. layer was separated and extracted again with AcOEt. The combined organic solution was washed with water, dried and evaporated. The residue (ca, 70 g) was chromatographed on silica gel (500 g). Elution with AcOEt-n-hexane (1:5) afforded a semi-crystalline mixture of 5a and 6a. Recrystallization from cyclohexane-benzene gave pure 6a (17.47 g, 44%). Further elution with AcOEt-n-hexane (1:1) yielded 1,8-dimethyl-5,5-dioxo-4-oxa-5-thia-naphtho[2,1-c]isoxazole (8). Recrystallization from acetone-n-hexane gave white needles of mp 177-178° (1.02 g, 3%). IR ν_{max}^{nujol} cm^{-1} : 1650, 1610, 1520, 1470, 1390, 1195. ^{1}H-NMR (acetone-d_6) δ : 2.63 (3H, s, CH_3-C_8), 2.97 (3H, s, CH_3-C_1), 7.73 (1H, dm, J=8 Hz, H-C_7), 8.01 (1H, m, H-C_9), 8.15 (1H, d, J=8 Hz, H-C_6). ^{13}C-NMR (acetone-d_6) ppm : 14.0 (q), 21.7 (q) (CH_3-C_1 and C_8); 100.8(s,C_{9b});125.8 (d), 126.9 (d), 130.5 (d) (C_6, C_7 and C_9); 126.1 (s), 127.7 (s) (C_8 and C_{9a}); 147.4 (s), 165.5 (s), 170.2 (s) (C_1, C_{3a}, and C_{5a}). MS (m/e) : 251 (M^+). Anal. Calcd. for $C_{11}H_9NO_4S$: C, 52.58; H, 3.61; N, 5.58; S, 12.76. Found : C, 52.55; H, 3.74; N, 5.75; S, 12.71.

When $Pd(OAc)_2$ (0.1 eq.) was used as the catalyst, 6a was obtained in 23% yield, accompanied by 8 (12%). The addition of Ph_3P (0.1 eq.) did not improve the yield of 6a.

Phenylation of 5b with iodobenzene ---- Under the similar conditions as described above using 5% Pd-C (12.76 g, 6 mmol) as the catalyst, 5b (18.90 g, 60 mmol) was phenylated. After work-up, the semi-crystalline crude product (37.16 g) was hydrolyzed in a mixture of dioxane (250 ml) and water (120 ml) containing NaOH (10 g). After stirred at r. t. for 30 min, the mixture diluted with water (250 ml) was washed with Et_2O (250 ml). The aq. layer was acidified with 10% aq. HCl to pH 3, and extracted with Et_2O (2 x 250 ml). The combined extracts were dried and evaporated. The crystalline residue (11.14 g) was recrystallized from acetone to yield 7 (5.79 g) of mp 197-199°. Concentration of the mother liquor afforded further ammount of 7. Total yield, 6.68 g(47.5 %).

4-(p-Chlorophenyl)-3-hydroxy-5-methylisoxazole (9) ---- A mixture of 5a (10.1 g, 40 mmol), p-chloroiodobenzene (11.45 g, 40 mmol), $NaHCO_3$ (5.04 g), 10% Pd-C (8.50 g, 8 mmol) and HMPT (80 ml) was heated at 100° for 14 hr under Ar. After similar work-up and hydrolysis as described above, 9 (3.59 g, 43%) of mp 188.5-189.5° (AcOEt-n-hexane) was obtained. IRν_{max}^{nujol} cm^{-1} : 2300-3200(br.), 1645, 1595, 1560, 1540, 1495. NMR (DMSO-d_6) δ : 2.44 (3H, s), 7.3-7.8 (4H, s, aromatic H), 11.77 (1H, br., OH). MS (m/e) : 209 (M^+). Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.85; N, 6.68; Cl, 16.91. Found : C, 57.52; H, 3.84; N, 6.35; Cl, 16.52.

3-(2-Iodobenzoyloxy)-5-methylisoxazole (10)---- To a solution of 3 (4.95 g, 50 mmol) and 2-iodobenzoyl chloride (13.33 g, 50 mmol) in benzene (100 ml) was added dropwise a solution of Et_3N (10.5 ml) in benzene (20 ml) during 20 min at 15-20°, and the stirring was continued for 1 hr. After usual work up, the oily residue (19.27 g) was chromatographed over silica gel (150 g). Elution with 15-20% AcOEt in n-hexane yielded 10 (14.67 g, 89%) of mp 58-59.5°(AcOEt-n-hexane). NMR δ : 2.47 (3H, s, CH_3), 6.37 (1H, s, H-C_4), 7.1-8.3 (4H, m, aromatic H). Anal. Calcd. for $C_{11}H_8INO_3$: C, 40.15; H, 2.45; N, 4.26; I, 38.56. Found : C, 40.11; H, 2.38; N, 4.49; I, 38.55.

1-Methyl-4-oxa-5-oxo-naphtho[2,1-c]isoxazole (11) ---- A mixture of 10 (658 mg, 2 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol), Ph_3P (53 mg, 0.2 mmol), $NaHCO_3$ (168 mg, 2 mmol) and HMPT (14 ml) was heated at 70-75° for 6 hr. After usual work-up as described before, the crude product (428 mg) was chromatographed over silica gel (10 g). Elution with AcOEt-n-hexane (1:5) afforded 11 (181 mg, 45%) of mp 206-207° (acetone). IR ν_{max}^{nujol} cm^{-1} : 1760, 1660, 1605, 1230. NMR (DMF-d_7) δ : 2.90 (3H, s, CH_3), 7.5-8.5 (4H, m, aromatic H). MS (m/e) : 201 (M^+). Anal. Calcd. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found : C, 65.39; H, 3.45; N, 6.97.

4-(2-Carboxyphenyl)-3-hydroxy-5-methylisoxazole (12)---- Usual hydrolysis of 11 (1.430 g) as described before afforded 12 (1.440 g, 92%) of mp 212-214° (d) (acetone). IR ν_{max}^{nujol} cm^{-1} : 3200-2300 (br.), 1695, 1660, 1600, 1580, 1545. NMR (DMSO-d_6) δ : 2.25 (3H, s, CH_3), 7.3-8.1 (4H, m, aromatic H), 12.0 (2H, br., OH). MS (m/e) : 219 (M^+), 201 (M^+-H_2O). Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 3.69. Found : C, 60.42; H, 4.17; N, 6.35.

5-Methyl-3-(2-tetrahydropyranyloxymethyl)isoxazole (13a)---- Methyl 5-methylisoxazole-3-carboxylate (19.04 g) was reduced with $LiAlH_4$[13]. The crude product was tetrahydropyranylated in usual way, yielding 13a (17.80 g, 67%) of bp 121-122° /6 mmHg, after silica gel chromatography. Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found : C, 60.84; H, 7.76; N, 6.73.

5-Phenyl-3-(2-tetrahydropyranyloxymethyl)isoxazole (13b)---- 3-Hydroxymethyl-5-phenylisoxazole of mp 98-99° (AcOEt) was prepared according to Kano et al.[13] Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found : C, 68.57; H, 5.17; N, 7.87. Treatment of this alcohol with dihydropyran in CH_2Cl_2 containing p-TsOH afforded 13a, as a viscous oil after silica gel chromatography. NMR δ : 1.1-1.2 (6H, m), 3.3-4.2 (2H, m), 4.80 (2H, ABq, δ_A=4.66, δ_B=4.86, J=12 Hz, CH_2-C_3), 4.80 (1H, m, overlapped, O-CH-O), 6.60 (1H, s, H-C_4), 7.3-8.0 (5H, m, aromatic H).

5-(p-Chlorophenyl)-3-(2-tetrahydropyranyloxymethyl)isoxazole (13c)---- Ethyl 5-(p-chlorophenyl)isoxazole-3-carboxylate was reduced with $LiAlH_4$[13] to 5-(p-chlorophenyl)-3-hydroxymethylisoxazole of mp 95-96° (AcOEt-n-hexane). Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.85; N, 6.68; Cl, 16.91. Found : C, 57.33; H, 3.77; N, 6.62; Cl, 17.04. Tetrahydropyranylation of this alcohol yielded 13c (90%) of mp 76-78° (AcOEt-n-hexane). Anal. Calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.52; N, 4.77; Cl, 12.07. Found : C, 61.58; H, 5.39; N, 4.77; Cl, 12.10.

3-Hydroxymethyl-5-methyl-4-phenylisoxazole (14a)---- A mixture of 13a (14.91 g, 75.6 mmol), iodobenzene (23.13 g, 113.4 mmol), $Pd(OAc)_2$ (1.70 g, 7.56 mmol), $NaHCO_3$ (9.52 g, 113.4 mmol) and HMPT (90 ml) was heated at 95-100°. After 3 hr, further amount of the catalyst (1.70 g) was added. After 6hr, the mixture was poured into a mixture of AcOEt (1 l) and water (1 l) containig $Na_2S_2O_3$ (2 g). After filtration through celite, the organic layer was separated and the aq. layer extracted again with AcOEt. The combined organic solution was washed with water, dried and evaporated. The residue was chromatographed over silica gel (250 g). The fraction eluted with 3-10% AcOEt in n-hexane gave a mixture of 13a and the phenylated product (12.56 g), which was hydrolyzed in a mixture of EtOH (100 ml) and 10% aq. HCl (20 ml). After 2hr, the mixture was diluted with water (1 l) and extracted twice with AcOEt. The combined extracts were dried and evaporated. The oily residue (7.9 g) was chromatographed over silica gel (150 g). Elution with 20-25% AcOEt in n-hexane gave 17 (4.30 g, 30%) of mp 55-56° (Et_2O-n-hexane). IR ν_{max}^{nujol} cm^{-1} : 3400, 1630, 1480. NMR δ : 2.42 (3H, s, CH_3), 3.16 (1H, t, J=6 Hz, OH), 4.70 (2H, d, J=6 Hz, CH_2-C_3), 7.40 (5H, br.s, aromatic H). MS (m/e) : 189 (M^+), 159 (M^+-CH_2O). Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found : C, 70.01; H, 5.91; N, 7.34.

4,5-Diphenyl-3-hydroxymethylisoxazole (14b)---- A mixture of 13b (420 mg, 1.62 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), iodobenzene (495 mg, 2.43 mmol), $NaHCO_3$ (252 mg, 3 mmol) and HMPT (4 ml) was heated at 120°. Further amount of the catalyst was added after 2 hr (18 mg) and 6 hr (36 mg), and heating was continued for 16 hr in total. Similar work-up, chromatography and hydrolysis as described above yielded 14b (175 mg, 43%) of mp 86-87° (AcOEt-n-hexane). NMR δ : 2.75 (1H, t, J=7 Hz, OH), 4.71 (2H, d, J=7 Hz, CH_2-C_3), 7.1-7.7 (10H, m, aromatic H). MS (m/e) : 251 (M^+), 220 (M^+-CH_2OH). Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found : C, 76.45; H, 5.14; N, 5.66.

5-(p-Chlorophenyl)-3-hydroxymethyl-4-phenylisoxazole (14c)---- A mixture of 13c (37.69 g, 128 mmol), iodobenzene (39.17 g, 192 mmol), $Pd(OAc)_2$ (2.87 g, 12.87 mmol), $NaHCO_3$ (16.13 g, 192 mmol) and HMPT (300 ml) was heated at 120-125° for 7 hr. After similar work-up, chromatography and hydrolysis as described before, 14c (13.66 g, 37%) of mp 103-104° (AcOEt-n-hexane) was isolated. NMR δ : 3.07 (1H, t, J=6 Hz, OH), 4.68 (2H, d, J=6 Hz, CH_2-C_3), 7.1-7.7 (9H, m, aromatic H). MS (m/e): 287, 285 (M^+). Anal. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.25; H, 4.23; N, 4.90 ; Cl, 12.41. Found : C, 67.36; H, 4.13; N, 4.90; Cl, 12.42.

Oxidation of 14a-c with Jones reagent (2 eq., r. t., 30 min) gave the acids 15a-c, respectively.

5-Methyl-4-phenylisoxazole-3-carboxylic Acid (15a)---- Yield, 97%; mp 143-145° (d). Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found : C, 64.74; H, 4.46; N, 6.76.

4,5-Diphenylisoxazole-3-carboxylic Acid (15b)---- Yield, 83%; mp 154.5-156.5° (d). Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28. Found : C, 72.39; H, 4.04; N, 5.25.

5-(p-Chlorophenyl)-4-phenylisoxazole-3-carboxylic Acid (15c)---- Yield, 92%; mp 168-169°. Anal. Calcd. for $C_{16}H_{10}ClNO_3$: C, 64.12; H, 3.36; N, 4.67; Cl, 11.83. Found : C, 64.06; H, 3.34; N, 4.62; Cl, 11.79.

4,5-Diphenylisoxazole-3-acetic Acid (16b)---- Treatment of 14b with $SOCl_2$ yielded 3-chloromethyl-4,5-diphenylisoxazole (92%) of mp 87-88°. NMR δ : 4.50 (2H, s, CH_2-C_3), 7.1-7.8 (10H, m, aromatic H). Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.48; N, 5.19. Found : C, 71.34; H, 4.49; N, 5.23. According to the literature[13] this chloride was converted to 16b (79%) of mp 124-125° (Et_2O-n-hexane). NMR (acetone-d_6) δ : 3.70 (2H, s, CH_2-C_3), 7.1-7.7 (10H, m, aromatic H). Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found : C, 73.46; H, 4.64; N, 4.97.

5-(p-Chlorophenyl)-4-phenylisoxazole-3-acetic Acid (16c)---- Chlorination of 14c with $SOCl_2$ gave 3-chloromethyl-5-(p-chlorophenyl)-4-phenylisoxazole (87%) of mp 92-93°. NMR δ : 4.51 (2H, s), 7.0-7.9 (9H, m). Anal. Calcd. for $C_{16}H_{11}ClNO_2$: C, 63.12; H, 3.62; N, 4.60; Cl, 23.34. Found : C, 63.31; H, 3.72; N, 4.63; Cl, 23.55. From this chloride was prepared 16c (75%) of mp 154.5-156° (AcOEt-n-hexane) according to the literature[13]. NMR (acetone-d_6) δ : 3.70 (2H, s), 5.80 (1H, br.s, OH), 7.2-7.7 (9H, m). Anal. Calcd. for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46; Cl, 11.30. Found : C, 64.98; H, 3.82; N, 4.43; Cl, 11.39.

Muscimol (1) ---- To a solution of 3 (49.36 g, 0.50 mol) and benzoyl chloride (70.29 g, 0.50 mol) in benzene (1 l) was added dropwise Et_3N (83.5 ml, 0.60 mol) during 20 min at 10-20°. After 2 hr, the mixture was washed with water, dried and evaporated. The crystalline residue (99.57 g), NBS (96.7 g) and AIBN (30 mg) were dissolved in CCl_4 (900 ml), and heated to reflux by irradiation with a sun lamp. After 4 hr, the mixture was filtered and evaporated. The oily residue (130 g) was chromatographed on silica gel (1.25 kg). Elution with 15-20% AcOEt-n-hexane gave a crystalline substance, which was recrystallized from AcOEt-n-hexane to afford 5-bromomethyl-3-benzoyloxyisoxazole (36.25 g) of mp 55-57°. Concentration of the mother liquor yielded further amount of the monobromide. Total yield, 57.55 g (41% from 3). NMR δ : 4.46 (2H, s, CH_2-Br), 6.70 (1H, s, H-C_4), 7.3-8.4 (5H, m, C_6H_5). MS (m/e) : 283, 281 (M^+), 202 (M^+-Br). Anal. Calcd. for $C_{11}H_8BrNO_3$: C, 46.83; H, 2.86; N, 4.97. Found : C, 46.73; H, 2.80; N, 5.15. A solution of this bromide (51.48 g) in EtOH (500 ml) was added dropwise to a mixture of 40% aq. NH_4OH (1 l) and EtOH (500 ml) during 30 min at 15-20°. After stirred at r. t. for 1 hr, the mixture was concentrated to dryness. The residue was washed with AcOEt (2 x 300 ml) and dissolved in water. The aq. solution was washed with AcOEt (2 x 300 ml) and passed through a column containing ion-exchanger resin Dowex 50W-X2 (50-100 mesh, H-form, 900 ml). The column was washed with water until the eluate became neutral to litmus paper. Elution with 2% aq. NH_4OH afforded crystalline 1 (16.21 g, 32% from 3). Recrystallization from MeOH or aq. EtOH gave pure sample of mp 172-175°(d), which was identical with an authentic sample[15] in IR, NMR, MS spectroscopy and chromatographic properties.

3-(benzenesulphonyloxy)-5-methyl-4-phenylisoxazole (18b)---- By the reaction of 4 with benzenesuphonyl chloride as described in the preparation of 5a, was synthesized 18b (82%) of mp 73-74° (AcOEt-n-hexane). NMR δ : 2.45 (3H, s), 7.2-8.2 (10H, m, aromatic H). Anal. Calcd. for $C_{16}H_{13}NO_4S$: C. 60.94; H, 4.16; N, 4.46; S, 10.17. Found : C, 61.04; H, 4.15; N, 4.46; S, 10.33.

2-Phenylmuscimol (2) ---- A mixture of 18b (7.01 g), NBS (4.75 g), AIBN (10 mg) and CCl_4 (70 ml) was heated to reflux with a sun lamp. After 2.5 hr, the mixture was filtered and evaporated. The resulting viscous oil crystallized on standing to give an analytical sample of 3-benzenesulphonyloxy-5-bromomethyl-4-phenylisoxazole (mp 84-86°) after recrystallization from AcOEt-n-hexane. NMR δ : 4.45 (2H, s, CH_2-Br), 7.2-8.2 (10H, m, aromatic H). MS (m/e) : 395, 393 (M^+), 314 (M^+-Br). Anal. Calcd. for $C_{16}H_{12}BrNO_4S$: C, 48.74; H, 3.07; N, 3.55. Found : C, 48.56; H, 3.07; N, 3.49. A mixture of the crude bromide (4.50 g), 40% aq. NH_4OH (30 ml) and EtOH (10 ml) was stirred at r. t. for 16 hr. Similar work-up and ion-exchanger chromatography as described above, gave 2 (0.559 g, 22% from 4) of mp 201-203°(d) (aq. acetone). IR ν_{max}^{nujol} cm^{-1} : 3200-2000 (br.), 2660, 2200, 1640, 1580. 1490.

NMR (DMSO-d_6) δ : 3.90 (2H, s, CH_2-C_5), 7.3-7.8 (5H, m, C_6H_5). MS (m/e) : 190 (M^+), 173 (M^+-NH_3). Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found : C, 62.90; H, 5.26; N, 14.55.

5-Benzoyloxy-4-bromo-5-methylisoxazole (18c)---- Benzoylation of 4-bromo-3-hydroxy-5-methylisoxazole[4b] (17) as describrd in the synthesis of 1 yielded 18c (85%) of mp 96-98° (AcOEt-n-hexane) after silica gel chromatography. IR ν_{max}^{nujol} cm^{-1} : 1760. Anal. Calcd. for $C_{11}H_8BrNO_3$: C, 46.83; H, 2.86; N, 4.97. Found : C, 46.69; H, 2.81; N, 4.88.

4-Bromomuscimol (19) ---- A mixture of 18c (5.64 g), NBS (4.27 g), AIBN (10 mg) and CCl_4 (60 ml) was irradiated to reflux with a sun lamp. After 3 hr, the mixture was filtered and evaporated. The residue (7.19 g) was dissolved in a mixture of MeOH (50 ml) and 40% aq. NH_4OH (60 ml). After stirred at r. t. for 1 hr, the mixture was evaporated to dryness. Similar work-up of the residue followed by ion-exchanger chromatography as described in the synthesis of 1 gave crude 19 (1.75 g) of mp 171-175° (d), which was recrystallized and characterized as the hydrochloride of mp 175-177° (d) (aq. EtOH). Yield, 1.67 g (36% from 18c). IR ν_{max}^{nujol} cm^{-1} : 3300-2300 (br.), 1645, 1600, 1550. NMR (D_2O) δ : 4.40 (s, CH_2-C_5). MS (m/e) : 194, 192 (M^+ for $C_4H_5BrN_2O_2$), 177, 175 (M^+-NH_3), 163, 161 (M^+-CH_2NH_3). Anal. Calcd. for $C_4H_6BrClNO_2$: C, 20.93; H, 2.64; N, 12.21. Found : C, 20.67; H, 2.82; N, 11.89.

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Note added in proof

Recently, Itahara demonstrated the intermolecular oxidative coupling reaction of pyrroles and indoles with benzene using palladium(II) acetate : T. Itahara, J. Chem. Soc. Chem. Comm., 1981, 254.

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