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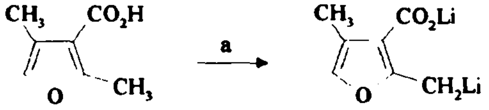
Side Chain Metalation of (5-substituted-2-furyl)oxazolines

Jean-Yves Lenoir, Pierre Ribéreau, Guy Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique de l'IRCOF
Unité de Recherche Associée au CNRS, INSA de Rouen, BP 08
76131 Mont-Saint-Aignan, France

Abstract : Side chain metalation at the 5-methyl or 5-benzyl position of 4,4-dimethyl-2-(5-substituted-2-furyl)oxazolines has been achived using butyllithium as metalating agent and THF-HMPA 4:1 as solvent. The lithiated species can be reacted with various electrophiles to give the expected products in good yields.

The metalation of furan has received a great deal of attention since the preparation of furyl sodium by Gilman in 1934.[1] The metalation of substituted furans was particularly studied[2] in order to improve the regioselectivity of these reactions, especially in the case of directing group substituted heterocycles.[3] Although side chain metalation is well known in pi-deficient series[4] or in benzene compounds,[5] it was scarcely described on pi-exceeding aromatic compounds. Tada and Takahashi[6] have reported the lithiation at the 2-methyl position of 2,4-dimethyl-3-furoic acid by treatment with LDA in THF (scheme 1).



Scheme 1 : a) LDA, THF, -78°C

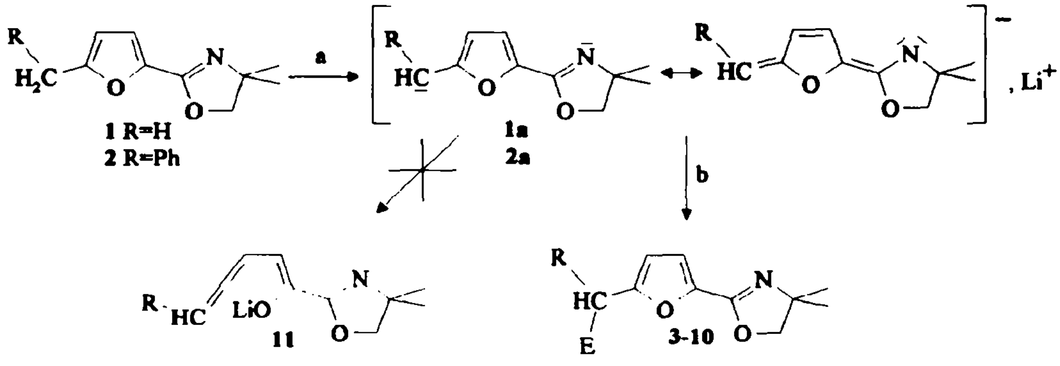
This is to our knowledge the sole reported example of side chain metalation of a furan compound.

During our investigations on the metalation of 2-(2-furyl)oxazolines, we found that it was possible to metalate 4,4-dimethyl-2-(5-methyl-2-furyl)oxazoline **1** on the 5-methyl position whereas the oxazoline moiety is far away from the reaction center and cannot promote the reaction by chelating the metalating agent, as can be assumed in the preceding case (scheme 1).

RESULTS AND DISCUSSION

Furyloxazoline **1** and **2** were obtained from 4,4-dimethyl-2-(2-furyl)oxazoline by treatment with butyllithium in THF-HMPA (4:1) at -78°C and addition of the lithiated species to a cold solution of either methyl iodide or benzyl bromide. Metalation of **1** has been achieved using butyllithium in THF-HMPA (4:1) at

-78°C (scheme 2). Deuterium exchange with EtOD showed that metalation took place with total regioselectivity on the methyl group. The stability of **1a** due to mesomerism (scheme 2) could account for its formation from **1**. The furyloxazoline **2** has also been metalated in the same conditions. Rearrangement[7] of **1a** and **2a** to the allenic enolate **11** has not been observed in the reaction conditions. The reaction of the metalated species **1a** and **2a** with several electrophiles has been tested and the results are summarized in table 1.



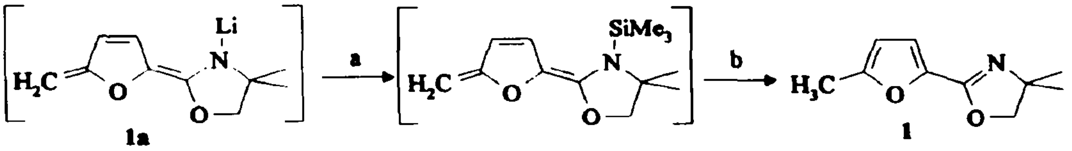
Scheme 2 : a) BuLi, THF-HMPA (4:1), -78°C ; b) electrophile, -78 - 0°C

Table 1. Preparation of 2-(5-substituted methyl-2-furyl)oxazolines **3-10**.

Entry	R	Electrophile	E	Product[a]	Yield (%)[b]
1	H	MeOD	D	**3**	95[c]
2	H	MeI	Me	**4**	69
3	H	Pr^{i}I	Pr^i	**5**	72
4	H	PhCHO	PhCH(OH)	**6**	81
5	H	PrCHO	PrCH(OH)	**7**	51
6	H	TMSCl	TMS	**8**	56
7	Ph	MeI	Me	**9**	87
8	Ph	PhCHO	PhCH(OH)	**10**	66

[a] All compounds gave satisfactory spectrometric data.
[b] Yields are for isolated products.
[c] Determined by ^{1}H NMR analysis.

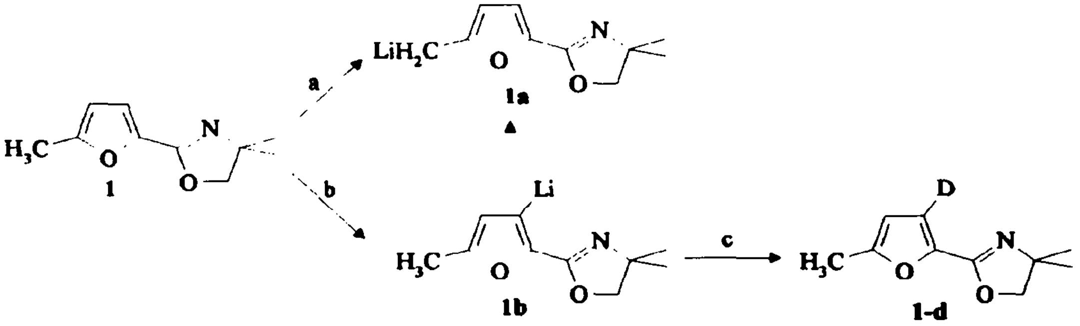
The low yield observed with butanal (entry 5) compared with benzaldehyde (entry 4) is probably due to an enolisation side reaction of the aliphatic aldehyde. With trimethylsilyl chloride used as electrophile (entry 6), a N-silylation reaction could account for the recovery of a large amount of starting material (scheme 3). On hydrolysis, the N-silylated species leads to compound **1**.



Scheme 3 : a) TMSCl ; b) hydrolysis

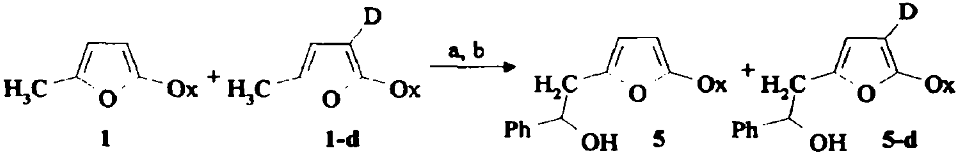
The lithiated species **1a** and **2a** show however a good reactivity toward usual electrophiles, affording the expected products in good yields.

It is of interest to note that the metalation of **1** with butyllithium in THF without HMPA at -78°C leads to C-3 lithiated species **1b** exclusively.[8] The choice of appropriate reaction conditions then permits different synthetic approaches (scheme 4), thus increasing the interest of these metalation reactions.



Scheme 4 : a) BuLi, THF-HMPA (4:1), -78°C ; b) BuLi, THF, -78°C ; c) EtOD

The formation of **1a** could result either from the direct metalation of the 5-methyl position or from the isomerisation of the C-3 metalated intermediate since the latter is formed without HMPA. In order to determine the correct mechanism, an equimolecular mixture of **1** and **1-d** deuteriated at C-3 in THF-HMPA (4:1) has been treated with 0.5 eq of butyllithium at -78°C. Subsequent addition of benzaldehyde led to a mixture of alcohols **5** and **5-d** (scheme 5).



Ox = 4,4-dimethyl-2-oxazolinyl

Scheme 5 : a) 0.5 BuLi, THF-HMPA (4:1), -78°C ; b) PhCHO

^{1}H NMR analysis of the reaction product showed that **5** and **5-d** were obtained in a 1:1 proportion along with starting materials **1** and **1-d** also in equivalent amounts. The absence of isotopic effect[9] tends to prove that the lithiation of the 5-methyl group took place directly without formation of the intermediate **1b**.

Work is in progress to extend metalation to other side chains.

EXPERIMENTAL

Preparation of 4,4-dimethyl-2-(5-substituted methyl-2-furyl)oxazolines **3-10**. A solution of 4,4-dimethyl-2-(5-methyl-2-furyl)oxazoline **1** (0.358 g, 2 mmol) or 4,4-dimethyl-2-(5-benzyl-2-furyl)oxazoline **2** (0.510 g,2 mmol) in THF-HMPA (4:1) (20 ml) was treated with butyllithium (2.2 mmol) at -78°C under argon. After 0.5 h stirring, electrophile (2.5 mmol) was added dropwise with the temperature held below -65°C. After a further 0.5 h stirring, the reaction mixture is allowed to warm at 0°C. After addition of water (10 ml) and ether (20 ml), the aqueous layer was separated. The organic layer was washed with water (4×10 ml), brine (10 ml), dried ($MgSO_4$) and evaporated to leave the crude product wich was purified by flash chromatography on silica.

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