

Selective Lithiation of 2-Methyloxazoles. Applications to Pivotal Bond Constructions in the Phorboxazole Nucleus

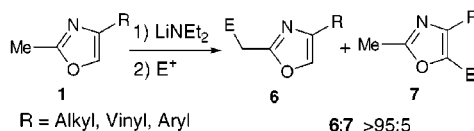
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ABSTRACT



The lithiation of 2-methyloxazoles with alkylolithium and hindered lithium amide bases generally results in the competitive formation of a mixture of 5-lithio- and 2-(lithiomethyl)oxazole isomers. Herein a synthetically useful lithiation method which allows for the selective formation of 2-(lithiomethyl)oxazole is described. Diethylamine has been found to be a kinetically competent proton source that will mediate the equilibration of the kinetically formed 5-lithiooxazole to its more stable 2-(lithiomethyl)oxazole counterpart. Application of this metalation strategy with lithium diethylamide to two important bond constructions relevant to a projected phorboxazole synthesis is presented.

The discovery of marine natural products containing 2,4-disubstituted oxazoles such as hennoxazole A,¹ theonezolid A,² the virginiamycins,³ the ulapaulides,⁴ and the phorboxazoles⁵ has renewed interest in the chemistry of the oxazole

nucleus. Our interest in the synthesis of the phorboxazoles (Figure 1) has led us to consider methods for the construction

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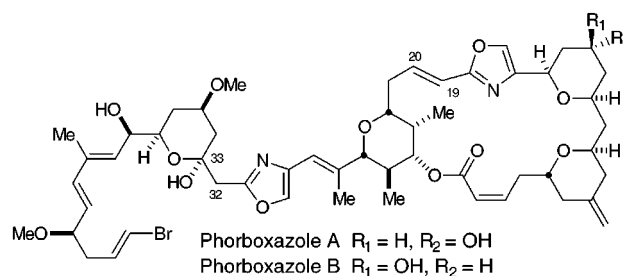
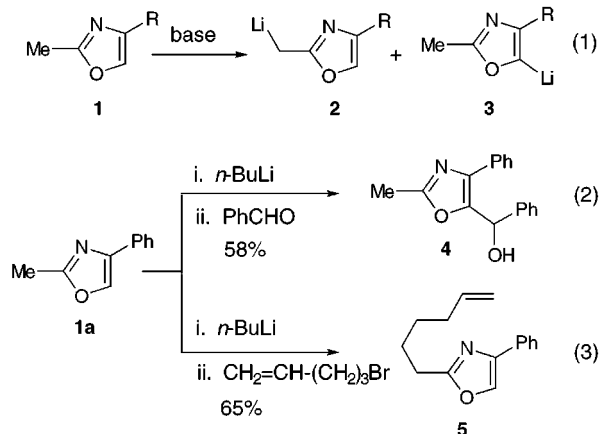


Figure 1. Phorboxazoles A and B.

of the C19–C20 and C32–C33 bonds. An attractive strategy for the formation of such bonds, outlined in Scheme 1, is the selective generation of a 2-(lithiomethyl)oxazole⁶ and its reaction with an electrophile (eq 1). This approach has

(6) The carbanion of **2** may be delocalized into the C=N π system.

Scheme 1



proven difficult due to competitive formation of the 5-lithio-oxazole **3**, as illustrated by the work of Hamana and Sugawara (eq 2).^{7,8} Only a handful of successful examples exist, including the alkylation reported by Whitney and Rickborn (eq 3).⁹ However, the factors responsible for this selectivity and its divergence from the Hamana result are poorly understood.¹⁰

I. Selective Alkylation. We felt that the lack of a general method for the selective elaboration of 2-methyloxazoles warranted further investigation. Our studies began with a survey of the regioselectivity afforded by different bases in an alkylation reaction (Table 1).¹¹ The oxazoles were lithiated

Table 1. Survey of Methods for the Selective Alkylation of Oxazoles and Thiazoles^a

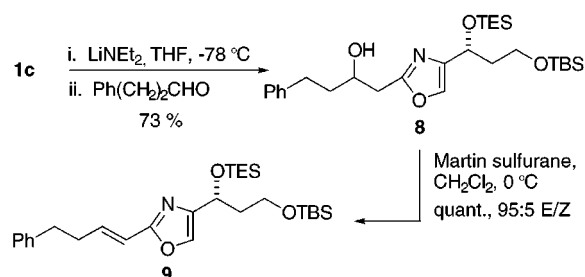
substrate	X	R	base (6:7) ^b		
			<i>n</i> -BuLi ^c	Li [†] Pr ₂	LiNEt ₂
1a^d	O	Ph	9:91	9:91	99:1
1b^e	O	CH ₂ OH	55:45	50:50	>95:5
1c	O		^f	76:24 ^g	>95:5
1d	O		61:39	34:66	>95:5
1e^h	S	Ph	<5:95	9:91	93:7 ⁱ

^a All reactions were carried out in THF and proceeded to $\geq 90\%$ conversion unless otherwise noted. ^b Product ratios were determined by ¹H NMR unless otherwise noted. ^c One equivalent of *n*-BuLi was used, unless otherwise noted. ^d Product ratios were determined by GC. ^e Two equivalents of *n*-BuLi and 2.4 equiv of the lithium amides were used. ^f Multiple products were observed. ^g Reaction proceeded to 55% conversion. ^h The thiazole and base were warmed to -50°C for 30 min and then cooled to -78°C prior to the addition of methyl triflate. ⁱ Reaction proceeded to 76% conversion.

at -78°C , and the resulting anions were quenched with methyl triflate to provide the 2-ethyloxazole **6** and 2,5-dimethyloxazole **7**. While *n*-butyllithium and lithium diisopropylamide (LDA) either are selective for formation of the 5-methylated product **7** (substrate **1a**) or are relatively nonselective (substrates **1b–d**), lithium diethylamide displays remarkable selectivity for the formation of the desired product **6** in all cases. This effect is not limited to oxazoles. In the case of thiazole **1e**, *n*-butyllithium and LDA are selective for the 5-methylated product **7e**, consistent with the findings of Meyers and Knaus,¹² while lithium diethylamide is highly selective for the formation of **6e**.

II. Synthetic Utility. With selective lithiation now possible, we investigated its utility for the elaboration of 2-methyloxazoles into naturally occurring oxazole motifs. The (*E*)-2-vinyloxazole of the phorbaxoxoles inspired the model study depicted in Scheme 2, aimed at the generation of the C19–

Scheme 2



C20 bond. Previous approaches to similar bonds have employed activated 2-(phosphonomethyl)oxazoles;¹³ however, the use of an unfunctionalized 2-methyloxazole has obvious advantages. To test this strategy, oxazole **1c** was treated with lithium diethylamide followed by hydrocinnamaldehyde to give **8** as a single regioisomer in 73% yield. The alcohol was then dehydrated with the Martin sulfurane¹⁴ to give **9** in quantitative yield and 95:5 *E/Z* selectivity. This approach provides a useful alternative for the construction of (*E*)-2-vinyloxazoles.

The construction of the masked β -keto-oxazole phorbaxoxazole subunit is also amenable to this strategy. We envisioned

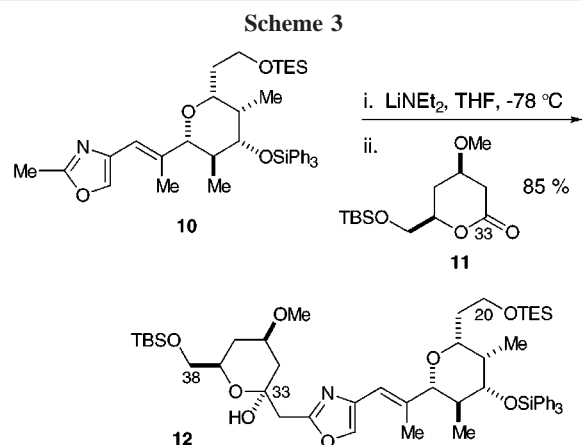
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that the C32–C33 bond could be formed by the union of a 2-methyloxazole and a lactone. Treatment of oxazole **10** with lithium diethylamide followed by introduction of lactone **11** gave the C20–C38 region of the phorboxazoles as a single regioisomer in 85% yield (Scheme 3).¹⁵



III. Origin of Regioselectivity. While the general utility of lithium diethylamide for the selective lithiation of 2-methyloxazoles was apparent, the origin of this selectivity was unclear. A series of experiments led us to conclude that the conjugate acid of the lithium amide was important in determining the regioselectivity of lithiation. A convenient method to investigate this hypothesis involved the lithiation of **1d** with *n*-butyllithium, followed by introduction of an amine and finally reaction with methyl triflate. The results of this study are shown in Table 2.

While *n*-butyllithium alone generates a mixture of alkylated products (entry 1), the introduction of diethylamine at $-78\text{ }^{\circ}\text{C}$ results in high selectivity for **6d**. The selectivity is identical with that seen when lithium diethylamide is used

(11) An alkylation was chosen to simplify the product identification. Reactions with other electrophiles occur with similar selectivity, provided the reactions take place at low temperature. A representative procedure is as follows. The oxazole **1d** (39 mg, 0.126 mmol, 1 equiv) was dissolved in anhydrous THF (0.76 mL) and the solution cooled with stirring to $-78\text{ }^{\circ}\text{C}$ under an argon atmosphere. A solution of lithium diethylamide was prepared by adding *n*-butyllithium (89 μL of a 1.97 M solution in hexanes, 0.176 mmol, 1.4 equiv) to a solution of diethylamine (20 μL , 0.189 mmol, 1.5 equiv) in THF (0.5 mL) at $-78\text{ }^{\circ}\text{C}$. The lithium diethylamide solution was warmed to $0\text{ }^{\circ}\text{C}$ for 10 min, and then recooled to $-78\text{ }^{\circ}\text{C}$ and added to the oxazole solution via cannula. The resulting yellow-orange reaction mixture was stirred for 10 min. Methyl triflate (29 μL , 0.252 mmol, 2 equiv) was then added, resulting in the immediate disappearance of color. The reaction mixture was stirred for 20 min at $-78\text{ }^{\circ}\text{C}$ and was then partitioned between saturated aqueous ammonium chloride and dichloromethane. The combined organic phases were dried (MgSO_4), filtered, and concentrated in vacuo to afford a clear, colorless oil (41.5 mg) that was identified by $^1\text{H NMR}$ to contain **6d** as the only methylated product and $\leq 3\%$ of the starting material **1d**.

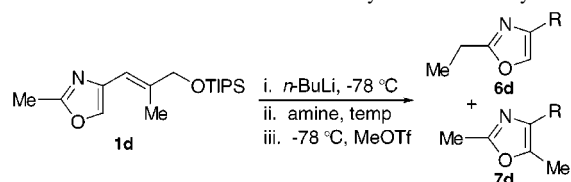
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(15) The details of the synthesis of fragments **10** and **11** will be reported in due course.

Table 2. Effect of Amines on the Selectivity of Oxazole Alkylation^a

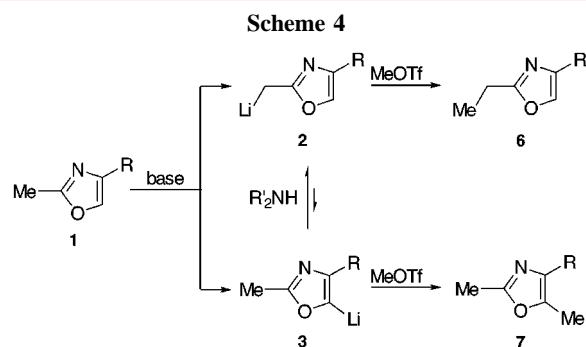


entry	amine ^b	temp ($^{\circ}\text{C}$) ^c	time (min)	6d : 7d ^d
1	-	-	-	61:39
2	Et_2NH	-78	10	>95:05
3	<i>i</i> - Pr_2NH	-78	10	66:34
4	TMP	-78	10	64:36
5	<i>i</i> - Pr_2NH	-50	10	82:18
6	TMP	-50	10	68:32
7	<i>i</i> - Pr_2NH	-50	60	>95:05
8	TMP	-50	60	>95:05
9 ^e	-	-50	60	55:45

^a All reactions were carried out in with 1 equiv of *n*-BuLi in THF and proceeded to $\geq 93\%$ conversion. ^b Three equivalents of amine was used in all reactions; this was necessary to facilitate a complete change in selectivity for entries 7 and 8 in a reasonable amount of time. ^c All reactions were quenched at $-78\text{ }^{\circ}\text{C}$. ^d Product ratios were determined by $^1\text{H NMR}$. ^e A small amount of decomposition was observed.

as the base (see Table 1). This effect is absent for the more encumbered diisopropylamine and tetramethylpiperidine at $-78\text{ }^{\circ}\text{C}$ (entries 3 and 4), but when the temperature is raised to $-50\text{ }^{\circ}\text{C}$ for 10 min prior to the introduction of methyl triflate, the product distribution begins to change (entries 5 and 6). Although diisopropylamine effects this change more rapidly than tetramethylpiperidine, if the reaction mixtures are stirred at $-50\text{ }^{\circ}\text{C}$ for 1 h prior to the introduction of methyl triflate, both reactions proceed to give **6d** in >95:5 selectivity. It is important to note that similar warming of a reaction mixture in the absence of amine does not cause a significant change in alkylation regioselectivity (entry 9).

Our interpretation of these findings is illustrated in Scheme 4. Treatment of the oxazole with *n*-butyllithium results in a

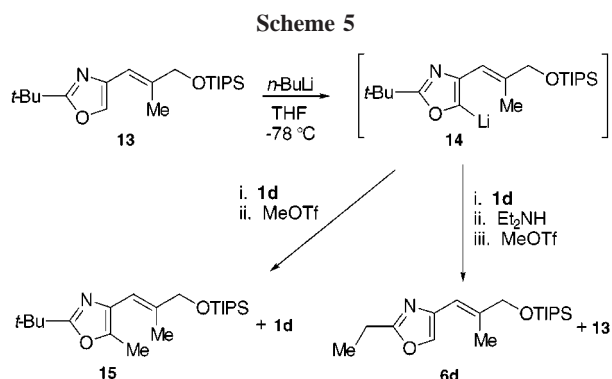


kinetic mixture of noninterconverting¹⁶ lithiated species **2** and **3**, which, upon addition of methyl triflate, give rise to **6**

(16) Meyers has found that, at low temperatures, lithiated thiazoles prepared with *n*-butyllithium do not interconvert to a significant extent.¹²

and **7**, respectively. In the presence of an amine, a pathway for the equilibration of the lithiated regioisomers is available, allowing for the conversion of **3** to the thermodynamically more stable **2**.¹⁷ The rate of equilibration is dependent on the steric encumbrance of the amine, with diethylamine effecting the most rapid equilibration and tetramethylpiperidine the slowest.¹⁸ Therefore, the remarkable selectivity observed in metalations with lithium diethylamide is apparently due to an equilibration process mediated by the diethylamine liberated during the reaction.¹⁹ However, at comparable temperatures, other bases generate a nonequilibrating kinetic mixture of lithiated oxazoles.

The feasibility of the proposed amine-mediated proton transfer was investigated in the crossover experiments shown in Scheme 5. When the lithiated 2-*tert*-butyloxazole **14** was



mixed with an equal amount of **1d** and treated with methyl triflate, **15** was generated as the only methylated product.²⁰ The introduction of diethylamine (1.5 equiv) prior to treatment with methyl triflate results in the formation of **6d** as the only methylated product, thus establishing the importance of the amine in promoting the equilibration of lithiated oxazoles.

(17) It is conceivable that **2** could give rise to the product **7** by ring alkylation and aromatization. Low-temperature ¹H NMR has allowed the observation of distinct intermediates consistent with **2** and **3** as well as their complete equilibration to **2**. Analysis of the products **6** and **7** formed upon quenching these reactions suggests that ring alkylation of **2** is not occurring. For more details, see the Supporting Information.

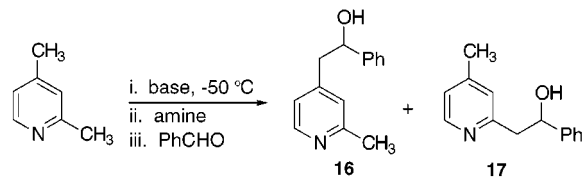
(18) This conclusion is supported by the results of Fraser et al., who have reported that the rate of proton exchange between amines and lithiated amides decreases with increasing steric bulk: Fraser, R. R.; Baignee, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, 23, 4195–4198.

(19) It cannot be ruled out that the kinetic selectivity of lithium diethylamide favors the formation of **2**.

(20) The products were identified by ¹H NMR.

The remarkable ability of amines to mediate the equilibration of metalated species has been largely overlooked. In the metalation of 2,4-lutidine, for example, Levine noted a divergence in the selectivity afforded by amide and alkyl-lithium bases which was attributed to kinetic effects.²¹ Consistent with Levine's results, lithium diethylamide and *n*-butyllithium give exclusively **16** and **17**, respectively (Table 3, entries 1 and 2). However, when diethylamine is

Table 3. Selective Lithiation of 2,4-Lutidine



entry	base	amine	16 : 17	yield (%)
1	LiNEt ₂	-	>95:5	95
2	<i>n</i> -BuLi	-	<5:95	86
3	<i>n</i> -BuLi	Et ₂ NH	>95:5	87

introduced to the anion generated with *n*-butyllithium, the selectivity is reversed (entry 3). While a kinetically controlled lithiation with *n*-butyllithium gives rise to **17**, amide bases deliver **16** by equilibration to the thermodynamically more stable 4-methyl anion.

In conclusion, we have described a selective metalation which provides a regioselective approach to the elaboration of 2-methyloxazoles. This method appears to be general and has been applied to the synthesis of 2,4-disubstituted oxazole systems relevant to the phorbaxozoles. In addition, we have identified that the selectivity of the process relies on the unique ability of diethylamine to effect the rapid equilibration of lithiated regioisomers at low temperatures.

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Supporting Information Available: Text giving experimental procedures and characterization data for the compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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