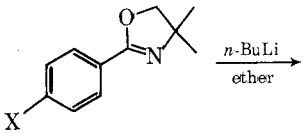
Ortho-Lithiation of Aryloxazolines

Summary: A method is described to convert aryloxazolines directly into their ortho-lithio and ortho-lithiomethyl derivatives which react with a variety of electrophiles in high yields.

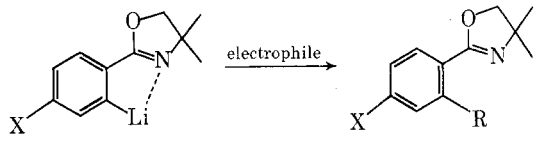
Sir: The heteroatom-facilitated ortho-lithiation has become a powerful tool in synthetic aromatic chemistry. The preparation of an appropriately functionalized 1,2-disubstituted derivative of benzene is often the starting point for the subsequent elaboration of bi- or multicyclic ring systems. Some drawbacks of the currently available ortho-lithiation of N-monosubstituted benzamides, developed by Hauser et al.,[1,2] are the varying yields, strongly dependent upon strict temperature control,[3,4] the use of 2 mol of BuLi/mol of amide coupled with the insolubility of the dilithio species and the relatively poor versatility of the secondary amide group for further transformation. A recently reported method by Meyers[5] makes use of the inertness of an oxazoline derived from *o*-bromobenzoic acid in the formation of a Grignard reagent. Although the yields are high, the method is limited by the availability of substituted *o*-bromobenzoic acids. We wish to report the direct ortho-lithiation of aryloxazolines, which proceeds with extreme ease, regiospecifically and nearly quantitatively.

The aryloxazolines **1** were prepared according to Meyers[5] and distilled under reduced pressure. All lithiations were performed in dry ether at ice-bath temperature with *n*-BuLi in hexane (cf. footnote *e*, Table I). In a typical example a solution of **1c** (3.07 g, 15 mmol) in 65 ml of ether was cooled under a N_2 atmosphere in an ice bath. Then 10.3 ml of a 1.6 *m* solution of *n*-BuLi/hexane (16.5 mmol) was added. After stirring at ice-bath temperature for 4 hr, a solution of 3.65 g of $(C_6H_5S)_2$ (16.5 mmol) in 30 ml of ether was added at once and the mixture stirred at room temperature for 16 hr. After work-up (H_2O, brine, Na_2SO_4), the residue (5.6 g) was crystallized from ether–hexane to give 4.2 g of **8**, mp 51° (89%).

Surprisingly, when the standard lithiation conditions were applied to the unsubstituted **1b**, **5** was obtained only to the extent of 80% with 15% of the product mixture being derived from addition of *n*-BuLi to the oxazoline (product isolated and identified after hydrolysis as valerophenone). While this competing reaction was essentially undetectable in the substituted cases (**1a** and **1c**), it could be suppressed by the use of sec BuLi at −70°.



1a, X = Cl
b, X = H[6]
c, X = OCH_3



2 **3-9** (see Table I)

The lithiation of **1a** proceeds extremely rapidly and reaches 40% after 1 hr at −78° when quenched with D_2O. The stability of **2**, however, permits lithiation to be carried out at the more practical ice-bath temperature. Although no quantitative studies have been carried out, it can be assumed that the rate-enhancing effect of the substituent X on the ortho-lithiation follows earlier observations with *p*-benzamides[3] and benzylamines and decreases in the order Cl > H > OCH_3. It is furthermore noteworthy that in **1c**, whose OCH_3 group could also give rise to ortho-metalation,[7] lithiation occurs regiospecifically ortho to the oxazoline group, as no isomeric products were detected. The variety of substrates which react with **2** accentuates the generality and versatility of this method.[8]

As has been demonstrated with *o*-toluamides[9,10] and *o*-toluic acid itself,[11] the analogous deprotonation of the aromatic CH_3 group can be observed with the oxazoline **10**. Again, lithiation proceeds rapidly (20 min at 0°) after the addition of 1.1 equiv of *n*-BuLi to an ethereal solution of **10** and produces the deep red anion **11**. The completion of its reaction with an electrophilic substrate is clearly evident by the disappearance of the red color.

Table I[a]

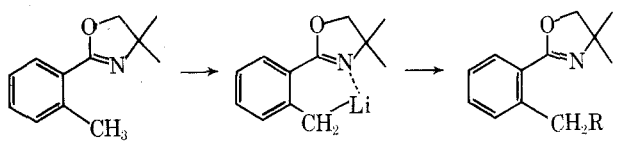
Compd	Lithiation time 2, hr	Electrophile	X	R	Yield,[b] % GC	Yield,[b] % Isold	Mp, °C
3	1	CH_3I[c]	Cl	CH_3	95	71[d]	135
4	1	I_2	Cl	I	94	66[d]	85
5	*e*	D_2O	H	D	92	86[f] (94% D)	
6	*e*	*t*-BuNCO	H	CONHtBu		81	103
7	4	$HCON(CH_3)_2$[g]	OCH_3	CHO	98	70	37
8	4	$(C_6H_5S)_2$	OCH_3	SC_6H_5		89	51
9	4	CH_3NCS	OCH_3	$CSNHCH_3$		77	115

[a] All compounds reported are new (with the exception of **5**[5]) and show satisfactory analytical data. [b] With the exception of **5** and **6** no attempts were made to optimize the yields. [c] 5 molar excess of CH_3I added. [d] HCl salt. [e] Addition of 1.1 molar equiv of *sec*-BuLi at −70°, warm up to 0°, quench with electrophile. [f] 2-D-Benzoic acid. [g] Two molar equivalents of DMF added.

Table II

Compd	Lithiation time, min	Electrophile	R	Yield,[a] % GC	Yield,[a] % Isold	Mp or distiln point, °C
12	20	$(CH_3S)_2$	SCH_3	88	85[b]	109
13	20	$CH_2{=}CHCH_2Br$	$CH_2CH{=}CH_2$	83	78	60 (0.1 mmHg)

[a] Yields were not optimized. [b] HCl salt.



10 11 12, 13 (see Table II)

One of the attractive and useful aspects of this new method of ortho-lithiation is the possibility for further modifications and transformations of the oxazoline group under mild conditions: (i) into ketones *via* N-alkylation and addition of an organometallic reagent,[12] (ii) into aldehydes by reduction,[13,14] (iii) into ester or acids by solvolysis.[5]

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Supplementary Material Available. Full experimental details and analytical data on compounds **3–9** and **12, 13** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy, or $2.50 for microfiche referring to code number JOC-75-2008.

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Synthetic Studies on Histrionicotoxins. I. A Stereocontrolled Synthesis of (±)-Perhydrohistrionicotoxin

Summary: A stereocontrolled synthesis of (±)-perhydrohistrionicotoxin (**18**) was achieved by using a reaction of acylaziridine **11** with dibutylcopper lithium as a key step.

Sir: Histrionicotoxins,[1] the toxic principles isolated from the venom of the Columbian frog *Dendrobates histrionicus*, are remarkably useful neurophysiological tools which selectively inhibit the ion transport mechanism of the cholinergic receptor.[2] Recent communication[3] on a synthesis of perhydrohistrionicotoxin prompted us to report our synthetic studies in this field.

The spiro ketolactam **4** was synthesized by the following simple procedures in 60% overall yield from **1**. Treatment of 2-nitrocyclohexanone ketal[4,5] **1** [bp 125–127° (7mmHg)] with methyl acrylate in *tert*-butyl alcohol containing Triton B, followed by hydrolysis (NaOH in aqueous methyl alcohol at room temperature), afforded the nitro acid[5] **2** (mp 130–131°). The nitro acid **2** was homologated to the nitro ester[5] **3** (oil) by Arndt–Eistert reactions, i.e., (1) $SOCl_2$ in C_6H_6 at 50°, (2) CH_2N_2 in Et_2O at room temperature, (3) $AgBF_4$–Et_3N in methyl alcohol at 0°. Catalytic hydrogenation of **3** (Raney Ni in methyl alcohol at 50°), followed by deketallization (aqueous TFA at 75°), afforded the spiro ketolactam[5] **4** (mp 150–152°).

A possibility to control the stereochemistry at the 6 and 7 positions was first examined. Namely, sodium borohydride reduction of **4** in methyl alcohol gave in 85% yield the alcohol[5] **5** (mp 160–162°), which was converted to the mesylate[5] **6** (mp 157–158°). The stereochemistry of the alcohol **5** was assigned based on the fact that sodium hydride treatment of **6** in wet THF yielded cleanly the acylaziridine[5] **7** (oil). Acetic acid treatment of **7** gave exclusively the acetate[5] **8** (mp 143–144°),[6] identical with the acetate obtained by acetylation of the alcohol **5**. This acetolysis result suggested that the required functionality with the desired stereochemistry could be introduced by opening the acylaziridine system in **7**. Thus, **7** was allowed to react with dibutylcopper lithium in THF at room temperature, to give exclusively the lactam **9** (oil) in ~65% yield.[5,6] On the other hand, butyllithium or butylmagnesium bromide reacted with **7** in a 1,2-addition fashion.[7]

In order to apply the described method to the real synthesis, the mesylate[5] **10** (melting point of the corresponding alcohol, i.e., X = OH in **10**, 134–135°) was stereospecifically synthesized from **4** in 35% overall yield by six successive operations [(1) $(EtO)_3CH$–H^+, (2) Δ,[8] (3) Br_2, (4) $NaBH_4$,[9] (5) *i*-PrONa–*i*-PrOH,[10] (6) MsCl–Py]. Sodium hydride treatment of **10** in wet benzene at room temperature yielded cleanly the acylaziridine[5] **11** (oil), which was allowed to react with dibutylcopper lithium in THF at room temperature to afford the lactam[5] **12** (oil) in 15% yield from **10**. One of the undesired products (~30%) in this reaction was the olefin[5] **13** (mp 115–117°); **13** was possibly derived from the halo intermediate **14**.[7]

The lactam **12** was converted to the thiolactam[5] **15** (melting point unrecorded) by P_2S_5 in refluxing benzene. The thiolactam **15** was converted to the imine[5] **16** (oil) by two steps, i.e., thioimino ether formation with Meerwein reagent and alkylation with pentyllithium in hexane–ether containing diisobutylaluminum hydride. In the last alkylation process, the activation of the carbon–nitrogen double bond and solvent system are critical.[11] Boron tribromide treatment of **16** in methylene chloride (i.e., **16** → **17**), followed by aluminum hydride reduction in cyclohexane, afforded a mixture of (±)-perhydrohistrionicotoxin (**18**) [six parts, melting point (in a sealed tube) as its hydrochloride, 159–161°] and (±)-*epi*-perhydrohistrionicotoxin (**19**) [one part, melting point (in a sealed tube) as its hydrochloride, 199–201°], which could be separated by preparative TLC or by direct crystallization and recrystallization as the hydrochloride. Stereochemistry of the aluminum hydride reduction is obviously controlled by a complex formation of the reducing reagent with the alcoholic function in **17**, because aluminum hydride reduction of **16** in THF or sodium borohydride reduction of **17** in methyl alcohol gave the