Methodology for the Synthesis of Substituted 1,3-Oxazoles

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Received 22 December 2009

Dedicated to Prof. Gerald Pattenden on the occasion of his 70th birthday

Abstract: The halogen dance isomerization is a facile and preparatively effective pathway for the synthesis of 2,4,5-trisubstituted 1,3-oxazoles.

Key words: oxazoles, halogen dance rearrangement, alkylation

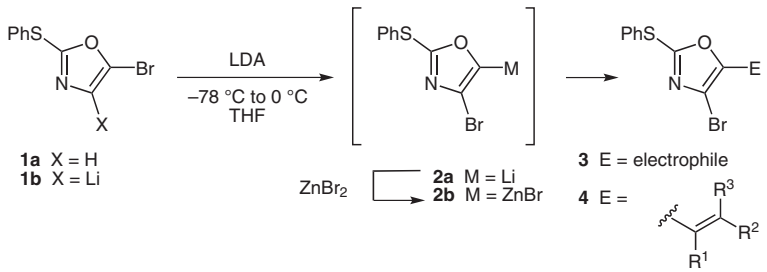
In recent years, structural elucidation studies of biologically significant natural products have frequently incorporated novel 1,3-oxazole ring systems within complex molecular architectures. Numerous examples include hennoxazole A,[1] phorboxazoles A and B,[2] diazonamides A and B,[3] rhizopodin,[4] telomestatin,[5] and the ulapualides.[6] In addition, 1,3-oxazole moieties are commonly displayed within depsipeptides as a result of oxidative cyclodehydrations of serine and threonine residues.[7] These structural features have inspired widespread inclusion of substituted 1,3-oxazoles in medicinal chemistry, and particularly in the design of peptidomimetics. The proliferation of complex structures for challenging syntheses has ignited renewed interests in the development of effective methodologies toward substituted oxazoles. We have previously described an oxidative cyclodehydration route as a general strategy for the de novo preparation of 2,4-disubstituted 1,3-oxazoles.[8] Studies toward the elaboration of the oxazole nucleus have reported cross-coupling reactions of alkenylation and arylation at C-2[9] as well as Stille reactions of 2-phenyl-1,3-oxazoles.[10]

Efforts for elaboration of the oxazole nucleus can be greatly facilitated by site-selective formation of a reactive carbanion. Kinetic deprotonation of the C-2 hydrogen of the parent oxazole provides access to a ring-closed carbanion as well as the ring-opened isonitrile enolate.[11] C-Acylations of the enolate produce 4,5-disubstituted oxazoles via the Cornforth rearrangement.[12] Examples of site-selective ring metalations via complex-induced proximity effects[13] (CIPE) have been recorded in [2,4]-bisoxazoles[14] and for 2-methyl-1,3-oxazole-4-carboxylic acid.[15] Furthermore, Stambuli and coworkers have recently described the selective C-5 deprotonation of 2-methylthio-1,3-oxazole leading to the production of 2,5-disubstituted oxazoles, and we have reported related studies of C-5 deprotonation using 2-phenylsulfonyl-1,3-oxazoles.[16]

In this letter, we describe the kinetic C-4 deprotonation of 5-bromo-2-phenylthio-1,3-oxazole (**1a**) which initially leads to the lithium species **1b**. Upon warming to 0 °C, anion **1b** undergoes efficient isomerization to afford the reactive 5-lithio-4-bromo-2-phenylthio-1,3-oxazole (**2a**). Reactions of **2a** with a variety of electrophiles yield the trisubstituted oxazoles **3**. Transmetalation of the lithium species **2a** provides the zinc reagent **2b** for effective Negishi cross-coupling processes to give products of alkenylation and arylation at the C-5 position (Scheme 1).

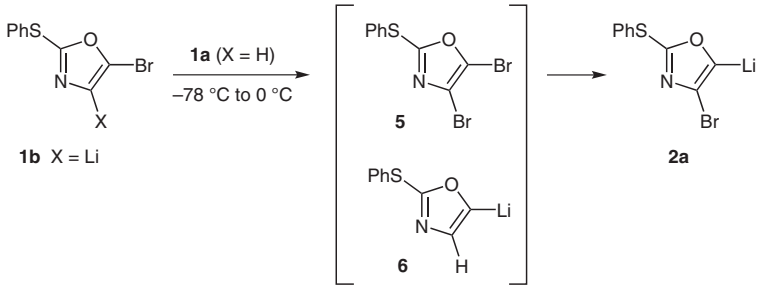
The nature of the isomerization which leads from the 5-bromo heterocycle **1a** to yield the 4-bromo derivative **2a** is described as the halogen dance (HD) reaction. This base-induced migration has been studied in aromatic and heteroaromatic systems.[17,18] Strangeland and Sammakia demonstrated the first example of the halogen dance in a 1,3-thiazole system,[19] and Stanetty and coworkers have recently published the only oxazole example of this halogen migration in their studies of 5-bromo-2-phenyl-1,3-oxazole.[20]

In the course of our studies of 2,5- and 2,4-disubstituted oxazoles, we have found that the base-catalyzed halogen exchange of 2-phenylthio-5-bromo-1,3-oxazole **1**[21] is a



Scheme 1

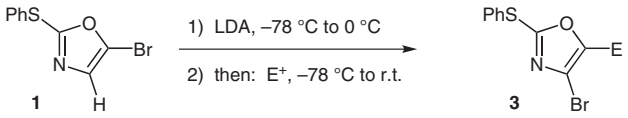
SYNLETT 2010, No. 4, pp 0591–0594
Advanced online publication: 08.02.2010
DOI: 10.1055/s-0029-1219374; Art ID: D37509ST



Scheme 2

facile process with considerable synthetic utility. Thus, treatment of **1a** with LDA at –78 °C leads to deprotonation at C-4 providing **1b** which subsequently undergoes rapid halogen exchange with starting **1a**. This process generates the intermediates **5** and **6** thereby facilitating a final bromine transfer to produce the more stable lithium reagent **2a** (Scheme 2). After stirring at 0 °C (45 min), solutions of **2a** were cooled to –78 °C for the introduction of various electrophiles. Upon warming to 22 °C, reaction mixtures were quenched, and the products were purified by flash silica gel chromatography prior to full characterization. A survey of our results is complied in Table 1, and illustrates useful yields in a number of alkylation processes including condensations with aldehydes and ketones (entries 5–9 of Table 1). Our conditions permit facile isomerization of the 5-bromo compound **1a** to yield the corresponding 4-bromo-1,3-oxazole (Table 1, entry 1), which serves as an important precursor for the regiocontrolled synthesis of 2,4-disubstituted oxazoles. Additionally, the regioselective introductions of 5-iodo, 5-stannyl, and 5-silyl functionality (Table 1, entries 2–4) advance new opportunities for site-specific reactivity in these heterocycles. Our efforts have also recorded the transmetalation of **2a** to provide **2b** via the addition of anhydrous $ZnBr_2$ in THF at 0 °C. As a result, these studies provide for cross-coupling reactions with aryl and alkenyl iodides (entries 10–13 of Table 1) affording 67% to 80% yields of highly functionalized 2,4,5-trisubstituted 1,3-oxazoles.[22]

Table 1 Preparation of 5-Substituted 4-Bromo-2-(Phenylthio)oxazole **2**



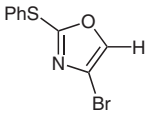
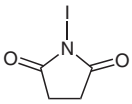
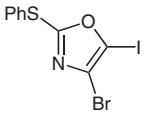
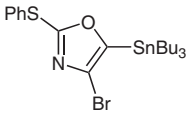
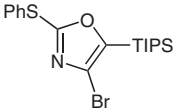
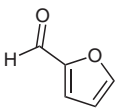
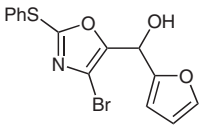
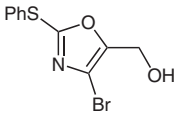
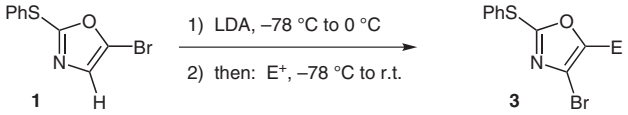
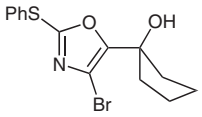
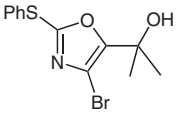
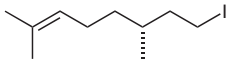
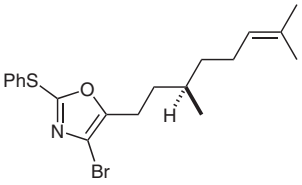
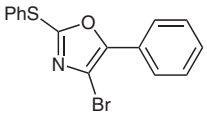
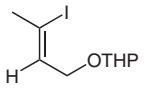
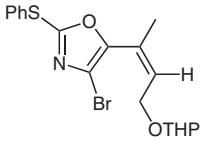
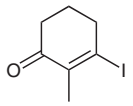
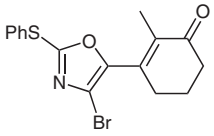
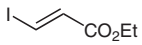
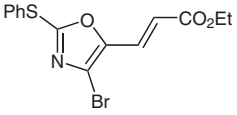
Entry	Cond.[a]	Electrophile	Product	Yield (%)
1	A	H_2O		88
2	A			87
3	A	*n*-Bu_3SnCl		83
4	A	TIPSOTf		89
5	A			82
6	A	HCHO		72

Table 1 Preparation of 5-Substituted (continued) 4-Bromo-2-(Phenylthio)oxazole **2** (continued)



Entry	Cond.[a]	Electrophile	Product	Yield (%)
7	A			79
8	A			74
9	B			87
10	C			80
11	C			67
12	C			72
13	C			77

[a] Conditions A: A concentrated solution of 5-bromo-2-phenylthio-1,3-oxazole (**1**, 1.0 equiv) in THF was added dropwise into a freshly prepared solution of LDA (1.5 equiv) in THF at –78 °C. After stirring at –78 °C for 10 min, the mixture was warmed to 0 °C using an ice bath and maintained at 0 °C for 45 min. Upon cooling to –78 °C, THF solutions of electrophilic reagents (1.5 equiv) were introduced with continued stirring for 15 min. Reactions were then allowed to warm to 22 °C and were quenched with aq sat. NH_4Cl. Extraction (Et_2O), drying the organic extracts over $MgSO_4$, and flash silica gel chromatography led to the purified products. Conditions B: Following the metalation of oxazole **1**, anhyd HMPA (10 equiv) was added at –78 °C. Alkyl iodide (1.5 equiv) in THF was then introduced at –78 °C, and the reaction mixture was warmed to 22 °C with stirring overnight. Isolation and purification as described in conditions A. Conditions C: Following the metalation of oxazole **1** as previously described, anhyd $ZnBr_2$ (1.2 equiv) in THF was added at 0 °C, and the mixture was allowed to warm to 22 °C with continued stirring for 1 h. A solution of aryl or alkenyl iodide (1.5 equiv) and $Pd(PPh_3)_4$ (10 mol%) in dry DMF was then added, and the reaction mixtures were stirred at 22 °C, or at 45 °C in the case of entry 12, for 18–24 h. Isolation and purification as described for conditions A above.

In summary, our studies have shown that the halogen dance isomerization is a synthetically viable process that can be used to develop molecular complexity in the preparation of 2,4,5-trisubstituted 1,3-oxazoles. Selective replacement reactions of the 2-phenylthio and 4-bromo substituents of our products will enhance the generality and scope of our observations. Applications for the development of this chemistry in natural product synthesis are currently under way in our laboratories.

Acknowledgment

We acknowledge the support of Indiana University and partial support of the National Institutes of Health (GM042897).

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(21) **Preparation of Starting Oxazole 1**
A CH_2Cl_2 solution of 2-phenylthio-1,3-oxazole (1.0 equiv) and anhyd Et_3N (1.5 equiv) was stirred at 0 °C, and bromine (1.5 equiv) in CH_2Cl_2 (1:1 by volume) was introduced by slow dropwise addition. The reaction mixture was allowed to warm slowly to 22 °C, and stirring was continued overnight. The reaction was quenched with aq sat. $NaHCO_3$ and was extracted with CH_2Cl_2. Organic phases were combined and washed with aq $NaHSO_3$ and then dried over anhyd Na_2SO_4. Evaporation of solvent and flash silica gel chromatography (8:1 hexane–EtOAc) provided 5-bromo-2-phenylthio-1,3-oxazole (75% yield).
(22) Yields of Table 1 are provided for purified products which were characterized by ^1H NMR and ^{13}C NMR spectroscopy, IR spectroscopy, and HRMS analysis.