# A TWO-STEP SYNTHESIS OF IMIDAZOLES FROM ALDEHYDES VIA 4-TOSYLOXAZOLINES†

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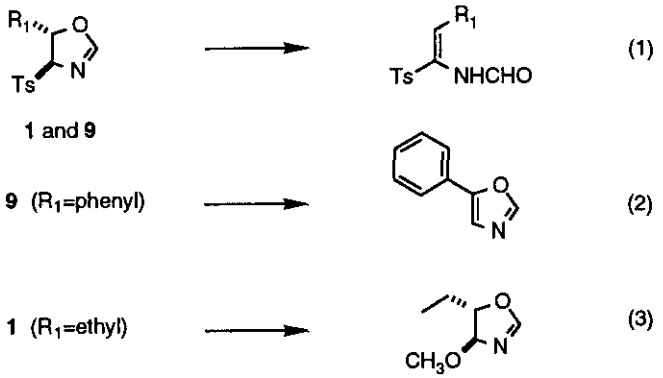
**Abstract** - Imidazoles with substituents in the 4- and 4, 5-positions were prepared by heating 4-tosyloxazolines in saturated methanolic ammonia. Similar treatment of these oxazolines with monoalkylamines regioselectively affords 1, 4-disubstituted imidazoles. When oxazolines bearing an ethyl group at the 4-position were heated with alkylamines, however, a regioisomeric mixture of di- or trisubstituted imidazoles was produced. These reactions proceed *via* an intermolecular condensation of α-amino ketones and amidines or intramolecular cyclization of α-amidino ketone intermediates, respectively.

In 1858 Debus[1] reported the reaction between glyoxal and ammonia, a reaction that pioneered a novel synthetic route to imidazole. Over the century, the importance of imidazoles in biological systems has attracted much interest into their chemical and biochemical properties. Today, over a 130 years later, research in imidazole chemistry continues unabated. Many of the useful synthetic methods for the construction of various substituted imidazoles require difficult preparations of starting materials such as α-functionalized carbonyl and α-diamino compounds.[2] One of the more recent developments in imidazole syntheses has been the use of α-anionic isocyanides having both nucleophilic and electrophilic centers.[3,4] In particular, the base-induced cycloaddition-elimination reaction of aldimines and (*p*-tolylsulfonyl)methyl isocyanide ($TsCH_2N{=}C$, TosMIC) has been reported as a convenient method for the preparation of 1,5-disubstituted imidazoles.[5] This process,

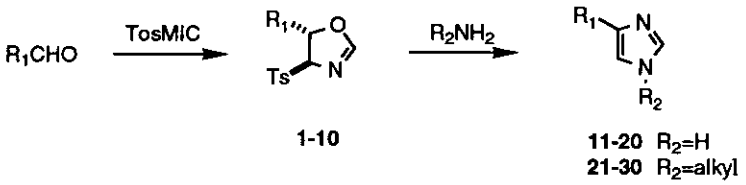
however, is not applicable for the formation of 1,4-disubstituted imidazoles although imidazoles without substituents on nitrogen have recently been prepared by using *N*-trimethylsilylimines and lithiotosylmethylisocyanates.[4f,6] Our interest in imidazole chemistry focuses on the development of a new method for the preparation of the imidazole nucleus that would complement existing procedures. The strategy is based on efficient generation of α-amino ketone intermediates that could undergo inter- and intramolecular cyclization reactions to give imidazoles.[7] According to literature, treatment of both tosyloxazolines (**1**) and (**9**) with $^{t}$BuOK/THF affords the formamide derivatives in equation (1).[6,8a] Although oxazoles can be obtained from exposure of aromatic substituted oxazolines such as (**9**) to $K_2CO_3/CH_3OH$ (eq. 2), we believe the process may not involve direct elimination of sulfinate.[5b,8b] In fact, under analogous conditions, using $K_2CO_3/CH_3OD$, we have found that aliphatic substituted oxazolines such as (**1**) give the *trans*-4-methoxyoxazoline[9] (eq. 3) along with 10% of the *cis* isomer without incorporation of deuterium and without formation of oxazoles. These results prompted further investigation and we now report the transformation of 4-tosyloxazolines (**1-10**) and (**31-35**) to imidazoles when treated with amines.




In the presence of a catalytic amount of sodium cyanide in ethanol, aldehydes ($R_1CHO$) underwent smooth, mildly exothermic [3+2] anionic cycloadditions with TosMIC giving the thermodynamically more stable *trans*-4-tosyloxazolines (**1-10**) in excellent yields[8] (Figure 1).

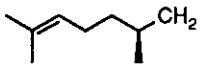
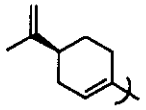
When oxazolines (**1-10**) were heated with a saturated solution of ammonia in methanol at 90-110 °C (in a resealable pressure tube; 15-20 h), good yields of 4-substituted imidazoles (**11-20**) were obtained. Similar transformations of **1-10** with monoalkylamines in benzene or xylene furnished 1,4-disubstituted imidazoles (**21-30**) as single regioisomers.

**Figure 1**




**1-10**

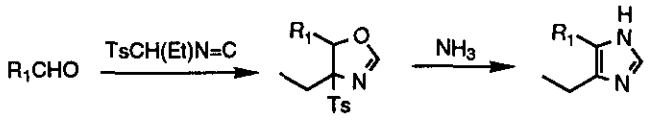
**11-20** $R_2$=H
**21-30** $R_2$=alkyl

| Oxazoline Yield (%) | Imidazole Yield (%) | $R_1$ | Imidazole Yield (%) | $R_2$ |
|---|---|---|---|---|
| **1** (92) | **11** (80) | Et | **21** (57) | Bu |
| **2** (87) | **12** (78) | $^t$Bu | **22** (63) | Me |
| **3** (91) | **13** (73) | $PhCH_2CH_2$ | **23** (55) | $PhCH_2$ |
| **4** (90) | **14** (70) | $MeO_2C(CH_2)_3$ | **24** (55) | Me |
| **5** (83) | **15** (68) |  | **25** (40) | Me |
| **6** (88) | **16** (72) | $PhCH_2OCH_2$ | **26** (10) | Me |
| **7** (85) | **17** (52) | MeCH=C(Me) | **27** (39) | Me |
| **8** (84) | **18** (65) |  | **28** (40) | Me |
| **9** (92) | **19** (61) | Ph | **29** (48) | Me |
| **10** (93) | **20** (75) | *p*-MeOPh | **30** (47) | Me |

This procedure can be extended to prepare 4, 5-disubstituted imidazoles as well. 4-Ethyl-4-tosyl-2-oxazolines (**31-35**) were prepared from the reaction of aldehydes ($R_1CHO$) and α-(*p*-tolylsulfonyl)propyl isocyanide ($TsCH(C_2H_5)N{=}C$)[10] with potassium *tert*-butoxide (cat.) in tetrahydrofuran[11] (Figure 2). With the exception of oxazolines (**31**) and (**34**), these

compounds were obtained as unstable oils and used immediately in the next reaction without full spectral characterization. Treatment of oxazolines (**31-35**) with ammonia gave **11** and 4, 5-disubstituted imidazoles (**36-39**).

**Figure 2**




**31-35** **36-39**

| Oxazoline Yield (%) | Imidazole Yield (%) | $R_1$ |
|---|---|---|
| **31** (81) | **11** (66) | H |
| **32** * | **36** (75) | *Me* |
| **33** * | **37** (75) | Bu |
| **34** (82) | **38** (47) | *p*-MeOPh |
| **35** * | **39** (76) | Et |

* = unstable oil, used immediately

When compounds (**31-34**) were heated with monoalkylamines, however, regioisomeric mixtures of disubstituted and trisubstituted imidazoles were produced (data not shown, Figure 3).

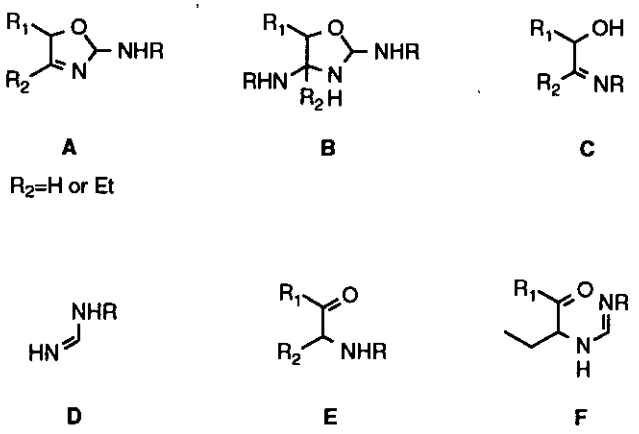
**Figure 3**


$R_1$ = H or alkyl
$R_2$ = alkyl

To account for the formation of the various imidazoles, we believe that the reaction is initiated by addition of amine to the imino function of the tosyloxazolines to afford aminooxazoline (**A**) (Figure 4). A second addition of amine to **A** (when $R_2$=H) followed by fragmentation of the resulting adduct (**B**) upon heating generates intermediates (**C**) and (**D**). In turn, the α-hydroxyimine (**C**) could then undergo isomerization by a 1, 2-hydride shift

affording α-amino ketone (**E**). When $R_2$=ethyl, the second addition of amine in **A** is thought to be suppressed or at least retarded by steric hindrance. Ring-opening, and proton shift creates amino ketone (**F**). Intermolecular condensation of amidine (**D**) and amino ketone (**E**) parallels the well-documented[2, 7] use of α-amino ketones and formamide for the synthesis imidazoles and intramolecular cyclization of α-amidino ketones (**F**) has precedence also.[2, 7]

**Figure 4**




## EXPERIMENTAL

Melting points are uncorrected. Proton nuclear magnetic resonance spectra were measured at 300 MHz. Analytical thin-layer chromatography (tlc) was conducted on Merck precoated glass backed silica gel 60 F-254 plates, 0.25 mm layer thickness. Flash chromatography was performed using 230-400 mesh silica gel. 4-Carbomethoxybutyraldehyde[12] and benzyloxyacetaldehyde[13] used for the preparation of oxazolines (**4**) and (**6**) were prepared according to literature procedures.

**General Procedure for the Preparation of 4-Tosyloxazolines (1-10).** To a stirred suspension of 5.0 mmol of tosylmethyl isocyanide (TosMIC) and 5.1 mmol of the aldehyde in 15 ml of dry ethanol was placed (0.5 mmol) of finely powdered sodium cyanide. Within minutes the slightly exothermic reaction mixture became clear, and white crystals of oxazoline quickly began to deposit from solution (15 min). Stirring continued for an

additional 10 min or until tlc ($CH_2Cl_2$-$Et_2O$, 95/5) indicated the disappearance of TosMIC. The mixture was filtered and the crystals washed with 15 ml of ether-hexane (1:1) and dried. A second crop was obtained from the mother liquor by concentration and trituration with ether-hexane (1:5). The formation of 1:1 diastereomeric mixtures in compounds (**5**) and (**8**) prevented crystallization of the products. In these cases, concentration of the reaction mixture, *in vacuo*, gave a sufficiently pure oil which was used immediately in the next reaction without further purification.

**5-Ethyl-4-tosyl-2-oxazoline (1).** mp 113-115 °C, 92% yield; $^1$H nmr δ 1.02 (t, 3H, J=7.5 Hz), 1.75 (m, 2H), 2.46 (s, 3H) 4.77 (dd, 1H, J=6.0, 2.2 Hz), 5.03 (dd, 1H, J=7.5, 6.0 Hz), 7.00 (d, 1H, J=2.2 Hz), 7.38 (d, 2H, J=8.0 Hz), 7.83 (d, 2H, J=8.0 Hz); ir 3010, 1615, 1320, 1150, 1090 cm$^{-1}$; uv λmax 227, 265, 273 nm; ms (m/z, rel intensity) 139 (4), 98 ($M^+$-Ts, 100), 91 (27), 71 (57).

**5-*tert*-Butyl-4-tosyl-2-oxazoline (2).** *mp 117-118 °C, 87% yield;* $^1$*H nmr* δ 0.95 (s, 9H), 2.46 (s, 3H), 4.76 (d, 1H, J=5.2 Hz), 4.84 (dd, 1H, J=5.2, 1.4 Hz), 7.04 (d, 1H, J=1.4 Hz) 7.38 (d, 2H, J=8.3 Hz), 7.84 (d, 2H, J=8.3 Hz); ir 3020, 1620, 1320, 1150, 1090 cm$^{-1}$; uv λmax 227, 265, 273 nm; ms (m/z, rel intensity) 157 (9), 126 ($M^+$-Ts, 78), 91 (34), 70 (97), 57 (100).

**5-(2-Phenylethyl)-4-tosyl-2-oxazoline (3).** mp 88-90 °C, 91% yield; $^1$H nmr δ 2.01 (q, 2H, J=7.3 Hz), 2.46 (s, 3H), 2.78 (m, 2H), 4.81 (dd, 1H, J=6.0, 1.4 Hz), 5.08 (dd, 1H, J=7.3, 6.0 Hz), 7.02 (d, 1H, J=1.4 Hz), 7.19-7.34 (m, 5H), 7.37 (d, 2H, J=8.0 Hz), 7.79 (d, 2H, J=8.0 Hz); ir 3020, 1620, 1320, 1150, 1090 cm$^{-1}$; uv λmax 227, 265, 273 nm; Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.49; H, 5.79; N, 4.11.

**5-(3-Carbomethoxypropyl)-4-tosyl-2-oxazoline (4).** mp 109-111 °C, 90% yield; $^1$H nmr δ 1.78 (m, 4H), 2.40 (m, 2H), 2.46 (s, 3H), 3.68 (s, 3H), 4.79 (dd, 1H, J=5.8, 2.4 Hz), 5.06 (q, 1H, J=5.8 Hz), 6.99 (d, 1H, J=2.4 Hz), 7.39 (d, 2H, J=8.0 Hz), 7.82 (d, 2H, J=8.0 Hz); ir 3020, 1735, 1615, 1440, 1320, 1150, 1085 cm$^{-1}$; uv λmax 227, 265, 273 nm; ms (m/z, rel intensity) 170

($M^+$-Ts, 100), 156 (8), 138 (24), 110 (16), 91 (25); Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30. Found: C, 55.32; H, 5.77; N, 4.21.

**5-[(*S*)-2,6-Dimethyl-5-heptenyl]-4-tosyl-2-oxazoline (5) as a 1:1 diastereomeric mixture**. Oil, 83% yield; $^1$H nmr δ 1.02 (dx2, 3H, J=7.0 Hz), 1.26-1.99 (m, 7H), 1.60 (s, 3H), 1.69 (s, 3H), 2.46 (s, 3H) 4.74 (dx2, 1H, J=6.0, 2.0 Hz), 5.11 (m, 2H), 6.99 (br, 1H), 7.38 (d, 2H, J=8.3 Hz), 7.82 (d, 2H, J=8.3 Hz). ir 3020, 1615, 1320, 1155, 1090 cm$^{-1}$; uv λmax 227, 265, 273 nm.

**5-Benzyloxymethyl-4-tosyl-2-oxazoline (6)**. mp 95-98 °C, 88% yield; $^1$H nmr δ 2.46 (s, 3H), 3.65 (dd, 1H, J=12.0, 4.0 Hz), 3.83 (dd, 1H, J=12.0, 4.0 Hz), 4.57 (s, 2H), 5.10 (dd, 1H, J=6.0, 2.0 Hz), 5.18 (m, 1H), 7.03 (d, 1H, J=2.0 Hz), 7.31 (m, 5H), 7.38 (d, 2H, J=8.3 Hz), 7.83 (d, 2H, J=8.3 Hz). ir 3020, 1620, 1320, 1150, 1090 cm$^{-1}$; uv λmax 226, 260, 273 nm.

**5-(*E*-1-Methyl-1-propenyl)-4-tosyl-2-oxazoline (7)**. mp 73-75 °C, 85% yield; $^1$H nmr δ 1.54 (s, 3H), 1.66 (d, 3H, J= 7.0 Hz), 2.45 (s, 3H), 4.83 (dd, 1H, J=6.0, 2.2 Hz), 5.41 (d, 1H, J=6.0 Hz), 5.74 (q, 1H, J=7.0 Hz), 7.08 (d, 1H, J=2.2 Hz), 7.38 (d, 2H, J=8.3 Hz), 7.83 (d, 2H, J=8.3 Hz); ir 3020, 1620, 1320, 1150, 1090 cm$^{-1}$; uv λmax 227, 264, 274 nm; Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.11; H, 6.11; N, 4.88.

**5-[(*S*)-4-Isopropenyl-1-cyclohexenyl]-4-tosyl-2-oxazoline (8) as a 1:1 diastereomeric mixture**. Oil, 84% yield; $^1$H nmr δ 1.47-2.25 (m, 7H), 1.73 (s, 3H), 2.46 (s, 3H), 4.72 (m, 2H), 4.86 (ddx2, 1H, J=6.0, 2.2 Hz), 5.42 (d, 1H, J=6.0 Hz), 5.92 (bt, 1H), 7.07 (dx2, 1H, J=2.2 Hz), 7.38 (d, 2H, J=8.3 Hz), 7.84 (d, 2H, J=8.3 Hz); ir 3020, 2920, 1610, 1320, 1150, 1090 cm$^{-1}$; uv λmax 228, 265, 274 nm.

**5-Phenyl-4-tosyl-2-oxazoline (9)**.[8a] mp 97-99 °C, 92% yield; $^1$H nmr δ 2.46 (s, 3H), 5.04 (dd, 1H, J=6.0, 1.5 Hz), 6.07 (d, 1H, J=6 Hz), 7.22 (d, 1H, J=1.5 Hz), 7.39 (m, 7H), 7.88 (d, 2H, J=8.3 Hz); ir 3020, 1620, 1320, 1155, 1090 cm$^{-1}$; uv λmax 227, 265, 274 nm.

**5-(4-Methoxyphenyl)-4-tosyl-2-oxazoline (10).** mp 130-132 °C, 93% yield; $^1$H nmr δ 2.46 (s, 3H), 3.81 (s, 3H), 5.03 (dd, 1H, J=5.7, 2.2 Hz), 6.00 (d, 1H, J=5.7 Hz), 6.91 (d, 2H, J=8.8 Hz), 7.20 (d, 1H, J=2.2 Hz), 7.24 (d, 2H, J=8.8 Hz), 7.38 (d, 2H, J=8.2 Hz), 7.84 (d, 2H, J=8.2 Hz); ir 3020, 1615, 1515, 1320, 1250, 1150, 1090 cm$^{-1}$; uv λmax 229, 265, 274, 282 nm; ms (m/z, rel intensity) 331 ($M^+$, 2), 176 ($M^+$-Ts, 88), 149 (100), 133 (27), 121 (40), 91 (21), 77 (15); Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.60; H, 5.05; N, 4.15.

**General Procedure for the Preparation of 4-Substituted Imidazoles 11-20.** In a resealable pressure tube, a solution of 1 mmol of oxazolines(1-10)and saturated solution of ammonia in dry methanol (8 ml) was heated between 90-110 °C for 15-20 h. Tlc ($CH_2Cl_2$-MeOH 9/1) of the reaction mixture indicated a clean transformation. Concentration and flash chromatography ($CH_2Cl_2$-MeOH 9/1) of the residue afforded 4-substituted imidazoles (**11-20**).

**4-Ethylimidazole (11).**[14] Oil, 80% yield; $^1$H nmr δ 1.26 (t, 3H, J=7.5 Hz), 2.26 (q, 2H, J=7.5 Hz), 6.79 (d, 1H, J=1.5 Hz), 7.57 (d, 1H, J=1.5 Hz), 9.53 (br, 1H, $D_2O$ exchanged); ir 3470, 3100, 2980, 1585, 1565, 1480, 1110, 940, 825 cm$^{-1}$.

**4-*tert*-Butylimidazole (12).**[15] mp 75-77 °C, 78% yield; $^1$H nmr δ 1.32 (s, 9H), 6.78 (d, 1H, J=1.5 Hz), 7.57 (d, 1H, J=1.5 Hz), 8.8 (br, 1H, $D_2O$ exchanged); ir 3470, 2980, 1550, 1480, 1460, 1370, 1110, 825 cm$^{-1}$.

**4-(2-Phenylethyl)imidazole (13).** mp 81-82 °C, 73% yield; $^1$H nmr δ 2.96 (s, 4H), 6.78 (d, 1H, J=1.5 Hz), 7.19-7.28 (m, 5H), 7.57 (d, 1H, J=1.5 Hz), 10.15 (br, 1H); ir 3460, 2950, 1500, 1455, 1080, 820 cm$^{-1}$; Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.68; H, 6.89; N, 16.10.

**4-(3-Carbomethoxypropyl)imidazole (14).** mp 74-75 °C, 70% yield; $^1$H nmr δ 1.98 (m, 2H), 2.37 (t, 2H, J=7.3 Hz), 2.67 (t, 2H, J=7.3 Hz), 3.67 (s, 3H), 6,80 (s, 1H), 7.57 (s, 1H); ir 3460, 2950, 1725, 1565, 1440, 825 cm$^{-1}$; Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.64. Found: C, 56.89; H, 7.15; N, 16.60. Note: This reaction was carried out in benzene.

When methanol was used as a solvent, the corresponding amide, mp 108-110 °C, was obtained in 73% yield.

**4-[(*S*)-2,6-Dimethyl-5-heptenyl]imidazole (15)**. mp 43-44 °C, 68% yield; $^1$H nmr δ 0.90 (d, 3H, J=6.2 Hz), 1.21-2.02 (m, 5H), 1.60 (s, 3H), 1.68 (s, 3H), 2.42 (dd, 1H, J=7.7, 14.7 Hz), 2.62 (dd, 1H, J=6.2, 14.7 Hz), 5.09 (m, 1H), 6.79 (s, 1H), 7.58 (s, 1H); ir 3460, 2930, 1460, 1380, 1230, 1110, 820 cm$^{-1}$; uv λmax 249 nm.

**4-Benzyloxymethylimidazole (16)**. Oil, 72% yield; $^1$H nmr δ 4.53 (s, 2H), 4.54 (s, 2H), 6.95 (s, 1H), 7.30 (m, 5H), 7.51 (s, 1H); ir 3460, 3000, 2870, 1500, 1455, 1360, 1070, 830 cm$^{-1}$; uv λmax 259 nm.

**4-(*E*-1-Methyl-1-propenyl)imidazole (17)**. Oil, 52% yield; $^1$H nmr δ 1.77 (d, 3H, J=7.6 Hz) 1.96 (s, 3H), 6.09 (q, 1H, J=7.6 Hz), 6.95 (s, 1H), 7.57 (s, 1H), 8.65 (br, 1H); ir 3470, 3000, 1665, 1440, 1380, 1120, 1010 cm$^{-1}$; uv λmax 247 nm.

**4-[(*S*)-4-(Isopropenyl)-1-cyclohexenyl]imidazole (18)**. mp 170-172 °C, 65% yield; $^1$H nmr δ 1.58-2.46 (m, 7H), 1.76 (s, 3H), 4.74 (s, 2H), 6.27 (s, 1H), 6.96 (s, 1H), 7.58 (s, 1H), 9.30 (br, 1H); ir 3460, 2940, 1645, 1460, 1440, 1380, 1120, 900 cm$^{-1}$; Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.56, H, 8.57; N, 14.88. Found: C, 76.44; H, 8.30; N, 14.75.

**4-Phenylimidazole (19)**.[16] mp 129-130 °C, 61% yield; $^1$H nmr δ 7.26 (t, 1H, J=8 Hz), 7.35 (s, 1H), 7.39 (m, 2H), 7.72 (s, 1H), 7.73 (d, 2H, J=8.0 Hz); ir 3460, 3000, 1610, 1500, 1065, 930, 830 cm$^{-1}$; uv λmax 261 nm.

**4-(4-Methoxyphenyl)imidazole (20)**.[16b] mp 136-138 °C, 75% yield; $^1$H nmr δ 3. 84 (s, 3H), 6.94 (d, 2H, J=9.0 Hz), 7.25 (d, 1H, J=1.5 Hz), 7.66 (d, 2H, J=9.0 Hz), 7.68 (d, 1H, J=1.5 Hz); ir 3470, 3000, 1620, 1560, 1520, 1250, 1070, 1040, 840 cm$^{-1}$; uv λmax 263 nm; Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.92; H, 5.77; N, 15.85.

**General Procedure for the Preparation of 1,4-Disubstituted Imidazoles (21-30).** In a resealable pressure tube, a solution of 1 mmol of oxazolines (**1-10**) and 4 mmol of alkylamine in 5 ml of benzene (for methylamine) or xylene (for butyl- and benzylamine) was heated between 110-120 °C (benzene) or 135-140 °C (xylene) for 15-20 h. Concentration of the reaction mixture and flash chromatography ($CH_2Cl_2$-MeOH 9/1) afforded 1,4-disubstituted imidazoles (**21-30**) as the sole regioisomer. The *N*-alkylformamide, a by-product from the reaction, can be removed by chromatography.

**1-Butyl-4-ethylimidazole (21).** Oil, 57% yield; $^1$H nmr δ 0.94 (t, 3H, J=7.3 Hz), 1.23 (t, 3H, J=7.3 Hz), 1.33 (m, 2H), 1.74 (m, 2H), 2.60 (q, 2H, J=7.3 Hz), 3.86 (t, 2H, J=7.3 Hz), 6.61 (s, 1H), 7.37 (s, 1H); ir 2970, 1500, 1460, 1160, 915, 820 cm$^{-1}$.

**1-Benzyl-4-*tert*-butylimidazole (22).** mp 58-60 °C, 63% yield; $^1$H nmr δ 1.28 (s, 9H), 5.04 (s, 2H), 6.59 (d, 1H, J=2 Hz), 7.17 (m, 2H), 7.35 (m, 3H), 7.46 (d, 1H, J=2 Hz); ir 2970, 1500, 1460, 1360, 1265, 1130, 970 cm$^{-1}$; uv λmax 260 nm; ms (m/z, rel intensity) 214 ($M^+$, 8), 199 (50), 149 (7.5), 135 (8.3), 107 (10), 91 (100), 71 (18); HRms, m/z Calcd for $C_{14}H_{18}N_2$ ($M^+$) 214.1470, found 214.1468.

**1-Methyl-4-(2-phenylethyl)imidazole (23).** Oil, 55% yield; $^1$H nmr δ 2.87 (m, 2H), 2.97 (m, 2H), 3.62 (s, 3H), 6.55 (s, 1H), 7.23 (m, 5H), 7.36 (s, 1H); ir 2950, 1600, 1510, 1455, 1420, 1170, 980 cm$^{-1}$; uv λmax 259 nm; ms (m/z, rel intensity) 186 ($M^+$, 49), 185 (10), 144 (2), 115 (4), 95 (100), 68 (8); HRms, m/z Calcd for $C_{12}H_{14}N_2$ ($M^+$) 186.1157, found 186.1157.

**1-Methyl-4-(3-carbomethoxypropyl)imidazole (24).** Oil, 55% yield; $^1$H nmr δ 1.97 (m, 2H), 2.37 (t, 2H, J=7.5 Hz), 2.59 (t, 2H, J=7.5 Hz), 3.63 (s, 3H), 3.66 (s, 3H), 6.62 (s, 1H), 7.32 (s, 1H); ir 2950, 1730, 1510, 1440, 1160, 820 cm$^{-1}$.

**1-Methyl-4-[(*S*)-2,6-Dimethyl-5-heptenyl]imidazole (25).** Oil, 40% yield; $^1$H nmr δ 0.89 (d, 3H, J=7.2 Hz), 1.18-2.02 (m, 5H), 1.60 (s, 3H), 1.67 (s, 3H), 2.33 (dd, 1H, J=14.0, 7.5 Hz),

2.55 (dd, 1H, J=14.0, 5.8 Hz), 3.62 (s, 3H), 5.11 (m, 1H), 6.57 (s, 1H), 7.31 (s, 1H); ir 2960, 2930, 1670, 1510, 1460, 1380, 1170, 990, 820 $cm^{-1}$.

**1-Methyl-4-benzyloxymethylimidazole (26)**. Oil, 10% yield; $^1H$ nmr δ 3.68 (s, 3H), 4.52 (s, 2H), 4.63 (s, 2H), 6.90 (s, 1H), 7.35 (m, 5H), 7.43 (s, 1H); ir 2950, 1500, 1460, 1350, 970 $cm^{-1}$; uv λmax 260 nm.

**1-Methyl-4-(*E*-1-methyl-1-propenyl)imidazole (27)**: mp 65-66 °C, 39% yield; $^1H$ nmr δ 1.78 (d, 3H, J=7.0 Hz), 1.92 (s, 3H), 3.66 (s, 3H), 6.31 (q, 1H, J=7.0 Hz), 6.74 (s, 1H), 7.36 (s, 1H); ir 2950, 1545, 1500, 1420, 1195, 1050, 980, 825 $cm^{-1}$; uv λmax 239 nm.

**1-Methyl-4-[(*S*)-4-(isopropenyl)-1-cyclohexenyl]imidazole (28)**. mp 98-99 °C, 40% yield; $^1H$ nmr δ 1.5-2.4 (m, 7H), 1.77 (s, 3H), 3.65 (s, 3H), 4.75 (s, 2H), 6.46 (m, 1H), 6.75 (s, 1H), 7.37 (s, 1H); ir 2950, 1645, 1500, 1420, 1180, 1050, 910 $cm^{-1}$; uv λmax 241 nm; ms (m/z, rel intensity) 202 ($M^+$, 13), 187 (9), 173 (12), 161 (55), 147 (6), 133 (100), 93 (32); HRms, m/z Calcd for $C_{13}H_{18}N_2$ ($M^+$) 202.1470, found 202.1469.

**1-Methyl-4-phenylimidazole (29)**.[17] mp 108-110 °C, 48% yield; $^1H$ nmr δ 3.73 (s, 3H), 7.18 (s, 1H), 7.24 (m, 1H), 7.37 (m, 2H), 7.47 (s, 1H), 7.76 (m, 2H); ir 3010, 1610, 1500, 1480, 1200, 945 $cm^{-1}$; uv λmax 260 nm.

**1-Methyl-4-(4-methoxyphenyl)imidazole (30)**. mp 145-147 °C, 47% yield; $^1H$ nmr δ 3.71 (s, 3H), 3.83 (s, 3H), 6.92 (d, 2H, J=9.0 Hz), 7.08 (s, 1H), 7.45 (s, 1H), 7.68 (d, 2H, J=9.0 Hz); ir 3010, 1620, 1560, 1495, 1250, 1040, 950 $cm^{-1}$; uv λmax 262 nm; Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.15; H, 6.33; N, 14.72.

**General Procedure for the Preparation of 4-Ethyl-4-tosyloxazolines (31-35)**. To a stirred solution of 2.0 mmol of α-(*p*-tolylsulfonyl)propyl isocyanide[10] and 2.1 mmol of the aldehyde in 15 ml of THF was placed (0.2 mmol) of potassium *tert*-butoxide. The reaction was monitored by tlc ($CH_2Cl_2$-$Et_2O$ 95/5) until the disappearance of isocyanide which usually

occurred after 2 h. Concentration and trituration of the residue with 20% ether/hexane afforded oxazolines (**31**) and *trans*-**34** as colorless crystals. 4-Ethyl-5-methyl-4-tosyl-2-oxazoline (**32**), 5-butyl-4-ethyl-4-tosyl-2-oxazoline (**33**) and 4,5-diethyl-4-tosyl-2-oxazoline (**35**) were obtained as unstable oils and used immediately without full characterization.

**4-Ethyl-4-tosyl-2-oxazoline (31)**: mp 98-101 °C, 81% yield; $^1$H nmr δ 0.84 (t, 3H, J=7.3 Hz), 1.89 (m, 1H), 2.04 (m, 1H), 2.46 (s, 3H), 4.23 (d, 1H, J=10.5 Hz), 4.93 (d, 1H, J=10.5 Hz), 6.98 (s, 1H), 7.37 (d, 2H, J=8.5 Hz), 7.82 (d, 2H, J=8.5 Hz); ir 3020, 2980, 1620, 1300, 1150, 950, 820 cm$^{-1}$; uv λmax 228, 265, 274 nm; Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.79; H, 5.85; N, 5.45.

**4-Ethyl-5-(4-methoxyphenyl)-4-tosyl-2-oxazoline (34)**. mp 98-101 °C, 82% yield; $^1$H nmr δ 0.37 (t, 3H, 7.3 Hz), 1.72 (m, 2H), 2.45 (s, 3H), 3.82 (s, 3H), 6.24 (s, 1H), 6.91 (d, 2H, J=8.1 Hz), 7.22 (s, 1H), 7.33 (d, 2H, J=8.1 Hz), 7.37 (d, 2H, J=8.3 Hz), 7.87 (d, 2H, J=8.3 Hz); ir 3020, 1620, 1520, 1460, 1440, 1305, 1260, 1150 cm$^{-1}$; uv λmax 230, 265, 275, 284 nm; Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89, N, 3.90. Found: C, 63.41; H, 5.71; N, 3.80. Based on the high upfield shift of the ethyl-$CH_3$ protons we have assigned the *trans*-stereochemistry (phenyl and ethyl groups are *cis*) to oxazoline (**34**).

**General Procedure for the Preparation of 4,5-Disubstituted imidazoles (36-39)**. Imidazoles (**36-39**) were prepared by the general procedure used for 4-substituted imidazoles (**11-20**). 4-Ethylimidazole (**11**) was also obtained in 66% yield from the reaction of (**31**) and ammonia.

**4-Ethyl-5-methylimidazole (36)**. mp 59-61 °C, 75% yield; $^1$H nmr δ 1.20 (t, 3H, J=7.5 Hz), 2.19, (s, 3H), 2.56 (q, 2H, J=7.5 Hz), 6.60 (br, 1H), 7.44 (s, 1H); ir 3460, 2980, 1600, 1490, 1440, 1210 cm$^{-1}$; Anal. Calcd for $C_6H_{10}N_2$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.41; H, 9.12; N, 25.31.

**4-Butyl-5-ethylimidazole (37)**. mp 42-43 °C, 75% yield; $^1$H nmr δ 0.92 (t, 3H, J=7.3 Hz), 1.21 (t, 3H, J=7.6 Hz), 1.34 (m, 2H), 1.57 (m, 2H), 2.51 (t, 2H, J=7.3 Hz), 2.54 (q, 2H, J=7.6

Hz), 6.40 (br, 1H), 7.45 (s, 1H); ir 3460, 2960, 1600, 1490, 1470, 1020 $cm^{-1}$; ms (m/z, rel intensity) 152 ($M^+$, 21), 137 (6), 123 (7), 109 (100), 95 (15), 81 (6); HRms, m/z Calcd for $C_9H_{16}N_2$ ($M^+$) 152.1313, found 152.1313.

**5-Ethyl-4-(4-methoxyphenyl)imidazole (38).** mp 206-207 °C, 47% yield; $^1H$ nmr δ 1.29 (t, 3H, J=7.4 Hz), 2.80 (q, 2H, J=7.4 Hz), 3.84 (s, 3H), 6.95 (d, 2H, J=8.8 Hz), 7.48 (d, 2H, J=8.8 Hz), 7.56 (s, 1H); ir 3460, 2960, 1620, 1520, 1440, 1250, 1040, 910 $cm^{-1}$; uv λmax 260 nm; Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.15; H, 6.88; N, 13.79.

**4, 5-Diethylimidazole (39).**[18] mp 117-118 °C, 76% yield; $^1H$ nmr δ 1.21 (t, 6H, J=7.6 Hz), 2.57 (q, 4H, J=7.6 Hz), 7.45 (s, 1H); ir 3460, 2970, 1600, 1460, 1240, 1020 $cm^{-1}$.

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