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REGIOSELECTIVE METALATION OF THIAZOLO[5,4-b]PYRIDINES

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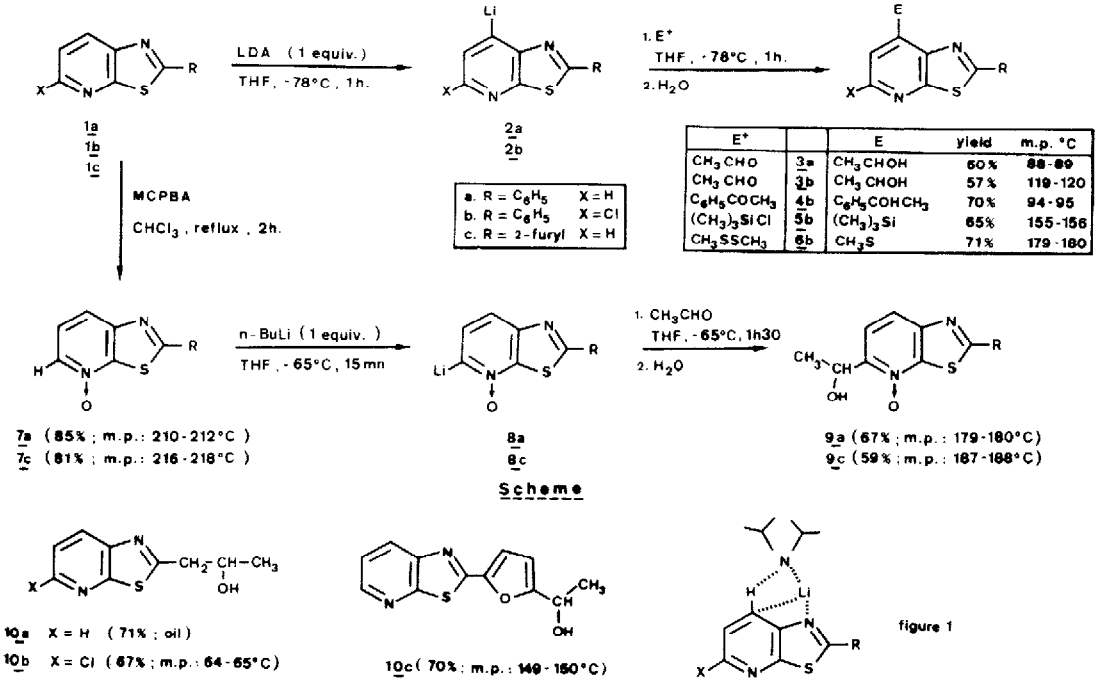
Summary :Lithiation with LDA of thiazolo[5,4-b]pyridines occurs regioselectively on the position in the pyridine ring.

Thiazolopyridines are a class of fused polyheterocycles possessing numerous and diversified pharmacological properties[1]. Their activities depend mainly on the nature of the substituants connected to the basic heterocyclic framework. Unfortunately the reported synthetic methods for the elaboration of these models only permit the exclusive introduction of the various substituants on the 2 position[1,2]. Consequently they always leave the pyridine part of the heterocycle unsubstituted.

The utilisation of lithium diisopropylamide (LDA) as a hydrogen-metal interconversion agent has considerably broadened the scope of the specific functionalization methods[3] for π-deficient heterocycles such as pyridine and quinoleine. With the aim of a subsequent functionalization, we have thus investigated the different lithiation sites on the pyridine ring of some thiazolopyridines using LDA. The thiazolo[5,4-b]pyridines 1 appear to be the appropriate models for this investigation since the α, β and γ positions of the pyridine part are accessible. However it was necessary to block the 2 position of the heterocycle with a group inert to the metalation agent[4]. The investigation was then previously achieved on the 2-phenyl thiazolo[5,4-b]pyridines 1a,b[2]. Thus the direct metalation of 1a with LDA occurs exclusively at the γ position of the pyridine ring (scheme). The lithiated species 2a is quenched by ethanal, which gives rise to the alcohol 3a. This regioselectivity can be accounted for by a coordination phenomenon between the metal and the unbound electron pair on the nitrogen atom of the thiazole part of the molecule (fig. 1). This hypothesis is corroborated by the chemical behaviour of the chlorinated derivative 1b. It is indeed well known that the introduction of a chlorine atom at the α position of a pyridine ring induces an ortho-directed effect which results in the metalation at the α position[3]. However, the metalation of 1b with LDA is still directed on the α position (scheme), which clearly indicates the preponderant involvment of the nitrogen atom of the thiazole ring in the stabilization of the lithiated species 2b.

Thus the preferential site for the lithiation of the thiazolo[5,4-b]pyridines seems to be the α position. It is however possible to conceive of the α lithiation by taking advantage of its conversion into the N-oxide form which would notably modify the reactivity, as amply demonstrated in the pyridine series[7]. As anticipated the N-oxidation of compounds 1a,c carried out with MCPBA effectively allows the lithiation of the resulting compounds 7a,c at the α position and permits access to the compounds 9a,c substituted at the 6 position of the fused polyheterocycles.



E+		E	yield	m.p. °C
CH_3CHO	3a	CH_3CHOH	60%	88-89
CH_3CHO	3b	CH_3CHOH	57%	119-120
$C_6H_5COCH_3$	4b	$C_6H_5COHCH_3$	70%	94-95
$(CH_3)_3SiCl$	5b	$(CH_3)_3Si$	65%	155-156
CH_3SSCH_3	6b	CH_3S	71%	179-180

Scheme

figure 1

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(4) The presence of an hydrocarbon aromatic unit on the 2 position is a prerequisite to the lithiation reactions on the pyridine ring. Indeed in the case of the 2-methyl thiazolo[5,4-b]pyridine, lithiation occurs regioselectively on the methyl group which can give rise to the alcohols 10a,b[5]. This is not surprising since a wide variety of heterocycles having an active methylene group are used as masked enolate[6]. On the other hand, lithiation of the 2-furyl thiazolo[5,4-b]pyridine 1c occurs exclusively at the α position of the furan ring as illustrated by the formation of 10c.

(5) All new compounds give satisfactory spectral data and elemental analyses.

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