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New Aspects in the Regioselective Functionalization of Furans. Synthesis of Tri- and Tetrasubstituted Furan Derivatives.

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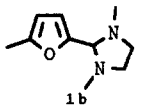
Abstract: Application of directed ortho metalation reaction and electrophilic aromatic substitution allows for the regioselective synthesis of tri- and tetrasubstituted furans, thus superseding classical *de novo* furan construction modes.

Furan derivatives are of increasing interest in organic synthesis[1] as a direct consequence of the easiness in their transformation into a wide range of highly functionalized open chain and cyclic structures[2]. However, although the construction of mono- and disubstituted furan moieties has received a great deal of attention in recent years[3], the number of syntheses completed for tri- and tetrasubstituted furans are at present fairly meagre, and a general protocol is still lacking[4]. We wished to develop a regioselective functionalization of the furan moiety based on the tandem directed ortho metalation reaction[5]-electrophilic aromatic substitution[6], using rather inexpensive commercial furan derivatives as starting materials, with the aim of superseding classical *de novo* furan construction modes.

In order to prepare 2,3,5-trisubstituted furan derivatives, and taking into account both the wide accessibility of furfural as well as the well known ortho-directing ability of the imidazolidine moiety, together with the mild reaction conditions described[7] for its back-conversion into the aldehyde functionality[8], we decided, at first, to examine the β-functionalization of furylimidazolidine **1b** (Table 1) in the hope of attaining good levels of β-metalation in the presence of the methyl C5-blocking substituent, which would preclude the furan oxygen overriding effect observed[7] in the metalation reaction of **1a**.

Table 1 *Functionalization of Furylimidazolidine* **1b**

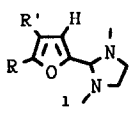


Entry	Solvent	Base	Temp. (°C)	React. time (min)	Recovered **1b** (%)
1	THF	BuLi	-78	60	90
2	THF-TMEDA	BuLi	-78	60	75
3	Et_2O	BuLi	-78	60	70
4	Et_2O-TMEDA	BuLi	-78	60	65
5	DME	BuLi	-78	60	75
6	DME-TMEDA	BuLi	-78	60	80
7	Hexane	BuLi	-78	60	50
8	Hexane-TMEDA	BuLi	-78	60	--
9	THF	BuLi	-23	60	50
10	THF	BuLi	-78	120	70
11	THF	MeLi	-78	60	--
12	THF	BuLi	-78	60	--

However, to our amaze, unreacted **1b** together with polymeric material was recovered in the range of experiments shown in Table 1, with no β-lithiated product being detected after MeI quenching.

At this stage the values of $^1J(^{13}C3\text{-}H)$ coupling constants of furylimidazolidines **1** was examined (Scheme I). A comparison of **1a** with **1b** reveals a strong diminution in the

Scheme I



1	R	R'	$^1J(^{13}C3\text{-}H)$, H
a	H	H	179.8
b	CH_3	H	172.3
c	$CH(OEt)_2$	H	173.2
d	CH_3	Br	179.3
e	CH_3	CH_3	169.8

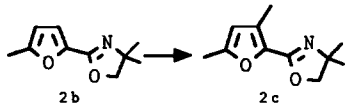
coupling constant value for the latter, which, in turn, could be associated with a decrease in kinetic acidity[9]. Therefore, in a first attempt to circumvent this drawback, we synthesized furylimidazolidine **1c**. This showed an enhanced coupling constant value with respect to **1b**, which, however, was found not to be enough for a successful β-metalation in any of the aforementioned conditions. Last, we prepared the bromo-derivative **1d** which showed a coupling constant value of the same range than **1a**. However, treatment of **1d** with BuLi in THF followed by MeI gave rise to furylimidazolidine **1e**, as a consequence of preferential Li-Br interchange, thus providing a novel access to 2,4,5-trisubstituted furan derivatives.

In the light of these results, we decided to replace the imidazolidine moiety by the oxazoline one, which, albeit its more powerful ortho-directing character[5], requires somewhat elaborated deprotection techniques[10] in order to recover the aldehyde functionality[8].

Nevertheless, in a similar fashion as observed for furylimidazolidines, and in spite of the described efficiency[11] of the oxazoline moiety in the β-functionalization of

compound **2a**, no C3-lithiation of the C5 methyl analogue **2b** took place following literature conditions[11] (Scheme II). However, the use of an excess of base together with

Scheme II



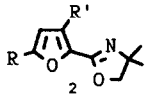
2b **2c**

Reaction time (min)	Observed Ratio[a]
15	100 : 0
30	55 : 45
60	22 : 88
120	15 : 85
120	0 : 100

a) Monitored by ^{1}H-NMR 300 MHz

an eight-fold time increase allowed for the obtainment of furyloxazoline **2c**. The result has been extended to the synthesis of compounds **2d-f**, thus allowing for the synthesis of 2,3,5-trisubstituted furan derivatives (Scheme III).

Scheme III

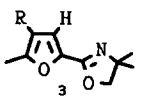


2	R	R'
a	H	H
b	CH_3	H
c	CH_3	CH_3
d	CH_3	CH_2=CH-CH_2
e	CH_3	Ph-CH_2
f	CH_3	CO_2H

The observed reactivity diminution against β-lithiation on going from furyloxazoline **2a** to **2b** could be ascribed, analogously to the case of furylimidazolidines **1a-d**, to a kinetic acidity diminution in the presence of the C5 methyl substituent. As a matter of fact, an inspection of $^1J(^{13}C3\text{-}H)$ values reveals a decrease in the coupling constant value for compound **2b** (177.0 Hz) as compared with **2a** (183.3 Hz). In this case, however, the strong ability of the oxazoline system as directed metalation group did not prevent the reaction, although stronger conditions were required.

On the other hand, synthesis of 2,4,5-trisubstituted furans **3** was performed by functionalization of C4 in compound **2b** *via* electrophilic aromatic substitution[6], in spite of the strong electron-withdrawing effect of the oxazoline moiety and its proneness to N-quaternization. Therefore, treatment with the appropriate electrophile in the presence of an excess of $AlCl_3$ as catalyst in CS_2 or $CHCl_2$ solution afforded furyloxazolines **3a-c** (Scheme IV).

Scheme IV



3	R	$^1J(^{13}C3\text{-}H)$, Hz
a	^{t}Bu	174.2
b	CH_3CO	178.5
c	Br	182.0
d	CH_3	174.0

As inferred from the inspection of $^1J(^{13}C3\text{-}H)$ values for compounds **3a-c** and **3d**, the introduction of an alkyl substituent at C4 further diminishes the acidity of H3, whereas the presence of electron withdrawing substituents raises up the coupling constant value, which, in the case of the bromo-derivative **3c**, attains analogous range to that of compound **2a**.

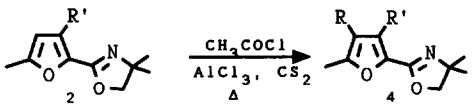
Notwithstanding the enhanced H3 kinetic acidity of compound **3c**, further

functionalization at C4 can be carried out by selective Li-Br interchange with ^{t}BuLi, followed by treatment with electrophiles, as exemplified for the synthesis of compound **3d**, thus widening the scope of the procedure[12].

Finally, tandem application of ortho-directed metalation and electrophilic aromatic substitution in furyloxazolines allows for the regioselective synthesis of 2,3,4,5-tetrasubstituted furan derivatives. Naturally, the order of application of subsequent reaction steps should ensure the chemical compatibility of the substituents introduced in the first one with the reaction conditions required for the second.

Several examples illustrate the proposed methodology. Therefore, treatment of furyloxazolines **2c,d** -obtained *via* β-metalation of compound **2b**- with acetyl chloride in the presence of an excess of $AlCl_3$ in CS_2 solution allows for the synthesis of compounds **4a,b** (Scheme V). It has to be pointed out that, in these cases, an inversion of the

Scheme V

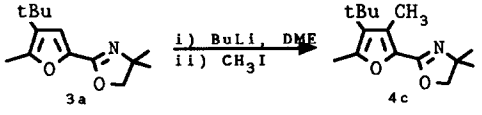


2	4	R	R'
c	a	$COCH_3$	CH_3
d	b	$COCH_3$	CH_2-CH-CH_2

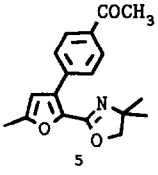
reaction sequence is not possible, as a consequence of the chemical lability of the acetyl group against metalating agents.

On the other hand, treatment of compound **3a** -obtained by electrophilic aromatic substitution of furyloxazoline **2b**- with BuLi in DME, followed by CH_3I quenching, allowed for the synthesis of compound **4c** (Scheme VI).

Scheme VI



Scheme VII



In this case, due to the diminished kinetic acidity of compound **3a** in comparison with furyloxazolines **2a** and **2b** (Scheme III), the metalation step had to be increased up to 4 h.

However, a limitation was encountered with furyloxazoline **2e**, which upon treatment with acetyl chloride in the aforementioned conditions, successfully used for furan-C4 functionalization of compounds **2c,d**, gave rise to 2-[3-(4-acetylbenzyl)-5-methyl-2-furyl]-4,4-dimethyloxazoline **5** (Scheme VII).

In summary, the results show that, in the presence of a methyl substituent at C5, the kinetic acidity of C3, inferred by observation of $^{1}J(^{13}C3\text{-}H)$, diminishes to an extent that prevents lithiation of furylimidazolidines and requires forcing conditions for the metalation of furyloxazolines. As far as we know, the only precedent in the literature dealing with the β- functionalization of a C5-substituted furyloxazoline[5i] is that of

4,4-dimethyl-2-(5-trimethylsilyl-2-furyl)oxazoline.

As a matter of fact, a survey of literature data[5] reveals the occurrence of analogous drawbacks in the presence of methyl substituents also in carbocyclic chemistry. Thus, the lithiation of 4,4-dimethyl-2-(3-methyl-4-methoxyphenyl)oxazoline, which has been reported[13] to yield a sole regioisomer due to steric considerations[14], is, to our knowledge, a consequence of the decrease of kinetic acidity at C2 in comparison with C6 due to the presence of the methyl substituent at C3[15].

At any rate, the procedure reported provides a double means of synthesizing highly functionalized furan systems, starting either from compounds **2** or **3**, depending on the ability of the present functionality to withstand the reaction conditions used in each case.

EXPERIMENTAL

General. ^{1}H N.mr. spectra were recorded on a Varian FX-300 spectrometer operating at 300 MHz. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. M.p.'s were recorded on a Büchi 512 apparatus, and are uncorrected.

Synthesis of Furylimidazolidines (**1a-c**). General Procedure

The corresponding aldehyde (104 mmol) and 10.4 g (118 mmol) of N,N'-dimethylethylenediamine were refluxed in benzene solution for 12 h, following the method of Carpenter and Chadwick[7] for compound **1a**.

The following imidazolidines were prepared by this method.

1,3-Dimethyl-2-(5- methyl-2-furyl)imidazolidine (**1b**)

Reaction with 11.5 g of 5-methylfurfural gave compound **1b** in 80% yield (oil): IR (thin film) 1575, 1500, 820 cm^{-1}; ^{1}H N.m.r ($CDCl_3$) δ 2.28 (s, 6H, CH_3N), 2.30 (s, 3H, CH_3-furan), 2.54 - 2.56 (m, 2H, CH_2), 3.34 - 3.36 (m, 2H, CH_2), 3.46 (s, 1H, CH imidaz.), 5.90, 5.91 (d, J_{34}= 2.9 Hz, 1H, H4 furan), 6.25, 6.26 (d, J_{34}= 2.9 Hz, 1H, H3 furan); ^{13}C N.mr.($CDCl_3$) δ 13.59 (CH_3-furan), 39.78 (CH_3N), 52.94 (CH_2N), 85.05 (CH imidaz.), 105.55 (J_{CH}= 171.2 Hz, C4 furan), 110.90 (J_{CH}= 172.3 Hz, C3 furan), 150.06 (C2 furan), 152.79 (C5 furan). Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95. Found C, 66.71; H, 9.01.

1,3-Dimethyl-2-(5-diethoxymethyl-2-furyl)imidazolidine (**1c**)

Reaction with 20.8 g of 5-diethoxymethyl-2-furancarboxaldehyde[8b] gave compound **1c** in 75% yield (oil): IR (thin film) 1580, 1500, 850 cm^{-1}; ^{1}H N.m.r ($CDCl_3$) δ 1.21 (q, J = 6.9 Hz, 6H, CH_3CH_2), 2.29 (s, 6H, CH_3N), 2.59 - 2.60 (m, 2H, CH_2N), 2.59 - 3.31 (m, 2H, CH_2N), 3.59 (t, J = 6.9 Hz, 4H, CH_2O), 3.67 (s, 1H, CH imidaz.), 5.42 (s, 1H, $CH(OEt)_2$), 6.37, 6.38 (d, J_{34}= 3.3 Hz, H3 furan), 6.39, 6.41 (d, J_{34}= 3.3 Hz, H4 furan); ^{13}C N.m.r ($CDCl_3$) δ 14.89 ($\underline{C}H_3CH_2$), 39.52 (CH_3N), 52.42 (CH_2N), 60.86 (CH_2O), 84.04 (CH imidaz.), 96.05 ($\underline{C}H(OEt)_2$), 108.25 (J_{CH}= 180.3 Hz, C4 furan), 109.09 (J_{CH} = 173.2 Hz, C3 furan), 151.89 (C2 furan), 152.92 (C5 furan). Anal. Calcd for $C_{14}H_{24}N_2O_3$: C, 62.66; H, 9.01. Found: C, 62.84; H, 9.14.

1,2-Dimethyl-2-(4-bromo-5-methyl-2-furyl)imidazolidine (**1d**)

Reaction with 19.6 g of 4-bromo-5-methyl-2-furancarboxaldehyde[4b] gave compound **1d** in 80% yield (oil): IR (thin film) 1570, 1510, 800 cm^{-1}; ^{1}H N.m.r ($CDCl_3$) δ 2.28 (s, 6H, CH_3N), 2.29 (s, 3H, CH_3-furan), 2.56 - 3.34 (m, 4H, CH_2), 3.46 (s, 1H, CH imidaz.), 6.36 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 12.35 (CH_3-furan), 39.68 (CH_3N), 52.96 (CH_2N),

84.59 (CH imidaz.), 96.00 (C4 furan), 113.55 (J_{CH}= 179.3 Hz, C3 furan), 149.91 (C5 furan), 150.69 (C2 furan). Anal. Calcd for $C_{10}H_{14}BrN_2O$: C, 46.53; H, 5.47.Found: 46.68; H, 5.62.

1,3-Dimethyl-2-(4,5-dimethyl-2-furyl)imidazolidine (**1e**).

To a solution of 130 mg (0.5 mmol) of imidazolidine **1d** in 2 mL of anhydrous THF at -78°C was added dropwise 0.3 mL (0.5 mmol) of a 1.6 M solution of BuLi in hexane. After 15 min of stirring, CH_3I (0.5 mL) was added and the reaction mixture was stirred for a further 0.5 h at -78°C and then for 12 h at room temperature. The solvent was then removed under reduced pressure, and the product extracted from the residue with ether (3 x 20 mL). The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with 1:1 hexane/ethyl acetate as the eluent, giving 75 mg of **1e** (80%) as a light yellow oil: IR (thin film) 1600, 1510, 790 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.87 (s, 3H, CH_3-C4 furan), 2.28 (s, 6H, CH_3N), 2.20 (s, 3H, CH_3-C5 furan), 2.54 - 2.56 (m, 2H, CH_2N), 3.34 - 3.36 (m, 2H, CH_2N), 3.56 (s, 1H, CH imidaz.), 6.27 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 11.63 (CH_3-C4 furan), 13.63 (CH_3-C5 furan), 39.65 (CH_3N), 52.93 (CH_2N), 84.79 (CH imidaz.), 111.83 (C4 furan), 112.48 (C3 furan), 151.23 (C5 furan), 153.01 (C2 furan). Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34. Found: C, 68.31; H 9.55.

4,4-Dimethyl-2-(5-methyl-2-furyl)oxazoline (**2b**).

To a solution of 900 mg (5.45 mmol) of oxazoline **2a**[11] in 20 mL of anhydrous Et_2O at -78°C was added dropwise 2.2 mL (5.5 mmol) of a 2.5 M solution of BuLi in hexane. After stirring for 15 min at -78°C and at 0°C for 30 min, CH_3I (3.5 mL) was added and the reaction mixture was stirred for a further 0.5 h at -78°C and then for 12 h at room temperature. The solvent was then removed under reduced pressure, and the product extracted from the residue with ether (3 x 50 mL). The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with 5:5:1 hexane/chloroform/ethyl acetate as the eluent, giving 780 mg of **2b** (80%) as a light yellow oil: IR (thin film) 1680, 1600, 1580, 880, 730 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.36 (s, 6H, CH_3-oxazol.), 2.35 (s, 3H, CH_3-furan), 4.05 (s, 2H, CH_2), 6.05 (d, J_{34}= 3.0 Hz, 1H, H3 furan), 6.80 (d, J_{CH}= 3.0 Hz, 1H, H4 furan); ^{13}C N.m.r ($CDCl_3$) δ 13.46 (CH_3-furan), 28.04 (CH_3-oxazol.), 67.27 (C4 oxazol.), 78.73 (C5 oxazol.), 107.49 (J_{CH}= 175.0 Hz, C4 furan), 115.04 (J_{CH}= 177.03, C3 furan), 141.14 (C2 furan), 154.18 (C5 furan), 155.45 (C=N). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.16; H 7.52.

Synthesis of Furyloxazolines (**2c-f**) and (**4c**). General Procedure

To a solution of the corresponding oxazoline (1.39 mmol) in 5 mL of anhydrous DME at -78°C was added dropwise 0.63 mL (1.6 mmol) of a 2.5 M solution of BuLi in hexane. After stirring for 2 h at -78°C , an excess of the corresponding electrophile (1.5 mL) was added and the reaction mixture was stirred for a further 0.5 h at -78°C and then for 12 h at room temperature. The solvent was then removed under reduced pressure, and the product extracted from the residue with ether (3 x 50 mL). The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was percolated on silica gel with 1:1 hexane/ethyl acetate as the eluent.

The following oxazolines were prepared by this method.

4,4-Dimethyl-2-(3,5-dimethyl-2-furyl)oxazoline (**2c**)

Reaction of **2b** with CH_3I gave 230 mg of compound **2c** (85%) as a light yellow oil: IR (thin film) 1675, 1590, 1550, 850, 750 cm^{-1}; ^1H N.mr. ($CDCl_3$) δ 1.35 (s, 6H,

CH_3-oxazol.), 2.21 (s, 3H, CH_3-C3 furan), 2.28 (s, 3H, CH_3-C5 furan), 4.03 (s, 2H, CH_2), 5.91 (s, 1H, H4 furan); ^{13}C N.m.r ($CDCl_3$) δ 10.89 (CH_3-C3 furan), 13.51 (CH_3-C5 furan), 28.22 (CH_3-C4 oxazol.), 66.67 (C4 oxazol.), 78.64 (C5-oxazol.), 110.98 (C4 furan), 127.33 (C3 furan), 137.08 (C2 furan), 154.28 (C5 furan), 155.43 (C=N). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.59; H, 7.91.

2-(3-Allyl-5-methyl-2-furyl)-4,4-dimethyloxazoline **(2d)**

Reaction of **2b** with allyl bromide gave compound **2d** in 70% yield (oil): IR (CCl_4) 1670, 1650, 1620, 1550, 930 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.36 (s, 6H, CH_3-oxazol.), 2.30 (s, 3H, CH_3-furan), 3.44 - 3.46 (d, J = 6.6 Hz, CH_2-furan), 4.03 (s, 2H, CH_2 oxazol.), 5.04 (m, 2H, CH_2=), 5.85 (m, 1H, CH=), 5.96 (H4 furan); ^{13}C N.m.r ($CDCl_3$) δ 13.79 (CH_3-furan), 28.26 (CH_3-oxazol.), 29.68 (CH_2-furan), 67.78 (C4 oxazol.), 78.77 (C5 oxazol.), 109.80 (C4 furan), 115.55 (CH_2=), 129.78 (C3 furan), 136.01 (CH=), 137.05 (C2 furan), 154.69 (C5 furan), 155.35 (C=N). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81. Found: C, 71.36; H, 7.91.

2-(3-Benzyl-5-methyl-2-furyl)-4,4-dimethyloxazoline **(2e)**

Reaction of **2b** with benzyl bromide gave compound **2e** in 75% yield (oil): IR (CCl_4) 1720, 1650, 1550, 710 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.40 (s, 6H, CH_3-oxazol.), 2.27 (s, 3H, CH_3-furan), 4.06 (s, 2H, CH_2 oxazol.), 4.10 (s, 2H, CH_2-Ph), 5.85 (s, 1H, H4 furan), 7.20-7.29 (m, 5H, Ph); ^{13}C N.m.r ($CDCl_3$) δ 13.71 (CH_3-furan), 28.14 (CH_3-oxazol.), 31.35 (CH_2-Ph), 66.59 (C4 oxazol.), 79.03 (C5 oxazol.), 110.13 (C4 furan), 126.01 (C3 furan), 128.25, 128.48, 128.52, 131.23 (Ph), 137.29 (C2 furan), 155.51 (C=N), 157.98 C5. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11.Found: 75.94; H, 7.32.

2-(4,4-Dimethyl-2-oxazolin)-5-methyl-3-furancarboxylic acid **(2f)**

Reaction of **2b** with solid CO_2 (1.0 g) gave compound **2f** in 70% yield: mp 143-145 °C (hexane-ethyl acetate); IR (KBr) 3200-2800, 1700, 1680, 1600, 1560, 750 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.42 (s, 6H, CH_3-oxazol.), 2.36 (s, 3H, CH_3-furan), 4.28 (s, 6H, CH_2 oxazol.), 6.68 (s, 1H, H4 furan); ^{13}C N.m.r ($CDCl_3$) δ 13.56 (CH_3-furan), 28.02 (CH_3-oxazol.), 67.13 (C4 oxazol.), 80.63 (C5 oxazol.), 111.38 (C3 furan), 115.16 (C4 furan), 144.54 (C2 furan), 155.41 (C5 furan), 156.94 (C=N), 161.67 (CO_2H). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87. Found: C, 58.93; H, 6.14.

2-(4-tert-Butyl-3,5-dimethyl-2-furyl)-4,4-dimethyloxazoline **(4c)**

Compound **4c** was prepared analogously from **3a**, stirring the reaction mixture for 4 h at -78 °C prior to the introduction of methyl iodide, in 50% yield: IR (thin film) 1670, 1600, 1540, 750 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.25 (s, 9H, tert-Bu), 1.35 (s, 6H, CH_3 oxazol.), 2.39 (s, 3H, CH_3-C3 furan), 2.43 (s, 3H, CH_3-C5 furan), 4.04 (s, 2H, CH_2); ^{13}C N.m.r ($CDCl_3$) δ 11.03 (CH_3-C3 furan), 13.54 (CH_3-C5 furan), 28.14 (CH_3-oxazol.), 29.92 ($\underline{C}(CH_3)_3$), 30.71 ($C(\underline{CH_3})_3$), 67.35 (C4 oxazol.), 78.80 (C5 oxazol.), 127.07 (C3 furan), 133.25 (C4 furan), 136.92 (C2 furan), 149.74 (C5 furan), 154.97 (C=N). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.23. Found: C, 72.03; H, 9.06.

Synthesis of Furyloxazolines **(3a,b)**, **(4a,b)** and **(5)**. General Procedure.

To a solution of the corresponding oxazoline (0.84 mmol) in 3 mL of CS_2 were added 182 mg (1.87 mmol) of $AlCl_3$ and the corresponding electrophile (1.05 mmol). The mixture was refluxed for 6 h, poured into cold water (10 mL) and extracted with methylene chloride (3 x 10 mL). The combined extracts were washed with water and brine, dried

($MgSO_4$), and evaporated. The residue was percolated on silica gel with 1:1 hexane/ethyl acetate as the eluent.

The following oxazolines were prepared by this method.

2-(4-^{t}Butyl-5-methyl-2-furyl)-4,4-dimethyloxazoline (**3a**)

Reaction of **2b** with ^{t}butyl chloride gave 168 mg of compound **3a** (80%) as a light yellow oil: IR (thin film) 1680, 1590, 1550, 750 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.24 (s, 9H, tert-butyl), 1.34 (s, 6H, CH_3-oxazol.), 2.41 (s, 3H, CH_3-furan), 4.02 (s, 2H, CH_2), 6.82 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 13.62 (CH_3-furan), 28.26 (CH_3-oxazol.), 29.86 ($\underline{C}(CH_3)_3$), 30.63 ($C(\underline{C}H_3)_3$, 67.38 (C4 oxazol.), 78.88 (C5 oxazol.), 115.49 (J_{CH}= 174.2 Hz, C3 furan), 131.89 (C4 furan), 138.93 (C2 furan), 149.71 (C5 furan), 155.44 (C=N). Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.27. Found: C 69.82; H, 11.41.

2-(4-Acetyl-5-methyl-2-furyl)-4,4-dimethyloxazoline (**3b**).

Compound **3b** was analogously prepared from **2b** and acetyl chloride, in 75% yield (oil): IR (thin film) 2850, 1680, 1600, 1540, 750 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.40 (s, 6H, CH_3-oxazol.), 2.37 (s, 3H, CH_3-furan), 2.87 (s, 3H, CH_3CO), 4.11 (s, 2H, CH_2), 7.15 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 14.43 (CH_3-furan), 28.11 (CH_3-oxazol.), 28.90 (CH_3CO), 67.77 (C4 oxazol.), 79.13 (C5 oxazol.), 114.26 (J_{CH}= 178.5 Hz, C3 furan), 122.48 (C4 furan), 140.63 (C2 furan), 153.84 (C=N), 161.00 (C5 furan), 193.21 (CO). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 6514; H, 6.83. Found: C, 65.23; H, 6.91.

2-(4-Acetyl-3,5-dimethyl-2-furyl)-4,4-dimethyloxazoline (**4a**)

Compound **4a** was analogously prepared from **2c** and acetyl chloride in 65% yield (oil): IR (thin film) 2830, 1670, 1600, 1550 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.36 (s, 6H, CH_3-oxazol.), 2.23 (s, 3H, CH_3-C3 furan), 2.29 (s, 3H, CH_3-C5 furan), 2.91 (s, 3H, CH_3CO), 4.05 (CH_2); ^{13}C N.m.r ($CDCl_3$) δ 10.75 (CH_3-C3 furan), 13.87 (CH_3-C5 furan), 28.34 (CH_3-oxazol.), 67.71 (C4 oxazol), 78.65 (C5 oxazol), 125.55 (C4 furan), 126.78 (C3 furan), 137.17 (C2 furan), 159.32 (C5 furan), 154.01 (C=N), 192.57 (CO). Anal. Calcd for $C_{13}H_{18}NO_3$: C, 66.08; H, 7.68. Found: C, 66.39; H, 7.39.

2-(4-Acetyl-3-allyl-5-methyl-2-furyl)-4,4-dimethyloxazoline (**4b**).

Compound **4b** was prepared analogously from **2d** and acetyl chloride in 55% yield (oil): IR (thin film) 2840, 1680, 1660, 1610, 1540, 930 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.38 (s, 3H, CH_3-oxazol.), 2.24 (s, 3H, CH_3-furan), 2.31 (s, 3H, CH_3CO), 3.11 (d, J = 6.5 Hz, 2H, CH_2-furan), 4.04 (s, 2H, CH_2 oxazol.), 5.05 (m, 2H, CH_2=), 6.02 (m, 1H, CH=); ^{13}C N.m.r ($CDCl_3$) δ 14.72 (CH_3-furan), 28.14 (CH_3-oxazol.), 28.86 (CH_3CO), 29.76 (CH_2-furan), 67.75 (C5 oxazol.), 78.99 (C4 oxazol.), 116.03 (CH_2=), 124.04 (C4 furan), 127.32 (C3 furan), 136.23 (CH=), 137.41 (C2 furan), 154.89 (C=N), 161.03 (C5 furan). Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.68; H, 7.68. Found: C, 68.96; H, 7.84.

2-[3-(4-Acetylbenzyl)-5-methyl-2-furyl]-4,4-dimethyloxazoline (**5**).

Compound **5** was analogously prepared from **2e** and acetyl chloride in 60% yield (oil): IR (CCl_4) 2840, 1710, 1690, 1640, 1550 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 2.30 (s, 3H, CH_3-furan), 2.58 (s, 3H, CH_3CO), 4.05 (s, 2H, CH_2 oxazol.), 4.15 (s, 2H, CH_2-Ph), 5.82 (s, 1H, H4 furan), 7.31 (d, J= 9.5 Hz, 2H, H3 Ph), 7.88 (d, J = 9.5, 2H, H2 Ph); ^{13}C N.m.r ($CDCl_3$) δ 13.74 (CH_3-furan), 28.28 (CH_3-oxazol.), 32.01 (CH_2-Ph), 66.86 (C4 oxazol.), 79.13 (C5 oxazol.), 110.65 (C4 furan), 127.14 (C3 furan), 128.63, 128.78 (C2, C3 Ph), 135.55 (C1 Ph), 137.32 (C2 furan), 138.03 (C4 Ph), 155.61 (C=N), 158.14 (C5 furan). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.79. Found: C, 73.51; H, 6.83.

2-(4-Bromo-5-methyl-2-furyl)-4,4-dimethyloxazoline (3c).

To a solution of 200 mg (1.12 mmol) of **2b** in 5 mL of methylene chloride were added 244 mg (2.5 mmol) of $AlCl_3$ and 0.07 mL (1.4 mmol) of bromine. The mixture was stirred at room temperature for 24 h, poured into cold water (20 ml) and extracted with methylene chloride (3 x 20 mL). The combined extracts were washed with 40% sodium bisulfite solution, water and brine, dried ($MgSO_4$), and evaporated. The residue was percolated on silica gel with 1:1 hexane/ethyl acetate as eluent, giving 240 mg of 3c (80%) as a light yellow oil: IR (CCl_4) 1680, 1590, 1540 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.36 (s, 6H, CH_3-oxazol.), 2.34 (s, 3H, CH_3-furan), 4.05 (CH_2), 6.84 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 12.03 (CH_3-furan), 28.15 (CH_3-oxazol.), 67.64 (C4 oxazol.), 79.05 (C5 oxazol.), 97.66 (C4 furan), 117.36 (J_{CH}=182.0 Hz, C3 furan), 141.60 (C2 furan), 152.78 (C5 furan), 153.69 (C=N). Anal. Calcd for $C_{10}H_{12}BrO_2N$: C, 46.53; H, 4.68. Found: C, 46.64; 4.72.

4,4-Dimethyl-(4,5-dimethyl-2-furyl)oxazoline (3d)

To a solution of ^{t}BuLi 0.43 M in hexane (2.68 ml, 1.16 mmol) at -78 °C was added dropwise 2.3 mL of a 1:1.3 solution of oxazoline 3c (150 mg, 0.58 mmol) in hexane-Et_2O. After stirring for 15 min at -78 °C, CH_3I (0.5 mL) was added and the mixture was stirred for 1 h further at -78 °C and then for 12 h at room temperature. The solvent was then removed under reduced pressure, and the product extracted from the residue with ether (3 x 50 mL). The ether extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was percolated on silica gel with 2:1 hexane/ethyl acetate as the eluent, giving compound **3d** in 70% yield as a light yellow oil: IR (thin film) 1670, 1600, 1550, 850, 750 cm^{-1}; ^1H N.m.r ($CDCl_3$) δ 1.35 (s, 6H, CH_3-oxazol.), 1.95 (s, 3H, CH_3-C3 furan), 2.25 (s, 3H, CH_3-C5 furan), 4.03 (s, 2H, CH_2), 6.69 (s, 1H, H3 furan); ^{13}C N.m.r ($CDCl_3$) δ 11.84 (CH_3-C4 furan), 14.05 (CH_3-C5 furan), 28.28 (CH_3-C4 oxazol.), 67.43 (C4 oxazol.), 78.88 (C5-oxazol.), 116.24 (C4 furan), 117.40 (J_{CH}= 174.02 Hz, C3 furan), 139.02 (CC2 furan), 151.37 (C5 furan), 154.88 (C=N). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.46; H, 7.93

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