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EFFECTS OF BASE, ELECTROPHILE, AND SUBSTRATE ON THE SELECTIVE ALKYLATION OF HETEROAROMATIC SYSTEMS

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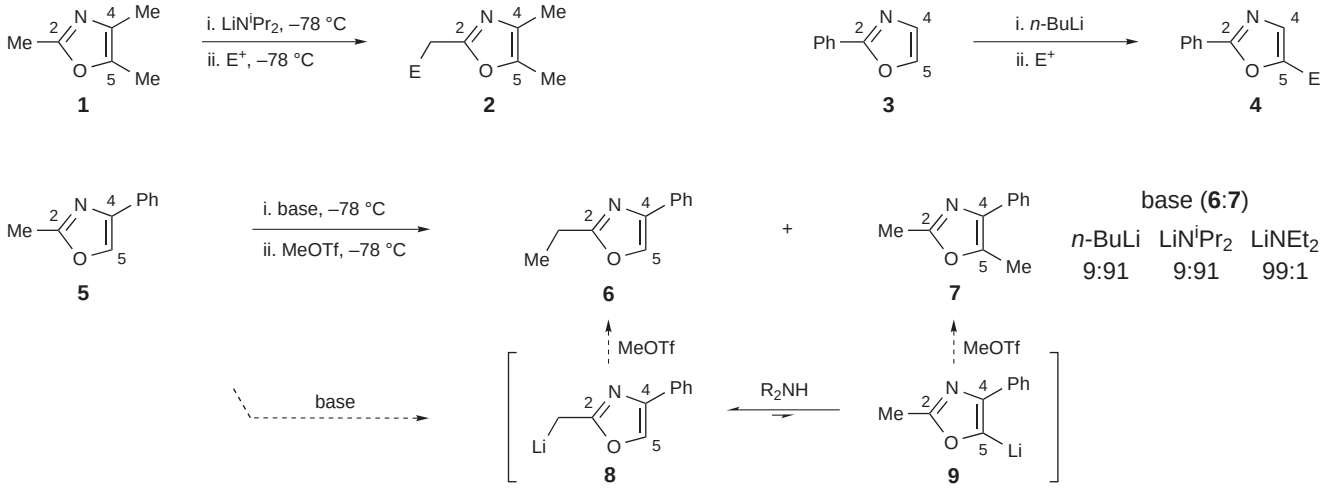
Abstract – Several heteroaromatic systems, including oxazoles, pyrazoles, and thiophenes, are regioselectively alkylated using lithium diethylamide. Effects of substrate, base, and electrophile on the selectivity of this process are surveyed and interpreted.

INTRODUCTION

The lithiation of aromatic heterocycles is an important method for the functionalization of heteroaromatic systems. Directed *ortho*-lithiations[1] and lateral lithiations[2] of appropriately substituted systems, followed by treatment with electrophiles, allow for the elaboration of a variety of aromatic assemblages. In the case of oxazoles, several different sites are available for functionalization (Scheme 1).[3] For example, in

Scheme 1. Alkylation Behavior of Substituted Oxazoles



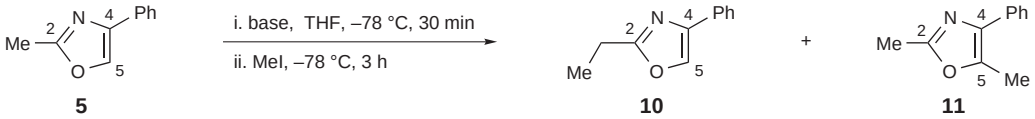
systems such as trimethyloxazole (**1**), lateral methylation at the C_2-methyl site is favored, presumably due to stabilization by the adjacent C=N π-system, and alkylated products such as **2** are formed.[4] When no acidic α-hydrogens are present, as in **3**, ring lithiation at C_5 occurs and alkylated products such as **4** are obtained.[5] In other cases, however, where two possible sites for lithiation exist and no strong directing

group is present, mixtures of products are observed. Lithiations of 2,4-disubstituted oxazoles, for instance, are not always selective.[6] As discovered in work with Evans toward the synthesis of phorboxazole,[7] systems such as **5**—where the C_4-substituent is typically an sp^2 carbon—give product mixtures favoring alkylation at the C_5-ring position under standard conditions. For example, lithiation of 2-methyl-4-phenyloxazole (**5**) using *n*-BuLi or LDA at –78 °C followed by alkylation with methyl triflate gives 9:91 ratios of products (**6**:**7**) favoring ring methylation. Of critical interest is the observation that the regioselectivity of these oxazole alkylations can be altered by the use of lithium diethylamide.[7] This reversal of regioselectivity is thought to arise from the ability of diethylamine to mediate the low-temperature equilibration between a kinetic mixture of lithiated intermediates (**8**) and (**9**), which otherwise do not interconvert.[8] The general ability of secondary amines to facilitate equilibrations such as this is little studied but of considerable potential application to a variety of reactive systems. Herein we explore the scope and synthetic utility of this method for the selective functionalization aromatic heterocycles by evaluating the effects of base, electrophile and substrate on alkylation selectivity.

RESULTS AND DISCUSSION

The low temperature equilibration of lithiated oxazoles can also be accomplished using bases other than lithium diethylamide. Several lithium dialkylamides were surveyed in the alkylation of 2-methyl-4-phenyloxazole (**5**, Table 1). For useful selectivity to be observed, the secondary amine conjugate acids of these amide bases must function as effective proton shuttles between the two lithiated oxazole intermediates (**8** and **9**). To act in this capacity, the pK_a of the secondary amine must be carefully balanced in the range between those of the two acidic oxazole protons (C_2-CH_2-**H** and C_5-**H**). Since amine size and pK_a have been shown to parallel each other,[9] a rough estimate of the relative acidities can be

Table 1. Survey of Bases for the Selective Alkylation of 2-Methyl-4-Phenyloxazole



5 **10** **11**

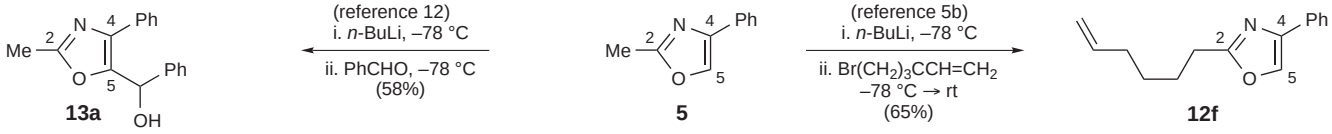
base[a]	pK_a of conjugate acid[9]	(**10**:**11**)[10]	conversion[10,b]
$LiN(SiMe_3)_2$	29.5	95:5	59%
LiNEtMe	30.9	>99:1	>99%
$LiNEt_2$	31.7	>99:1	89%
LiN^nPr_2	—	>99:1	97%
$LiNEt^iPr$	—	99:1	79%
LiN^nBu_2	—	53:47	67%[c]
LiN^iPr_2	34.4	23:77	72%[c]

[a] Lithium dialkylamides were prepared using 2.4 equiv of *n*-BuLi and 2.6 equiv of dialkylamine in THF at –78 °C, were warmed to 0 °C for 10 min, and then recooled to –78 °C before addition of **5**. [b] Double alkylation accounted for ≤8% of the product mixture unless otherwise indicated. [c] Double alkylation accounted for 21% of the product mixture.

deduced when the pK_as are unknown. Amine size also plays a role in the kinetics of the process, with rates of proton transfer being faster for smaller amines.[11] Several of the bases surveyed (LiNEtMe, $LiNEt_2$, LiN^nPr_2, and $LiNEt^iPr$) fall within the useful window for this particular transformation and give excellent levels of selectivity for the thermodynamic product (**10**) at –78 °C. With the larger stronger bases, LDA and LiN^nBu_2, the selectivity drops off substantially and significant amounts of double alkylation products are observed. The use of $LiN(TMS)_2$ leads to very high selectivity, but with only moderate conversion. This result may be due to insufficient basicity of this reagent. The ability to use different dialkyl amide bases, and evaluate them by size, could have potential for fine-tuning equilibrations of other substrate systems.

Prompted by an apparent discrepancy in the literature (Scheme 2), we also investigated the effect of electrophile choice on the regioselectivity of these alkylations. In 1983 Hamana and Sugasawa reported[12] that treatment of 2-methyl-4-phenyloxazole (**5**) with *n*-BuLi at –78 °C followed by addition of benzaldehyde gave alkylation only at the C_5-ring position (**13a**). Contrary to this, Whitney and Rickborn reported[5b] in 1991 that the identical substrate, when reacted the same way with 5-bromo-1-pentene and then warmed to ambient temperature, gave alkylation only at the C_2-methyl site (**12f**).

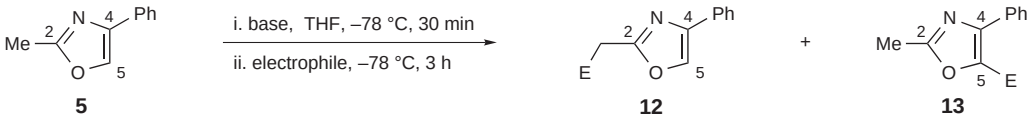
Scheme 2. An Apparent Discrepency in the Literature



The results of our electrophile survey (Table 2) demonstrate that the electrophile identity does play a role in the alkylation selectivity of **5** under some conditions.[13] When *n*-BuLi or LiN^iPr_2 are used as bases, there is a general trend toward increased selectivity toward **12** with decreasing reactivity of the electrophile. As expected for all cases, the starting material conversion (a function of reaction rate) also declines with decreasing electrophilicity. When $LiNEt_2$ is used, however, the selectivity remains uniformly high.

We rationalize these results simply by suggesting that the two lithiated oxazole intermediates (**8** and **9**) are not equally nucleophilic and therefore react at different rates. Under conditions of slow equilibration between **8** and **9**, very reactive electrophiles such as TMSCl (entry b) react indiscriminately with both intermediates and reflect the initial kinetic ratio of these two anions. Less reactive electrophiles, such as 5-bromo-1-pentene (entry f), are more selective for **8** so that the final product mixture does not correspond to the **8**:**9** ratio. When the reaction with 5-bromo-1-pentene (entry f) was run using 1.2 equiv of *n*-BuLi, 6 equiv of electrophile, and was allowed to warm to ambient temperature overnight, the conversion was 88% with 23% double alkylation—which is consistent with the literature report of Whitney and Rickborn—and dispels the apparent inconsistency.

Table 2. Survey of Electrophiles for the Selective Alkylation of 2-Methyl-4-Phenyloxazole[a]



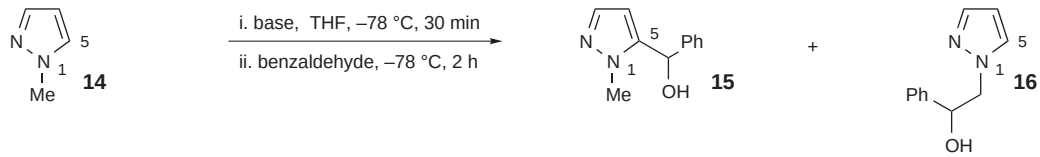
5 **12** **13**

entry	electrophile	E	*n*-BuLi		LiN^iPr_2		$LiNEt_2$	
			(**12**:**13**)	conversion	(**12**:**13**)	conversion	(**12**:**13**)	conversion
a	benzaldehyde	CHPh(OH)	<1:99	>99%	<1:99	>99%	98:2	86%
b[b]	TMSCl	TMS	4:96	97%	1:99	78%	>99:1	92%
c[c]	MeOTf	Me	9:91	≥90%	9:91	≥90%	99:1	≥90%
d	MeI	Me	14:86	83%	37:63	78%[d]	99:1	89%[e]
e	acetone	$CMe_2(OH)$	20:80	78%	58:42	61%	96:4[f]	88%[g]
f[h]	5-bromo-1-pentene	$(CH_2)_3CH{=}CH_2$	95:5	21%	>99:1	73%	>99:1	48%

[a] 2.4 equiv of base and 3 equiv of electrophile were used unless otherwise indicated. Lithium dialkylamides were prepared as in Table 1. Double alkylation accounted for ≤1% of the product mixture unless otherwise indicated. [b] 1.2 equiv of base was used. [c] Data from reference 7. [d] Double alkylation accounted for 21% of the product mixture. [e] Double alkylation accounted for 6% of the product mixture. [f] Optimized conditions: 1.45 equiv of base, 1.75 equiv of acetone. [g] Double alkylation accounted for 15% of the product mixture. [h] No products were observed at –78 °C so these reactions were warmed to 0 °C.

We next investigated the utility of this method for the selective alkylation of several other heteroaromatic systems. One system well-suited to this alkylation method is 1-methylpyrazole (**14**). This compound was reported[14] to give a mixture of benzaldehyde adducts at the C_5 ring position and at the N_1-methyl group (Table 3). Using lithium diethylamide, we could improve the selectivity to give reaction solely at the C_5-site. The best yield of **15** was obtained when the substrate was metallated using *n*-BuLi and was then equilibrated using a *catalytic* amount of diethylamine.

Table 3. Selective Alkylation of 1-Methylpyrazole[a]



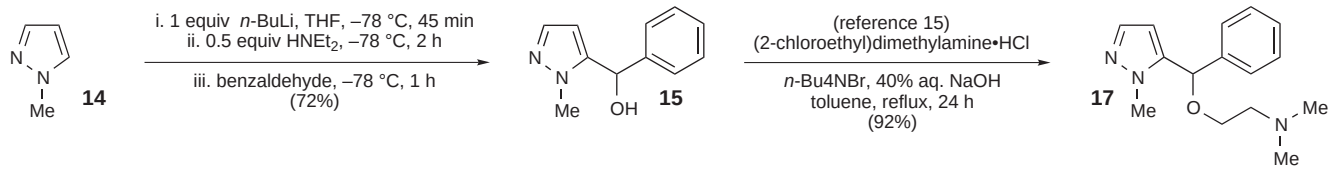
14 **15** **16**

entry	source	*n*-BuLi		LiN^iPr_2		$LiNEt_2$	
		(**15**:**16**)	conversion	(**15**:**16**)	conversion	(**15**:**16**)	conversion
a[b]	reference 14a	66:34	unknown				
b[c]	reference 14b	92:8	unknown	—	—	—	—
c	this work	63:37	79%	—	—	>99:1	85%[d]

[a] 1.2 equiv of base and 3 equiv of PhCHO were used unless otherwise indicated. [b] Reaction warmed to 10 °C and an 88% yield of the mixture was obtained. [c] Reaction warmed to 0 °C and a 57% yield of the mixture was obtained. [d] Optimal conditions: 0.5 equiv of $HNEt_2$ was added to a mixture of **14** and 1 equiv of *n*-BuLi at –78 °C for 5 h before addition of PhCHO.

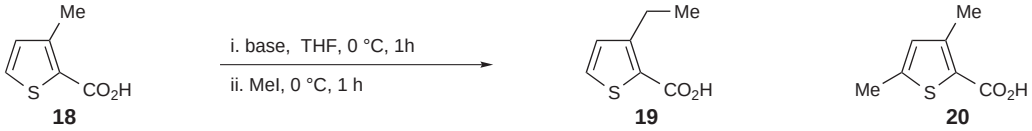
Benzaldehyde adduct (**15**) is an intermediate on the published synthetic route to E-3710 (Cizolirtine, **17)** (Scheme 3),[15] a potent analgesic currently in Phase II and III clinical trials.[16] The reported preparation of alcohol (**15**) is two steps from pyrazole (**14**) and has a 57% overall yield. Using the method described here, we can make the same racemic intermediate in a single step in 72% isolated yield.

Scheme 3. Application to the Synthesis of Cizolirtine



Another heteroaromatic system appropriate to this method is 3-methylthiophene-2-carboxylic acid (**18**, Table 4). This molecule was also reported to give a mixture of products upon alkylation of its dianion.[13] Again, using catalytic $HNEt_2$ to equilibrate the anionic intermediates, complete selectivity could be achieved, albeit with modest conversion. This system was the least well-behaved of all those studied. Sluggish reactivity required warming to 0 °C for alkylation to proceed at a reasonable rate.

Table 4. Selective Alkylation of 3-Methylthiophene-2-Carboxylic Acid[a]

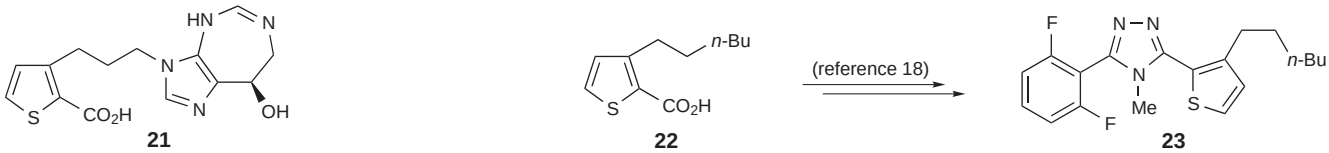


entry	source	*n*-BuLi		LiN^iPr2		$LiNEt_2$	
		(**19**:**20**)	conversion	(**19**:**20**)	conversion	(**19**:**20**)	conversion
a[b]	reference 13	—	—	65:35	unknown	—	—
b	this work	37:63	79%	27:73	92%	>95:5	47%[c]

[a] 2.5 equiv of base and 3 equiv of MeI were used unless otherwise indicated. [b] 2.0 equiv of base used. [c] For best conversion, 10 mol% $HNEt_2$ was added to a mixture of **18** and *n*-BuLi and the mixture stirred at –78 °C for 5 h before addition of PhCHO.

Several thiophene carboxylic acids amenable to preparation by this method are known (Scheme 4). For example, coformycin analog **21** is an inhibitor of AMP deaminase, which is a potential target for novel anti-ischemic drug therapy.[17] Triazole compounds such as **23** are useful as insecticides and acaricides.[18]

Scheme 4. Some Potential Synthetic Applications



The alkylation of 2-methyl-4-*t*-butyloxazole[19] has not been reported previously and provides a notable exception to the alkylation selectivities reported thus far. Unlike the phenyl-substituted system (**5**) this *t*-butyl-substituted oxazole displays identical kinetic and thermodynamic acidities. All three strong bases studied worked equally well for selective alkylation at the 2-methyl position of this substrate with a variety of electrophiles. Synthetic applications of this novel alkylation will be reported in due course.

CONCLUSION

These results demonstrate that amide bases are useful in mediating the selective alkylation of several heteroaromatic systems where distinct kinetic and thermodynamic acidities are observed. Bases other than lithium diethylamide are useful for this process within a size and pK_a range. Electrophile identity also plays a role in selectivity of these reactions in some instances. Continuing efforts to identify other systems suitable to this selective alkylation are underway. Additional application of this method toward a key bisoxazole fragment coupling in the synthesis of hennoxazole A is given in the following communication.[20]

ACKNOWLEDGEMENTS

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