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Oxazolo[4,5-*b*]pyridines. Regioselective Metalation of the 2-Diethylaminooxazolo[4,5-*b*]pyridine System and Formation of 7-Substituted Derivatives

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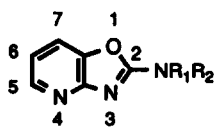
Abstract. Metalation of 2-diethylaminooxazolo[4,5-*b*]pyridine with *tert*-butyllithium occurs regioselectively in the 7-position of the heterocycle and the fused 2-dialkylaminooxazolo group thus functions as an *ortho*-directing group in this bicyclic system. Reaction of the resulting 7-lithio intermediate with electrophiles provides access to a variety of 7-substituted derivatives.

The 2-aminooxazolo[4,5-*b*]pyridine system **1** is a virtually unexplored heterocycle despite its potential for interesting chemistry and claims of biological activity[2] among certain of its derivatives with varied 2-amino substituents. We became interested in preparing derivatives of this ring system with substituents on the pyridine ring, particularly at the 7-position (**2**). Apart from some 5,6,7-trihalo analogues,[3] there are no reports of compounds with substituents on the pyridine ring of the heterocycle. We considered methods for generation of an organometallic derivative at C-7 as an approach to our target compounds **2**.



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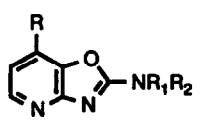
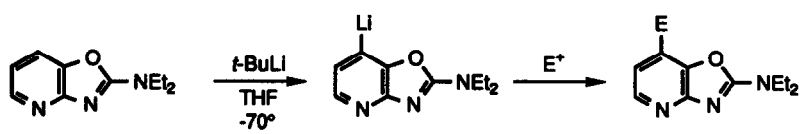


2

3 (R=H, $R_1 = R_2 = Et$)

Although direct metalation of pyridines is not normally a useful synthetic process because of addition reactions of organolithium reagents to the pyridine ring, access to lithiated pyridine intermediates has been achieved through halogen-metal exchange reactions[4] as well as through activation of the ring toward lithiation by a variety of *ortho*-directing groups.[5] As an approach to 7-substituted derivatives of 2-diethylaminooxazolo[4,5-*b*]pyridine (**3**), we examined the potential of the fused 2-dialkylaminooxazole ring to function as an *ortho*-directing group[6] and thereby to activate the 7-position toward lithiation. In this Letter, we report that metalation of **3** occurs at the 7-positon of the heterocycle and that the resulting 7-lithio intermediate (**4**) reacts with electrophiles to provide access to a variety of 7-substituted derivatives (**4**; equation 1).

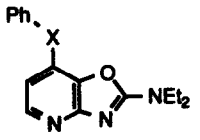


3 **4** **5** eq 1

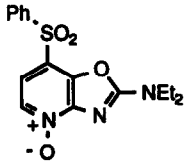
An initial requirement was to develop a synthesis of the previously unreported 2-dialkylamino derivatives (cf. **3**) required for the metalation studies. A survey of the literature uncovered only a few reports on the synthesis of 2-aminooxazolo[4,5-*b*]pyridines. The parent 2-amino compound has been prepared by treatment of *N*-(3-hydroxy-2-pyridyl)formamide oxime with sodium ethoxide or with *N,N*-dimethylformamide dimethyl acetal followed by hydrolysis,[7] and has also been obtained from the reaction of 2-amino-3-hydroxypyridine with cyanogen bromide[2a,b]; a related cyclization of 4,5,6-trihalo derivatives of 2-amino-3-hydroxypyridine with cyanogen chloride gave the corresponding 5,6,7-trihalo derivatives of the 2-amino system.[3] After examining several synthetic approaches to the previously unreported dialkyamino derivatives, we successfully prepared **3** through a one-pot condensation of 2-amino-3-hydroxypyridine with diethylcarbamoyl chloride in pyridine at 120° in the presence of a catalytic amount of dimethylaminopyridine (DMAP).[8] These conditions minimized the amount of 2-amino-3-(*N,N*-diethylcarbamoyloxy)pyridine[9] obtained and provided sufficient quantities of **3** for our metalation studies.

Metalation of the oxazolopyridine **3** with *t*-butyllithium (1.1 eq) proceedes rapidly and efficiently at -70° in THF to provide a deep red reaction mixture containing the 7-lithio compound **4**. Reaction of this anion at -70° with electrophiles followed by warming to ca. 0° leads to isolation in moderate to good yields of the 7-substituted compounds (**5a-5m**) shown in the Table. The position of substitution in the products is readily determined by the absence of a signal for H_7 and the presence of an AB pattern (J_{AB} ≈ 5.5 Hz) in the aromatic region of the nmr spectrum for H_5 (*ca.* δ 7) and H_6 (*ca.* δ 8).[10] As indicated in the Table, anion **4** reacts with alkyl halides and carbonyl compounds and also may be formylated, alkoxycarbonylated[11] and sulfenylated.

Furthermore, certain adducts **5** may be elaborated to provide additional types of 7-substitution. For example, oxidation (pyridinium dichromate, CH_2Cl_2) of the benzhydryl compound **5b** provides ketone **6** (91%), and oxidation (MCPBA, 2 equivalents; $CHCl_3$) of sulfide **5d** gives sulfoxide **7** (64%) and sulfone **8** (18%). Oxidation of **5d** with additional peracid (3.3 equivalents) causes oxidation of the pyridine nitrogen and the sulfone-*N*-oxide **9** is obtained (83%) from **5d**. Azide **5e** was reduced to the 7-amino compound (E = NH_2) with LAH in ether/THF (90%), the aldehyde **5f** was converted to acrylic ester **10** (71%) with the anion of triethylphosphonoacetate and acid **11** was obtained (77%) by basic hydrolysis.



6 X = CO; **7** X = SO; **8** X = SO_2



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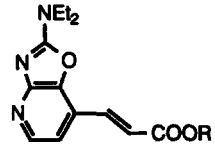


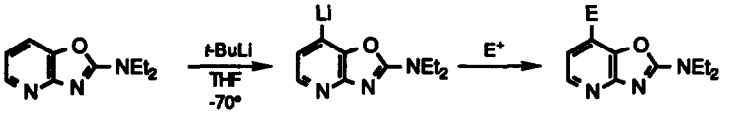
10 R = Et; **11** R = H

The preparation of the 7-methyl derivative **5a** is a representative procedure for the metalation: To a cold (-70°C) stirred solution of **3** (1.91g, 10 mmol) in dry THF (30 ml) under nitrogen was added dropwise during *ca.* 5 min a solution of *t*-butyllithium in pentane (1.7 M, 6.5 ml, 11 mmol). The deep red slurry was stirred for 0.5 hr at -70°C and then methyl iodide (1.7g, 12 mmol) was added dropwise. After 15 min at -70°C the reaction mixture was allowed to warm to 0°C and then quenched with methanol (5 ml). The bulk of the solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and water. The aqueous phase was extracted twice with methylene chloride and the combined organic layers were washed with water,

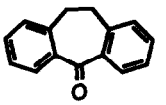
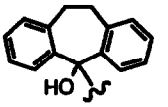
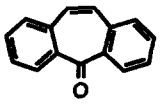
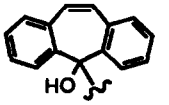
dried (Na_2SO_4) and concentrated. Flash chromatography of the residue on silica gel (150 g) eluting with 15% acetone in ether gave **5a** (1.77g, 86%) as white needles, mp 69-71°C.

In summary, 7-lithiation of 2-diethylaminooxazolo[4,5-*b*]pyridine with *t*-butyllithium followed by reaction with electrophiles provides a convenient route to 7-substituted derivatives of this oxazolopyridine system. This provides the first demonstration that a fused 2-dialkylaminooxazole ring can function as an *ortho*-directing group in pyridine metalations.

Table. Compounds **5** Prepared by Reactions of 7-Lithio Intermediate **4** with Electrophiles



3 **4** **5**

Compd	Electrophile (E^+)	E in 5	Yield(%)[a,b]	m.p.(°C)
5a	iodomethane	Me	86	69-71
5b	benzaldehyde	PhCH(OH)	55	133-135
5c	benzophenone	$Ph_2C(OH)$	84	188-189
5d	phenyl disulfide	PhS	65	80-82
5e	*p*-toluenesulfonyl azide	N_3	78	oil[c]
5f	dimethylformamide	CHO	83	70-72
5g	*t*-BuO_2C-O-CO_2-*t*-Bu	COO-*t*-Bu	38	89-90
5h	cyclopentanone	$(CH_2)_4C(OH)$	42[d]	155-156
5i	acetophenone	Ph(Me)C(OH)	50	133-135
5j	acetaldehyde	MeCH(OH)	60	107-109
5k	cinnamaldehyde	(*E*)-Ph-CH=CH-CH(OH)	41	128-129[d]
5l			53	258-259[d]
5m			78	280-284[d]

[a]Yield of product isolated by flash chromatography or by flash chromatograpy followed by recrystallization; yields are typically for a single run and have not been optimized. [b]All compounds gave satisfactory microanalytical data (within ±0.4% of theory for C, H and N) and exhibited the expected spectral properties. [c]Oil discolored upon storage at rt; MH^+ at *m/z* 233 (100); ir (neat) 2140 cm^{-1}. [d]77% yield based on recovered **3**.

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References and Notes

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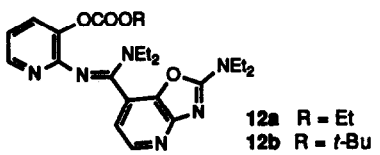
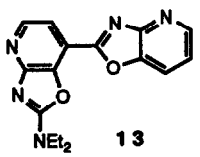
8. 2-Amino-3-pyridinol (200 g), diethylcarbamyl chloride (350 g), and DMAP (1 g) were heated at 120°C in pyridine (500 mL) for 4 days. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was treated with CH_2Cl_2 and water and then was filtered. The organic layer was washed with water and then extracted with 6 *N* HCl. The aqueous layer was extracted with CH_2Cl_2, made basic by addition of solid $NaHCO_3$, and then extracted with CH_2Cl_2. The extract was concentrated to give a dark oil (74 g) which was chromatographed (silica gel; 1:1 ether/CH_2Cl_2) to give **3** as a yellow oil. The oil was crystallized from ether at 0°C to give white crystals, mp 69-71°C, in 17% yield (50 g); ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 6 H), 3.63 (q, J = 7.2 Hz, 4 H), 6.86 (dd, J = 7.8, 5.2 Hz, 1H, H_6), 7.40 (dd, J = 7.8, 1.4 Hz, 1 H, H_7), 8.20 (dd, J = 5.2, 1.4 Hz, 1 H, H_5).
9. This 3-*O*-carbamoyl compound (mp 95-96°C) was the major product isolated when the reaction was carried out under reflux in solvents such as methylene chloride or dichloroethane.
10. The methylenes of the *N,N*-diethyl groups of the adducts often appeared in the nmr spectra as broadened quartets since these bands tend to coalesce at near ambient temperatures.
11. Alkoxycarbonylation of **4** with di-*t*-butyldicarbonate to give **5g** is preferable to reaction of **4** with ethyl chloroformate from which pure 7-carboethoxy compound (**5**, E = CO_2Et; mp 43-45°C) was isolated in only very low (*ca.* 5%) yield. Byproducts **12** (**12a**: mp 172-174°C; **12b**: mp 145-147°C) and **13** (mp 176-178°C), which appear to arise from attack of **4** at C-2 of another oxazolopyridine, were also isolated from reactions of **4** with ethyl chloroformate and di-*t*-butyldicarbonate.



12a R = Et
12b R = *t*-Bu



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