Communications

Metalation of Oxazole−Borane Complexes: A Practical Solution to the Problem of Electrocyclic Ring Opening of 2-Lithiooxazoles

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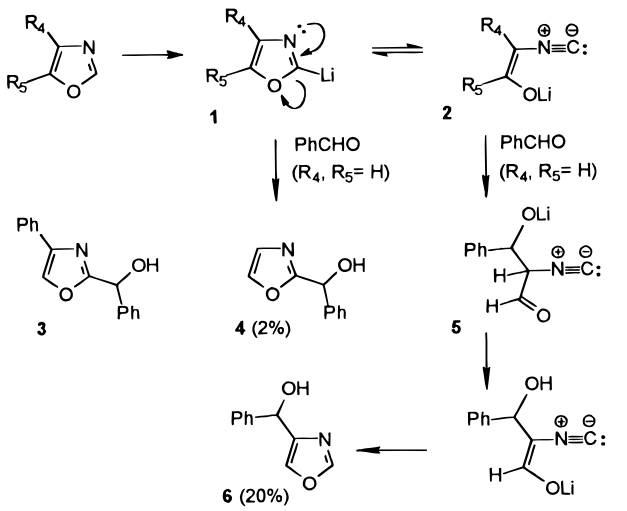
Attempts to trap 2-lithiooxazoles with electrophiles must contend with the complications due to the facile equilibrium between valence bond tautomers **1** and **2**.[1−3] Using benzaldehyde as the electrophile, Whitney and Rickborn reported variable yields of **3**, increasing from 35% to 75% as the time for reaction of **1**/**2** (R_4 = Ph; R_5 = H) with PhCHO was increased from 0.25 to 24 h (rt) prior to workup.[3a] According to these authors, the long reaction time allows anionic adducts derived from the acyclic tautomer **2** to equilibrate with the precursor(s) of cyclic **3**. In a related example, Hodges *et al.* found that metalation of the parent oxazole with butyllithium followed by reaction with benzaldehyde (−78 °C to rt, 24 h) affords only 2% of the "normal" product **4**, 34% of benzyl alcohol, and 20% of the 4-substituted oxazole **6**.[3b] The latter product is presumably derived from conversion of **2** into **5** followed by cyclization. An added complication is that **2** can react with oxophilic electrophiles at enolate oxygen as well as carbon,[1,3a,b,c] and direct metalation at C_4 is yet another possibility if C_2 and C_5 are blocked.[3a] The recently reported 2-chlorozinc analogs behave more predictably and can be intercepted at oxazole C_2 using acyl halides in the presence of CuI or Pd(0) catalysts.[4,5] However, no prior study has reported practical yields in the alkylation of 2-metalloxazoles at C_2.[3b,f,g]

It occurred to us that the undesired electrocyclic ring opening process from **1** to **2** might be prevented if the crucial electron pair at oxazole nitrogen could be locked in place by complexation with a suitable Lewis acid. Complexation was also expected to activate the C_2−H bond for metalation.[6] Suppression of the electrocyclic pathway has now been achieved by the simple expedient of borane complexation as described below, resulting in a practical method for the functionalization of oxazoles at C_2.



Commercial THF−borane was combined with 5-phenyloxaxole[7] **7a**, and the solution was concentrated to yield the crystalline borane complex **8**. Despite initial concerns that the oxazole ring might be reduced by borane,[8] **8** proved to be surprisingly stable and could be stored for several weeks at room temperature. Complex formation was at least 98% complete according to NMR assay, but **8** did not crystallize efficiently. Fortunately, isolation of **8** was not necessary, and good overall yields were obtained using oxazole borane complexes generated *in situ*. The first metalation experiments followed the 2-lithiooxazole precedent.[3a] Thus, **8** was generated in THF at room temperature (30 min) and was then treated with LiTMP/THF at −78 °C. The resulting solution of **9** was quenched with benzaldehyde, followed by decomplexation using 5% acetic acid in ethanol to give **10** (>90% yield, Table 1). Attempted deprotonation with LDA was not successful, but *n*-BuLi or *s*-BuLi (1.1 equiv, 30 min at −78 °C in THF) gave good results and were more convenient than LiTMP.[9] No complications due to nucleophilic addition to the iminium subunit were detected.[10] Reaction times as short as 30 min or as long as 16 h at −78 °C gave similar results, in contrast to the strongly time dependent aldehyde additions of the equilibrating tautomers **1**/**2** (R_4 = Ph; R_5 = H).[3a] Quenching of **9** with hydrocinnamaldehyde also worked well and produced the alcohol **11**.

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(9) To a solution of **7b**[7] (1.00 g, 6.89 mmol) in 34 mL of THF at rt under nitrogen was added BH_3−THF (6.9 mL, 1 M in THF, Aldrich). After 30 min, the solution was cooled to −78 °C, and *n*-BuLi (4.44 mL, 1.63 M in hexane, Aldrich) was added dropwise. After 30 min, benzaldehyde (0.77 mL, 7.58 mmol) was added. The mixture was stirred for 30 min, and 34 mL of 5% HOAc in ethanol was added. The cooling bath was removed, and the mixture was stirred for 18 h at rt to cleave the borane complex. Conventional workup (supporting information) gave **10**, isolated by crystallization from ether, two crops (1.4 g, 81%).

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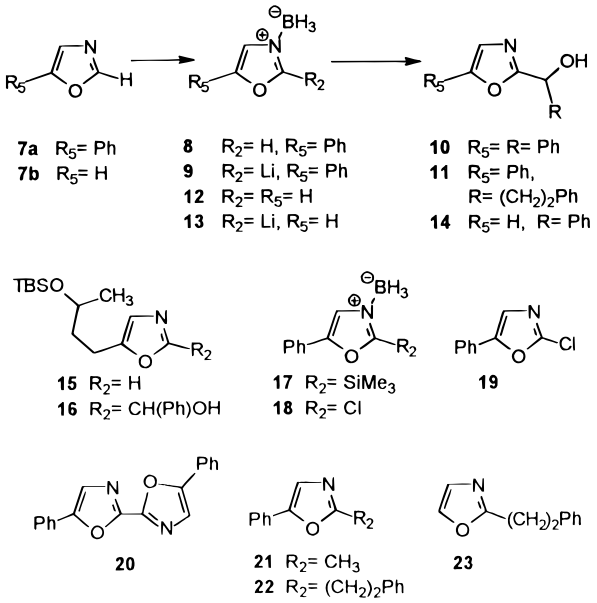
Table 1. Reaction of 2-Lithiooxazole−Borane Complexes with Aldehydes[a]

entry	oxazole	aldehyde	base	product	yield (%)
1	**7a**	PhCHO	LiTMP	**10**	94[b]
2	**7a**	PhCHO	*n*-BuLi	**10**	88;[c] 81[d]
3	**7a**	PhCHO	*s*-BuLi	**10**	90[b]
4	**7a**	$PhCH_2CH_2CHO$	*n*-BuLi	**11**	84[e]
5	**7b**	PhCHO	*s*-BuLi	**14**	70
6	**15**	PhCHO	*n*-BuLi	**16**	84

[a] Reactions were performed in THF at −78 °C using 1.05 equiv of base and 1.1 equiv of aldehyde. After reaction times of 30 min or longer (see notes), the resulting mixtures were quenched and decomplexed with 5% acetic acid in ethanol (18 h, rt). [b] Yield of major fraction after chromatography and crystallization; 16 h reaction time with PhCHO. [c] Yield of major fraction after chromatography; 2 h reaction time with PhCHO. [d] Yield of product crystallized after aqueous workup; 30 min reaction time with PhCHO. [e] Yield of crystallized product; 20 min reaction time with RCHO.



A similar complexation−metalation procedure proved effective for the parent oxazole **7b**.[3b,4] Thus, **12** was prepared in THF solution, and **13** was generated by treatment with butyllithium as before. Addition of benzaldehyde afforded **14** (70% isolated; Table 1, entry 5). No benzyl alcohol was observed (<3%), and no ring-opened products or C_4-substituted oxazoles were detected, in contrast to the results using 2-lithiooxazole **1**/**2** (R_4 = R_5 = H).[3b] In the same way, the 5-alkyloxazole **15**[11] was converted into **16** (84%; Table 1, entry 6).

To further define the scope of this methodology, the anion **9** derived from 5-phenyloxazole−borane complex (**8**) was trapped with a variety of electrophiles (Table 2). Trimethylchlorosilane afforded a 6:1 mixture of **17**:**8** according to NMR assay (Table 2, entry 1), but attempted decomplexation using protic conditions (5% acetic acid in ethanol) resulted only in the desilylated oxazole **7a**. Anion trapping with excess (2 equiv) hexachloroethane resulted in the formation of **19**[12] (Table 2, entry 2). On the other hand, if quenching was performed using 0.5 equiv of hexachloroethane, then the bis-oxazole **20**[1,13] was obtained in good yield (Table 2, entry 3). This product is presumably formed by reaction of the initial product **18** with **9**.

Table 2. Reactions of 2-Lithio-5-phenyloxazole−Borane Complex 9 with Electrophiles[a]

entry	electrophile	*T* (°C)	product	yield (%)
1	Me_3SiCl	−20	**17**	78[b]
2	C_2Cl_6(2 equiv)	−78	**19**	86
3	C_2Cl_6(0.5 equiv)	−78	**20**	79
4	CH_3I	−20	**21**	74[c]
5	$PhCH_2CH_2OTf$	−20	**22**	65[d]

[a] Reactions were performed in THF using 1.05 equiv of *n*-BuLi to generate the anion at −78 °C, followed by addition of the electrophile at the indicated temperature. After 16 h, the reactions were allowed to warm and were treated with 5% acetic acid/ethanol to decomplex the borane. [b] Yield of borane complex prior to acetic acid/ethanol treatment; 13% of unreacted **8** was also isolated. [c] Yield of sublimed product. [d] Ca. 5% recovered **7a** was also present.

Alkylation reactions of **9** were also studied (Table 2, entries 4 and 5). Treating the anion with iodomethane at −20 °C (16 h) afforded 2-methyl-5-phenyloxazole (**21**)[14] (74% yield). Attempts to perform a similar alkylation with phenethyl bromide or iodide failed to give significant conversion of **9**, but the corresponding triflate, $Ph(CH_2)_2$-OSO_2CF_3,[15] was sufficiently reactive at −20 °C (18 h) and afforded **22**[16] (65% yield). Similarly, oxazole (**7b**) was alkylated to give **23** (76%).[17] Prior literature attempts to alkylate oxazoles at C_2 resulted in yields of 30% or less.[3b,f,g] The reaction of **9** with benzoyl chloride was also explored briefly. However, a mixture of products was obtained including ca. 15% of the benzoate ester of alcohol **10**, apparently derived from reduction of the expected 2-benzoyl-5-phenyloxazole. The benzoylation was not explored further in view of the successful organozinc alternative.[4,5]

In summary, the 2-lithiooxazole complexes **9** and **13** have been shown to undergo facile reaction with representative electrophiles. The troublesome anionic electrocyclic ring opening reaction is completely suppressed using the borane complexation procedure.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for **8**, **10**, **11**, **14**, **16**, and **19**−**23** (17 pages).

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(17) **Note Added in Proof:** The same methods could be used for BH_3 activation, lithiation, and $PhCH_2CH_2OTf$ alkylation of thiazole (85% isolated yield).