

# Samarium Barbier Reactions of $\alpha$ -Iodomethyloxazoles and Thiazoles with Aliphatic Aldehydes

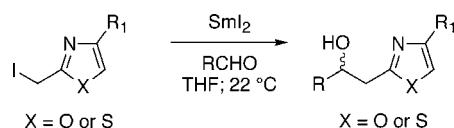
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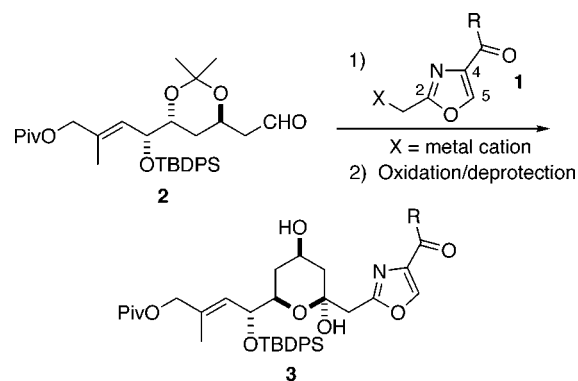
## ABSTRACT



The reductive coupling of substituted  $\alpha$ -iodomethyloxazoles and thiazoles with aliphatic aldehydes under Barbier conditions provides an effective method for the direct incorporation of intact heterocyclic systems.

The use of samarium diiodide (SmI<sub>2</sub>) in synthetic organic chemistry was first introduced by Henri Kagan.<sup>1</sup> Practitioners have demonstrated the scope of important processes carried out by this versatile electron-transfer reductant, and several timely reviews have charted the reactivity characteristics of this unique reagent.<sup>2–5</sup> Samarium Barbier reactions of alkyl bromides and iodides in the presence of carbonyl compounds have proven to be especially valuable as intramolecular transformations. Often, intermolecular Barbier conditions of simple alkyl halides provide little advantage compared to traditional Grignard reactions, where the use of SmI<sub>2</sub> may lead to competing dimerization of reactive allylic or benzylic halides and reduction or pinacol coupling of the aldehyde substrate. However, in cases in which the preparation and handling of the Grignard species proves difficult or the reagent displays basic rather than nucleophilic properties, the analogous samarium-induced reaction can be particularly beneficial. In the course of our studies toward phorboxazole A,<sup>6</sup> we sought a reliable method that would permit coupling

of the 2,4-disubstituted oxazole **1** with the  $\beta$ -alkoxy aldehyde **2** for overall conversion to the C<sub>28</sub>–C<sub>41</sub> component **3**. In 1981, Meyers first reported that 2-methyloxazole-4-carboxylates unexpectedly undergo C-5 ring metalation upon treatment with *n*-butyllithium.<sup>7</sup> No evidence for deprotonation of the C2 methyl group was observed, presumably owing to the directive effect of the C4 carbonyl unit. More recent



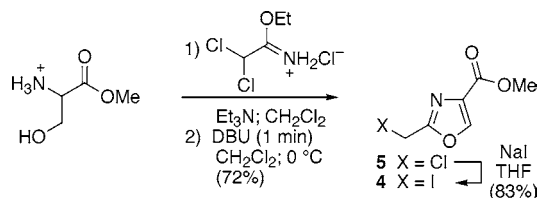
**Figure 1.** Formation of component **3** for studies toward phorboxazole A.

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studies utilizing lithium diethylamide as a base circumvent this problem.<sup>8</sup> On the other hand, Helquist<sup>9</sup> and Uguen<sup>10</sup> have described the conversion of methyl 2- $\alpha$ -halomethyloxazole-4-carboxylates to the corresponding nonbasic organozinc and organochromium derivatives for subsequent addition to aldehydes. Unfortunately, our efforts to prepare the analogous organozinc derivative of **1** (X = ZnBr or ZnI) led to sluggish reactions and low product yields. Herein, we communicate the deployment of samarium Barbier conditions leading to the successful coupling of a variety of substituted five-membered heterocycles with aliphatic aldehydes. The intact incorporation of substituted oxazoles or thiazoles provides encouragement for applications of complex molecular constructions as an alternative to de novo heterocyclic synthesis.

Initial investigations explored reactions of the  $\alpha$ -iodo-2-methyloxazole **4** as a prelude to our phorbazole studies. Multigram quantities of **4** were readily prepared from the condensation of ethyl dichloroacetimidate (Scheme 1) with

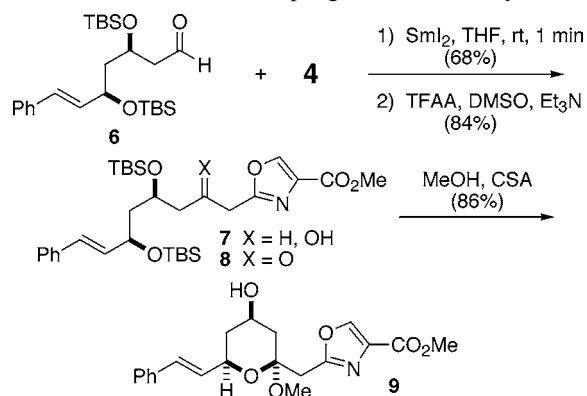
**Scheme 1.** Preparation of  $\alpha$ -Halo-2-methyl-oxazoles



serine methyl ester followed by brief exposure to DBU and halogen exchange of **5** with sodium iodide. Preliminary experiments of Scheme 2 established the SmI<sub>2</sub>-mediated coupling between **4** and model aldehyde **6**<sup>11</sup> under Barbier conditions in fewer than 5 min at temperatures ranging from  $-78$  to  $22$  °C and provided the  $\beta$ -hydroxyoxazole **7** as an inseparable mixture of diastereomers (68% yield). Stoichiometric quantities of aldehyde and iodide **4** were premixed in degassed THF and added via cannula to a freshly prepared solution of excess (2.5 equiv) SmI<sub>2</sub>. Structural verification of **7** was provided by oxidation under modified Swern conditions<sup>12</sup> and subsequent deprotection of ketone **8** with methanol in the presence of catalytic camphorsulfonic acid to yield the desired cyclic ketal **9**.

General characteristics of the samarium diiodide coupling are summarized in Table 1. Several representative oxazole and thiazole derivatives have been examined, although our survey made no attempt to optimize results for each case.

**Scheme 2.** Barbier Coupling of **4** with Aldehyde **6**



The requisite  $\alpha$ -iodomethylene functionality was routinely introduced by treatment of the precursor alcohol with Ph<sub>3</sub>P and iodine (Imid, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C) or via radical bromination with NBS (CHCl<sub>3</sub>) followed by NaI exchange in acetone. Experimentation has been focused on model studies to guide our efforts for total synthesis. Thus, the iodomethylene substituent is generally positioned at C2 of the parent heterocycle. Entries 1–3 demonstrate the incorporation of ester functionality at C4 of the oxazole. Preparatively useful addition reactions occur (55–87% yields) with aliphatic aldehydes, which include typical protecting groups for  $\beta$ -hydroxyl substituents. To gain a better understanding of this reaction, we examined the 2-iodomethyl benzoxazole (**23**) and analogous benzothiazole (**26**) examples of entries 6–9. Aromatic aldehydes were not useful and gave rise to competing pinacol coupling. However, aliphatic aldehydes displayed a range of reactivity exemplified by isobutyraldehyde (**19**) and  $\alpha$ -benzyloxyacetaldehyde (**21**). In the former case, reductive alkylations routinely exceeded 80% yields. Several side reactions were observed with  $\alpha$ -alkoxyaldehydes, including carbonyl reduction to the corresponding alcohols, as well as reductive elimination to produce benzyl alcohol as observed in the case of **21**. These processes limited the desired Barbier coupling to 35–45% yields. No significant improvements in yields were observed when reactions were conducted in tetrahydropyran,<sup>13</sup> with the addition of catalytic Ni(II) salts,<sup>14</sup> or in the presence of Lewis acids.<sup>15</sup> In the case of 2- $\alpha$ -iodomethyloxazoles and thiazoles, it is tempting to postulate a net two-electron reduction producing the *N*-metallo-enamine **37** for precomplexation in the six-membered array **38** by analogy to carbonyl coupling processes (Figure 2).

Although this hypothesis may warrant consideration, limited studies with 4- $\alpha$ -iodomethyl examples (Table 1, entries 10–14) suggest more broadly defined applications for this Barbier coupling. The C-4 substituted heterocycles

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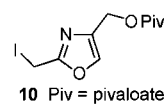
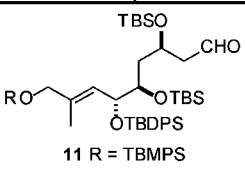
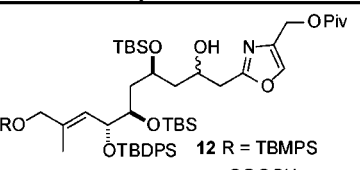
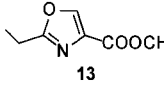
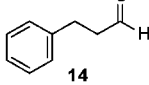
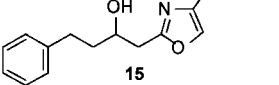
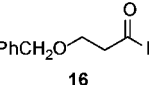
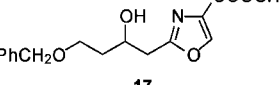
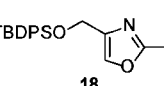

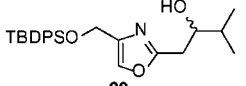
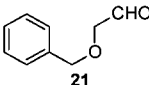
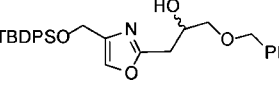
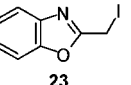
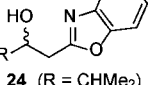
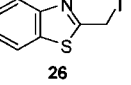
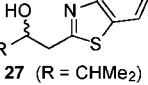
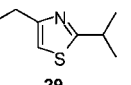
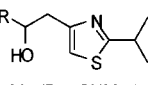
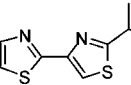
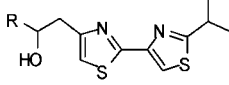
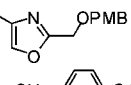
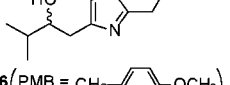
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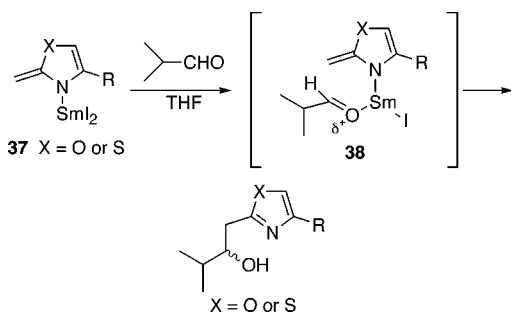
**Table 1.** Samarium Barbier Reactions of Substituted Oxazoles and Thiazoles with Aldehydes<sup>a,b</sup>

entry	heterocycle	aldehyde	product	yield <sup>c</sup>
1	 <b>10</b> Piv = pivaloate	 <b>11</b> R = TBMPs	 <b>12</b> R = TBMPs	76%
2	 <b>13</b>	 <b>14</b>	 <b>15</b>	60%
3	<b>13</b>	 <b>16</b>	 <b>17</b>	55%
4	 <b>18</b>	 <b>19</b>	 <b>20</b>	98%
5	<b>18</b>	 <b>21</b>	 <b>22</b>	40%
6	 <b>23</b>	<b>19</b>	 <b>24</b> (R = CHMe <sub>2</sub> )	87%
7	<b>23</b>	<b>21</b>	<b>25</b> (R = CH <sub>2</sub> OCH <sub>2</sub> Ph)	40%
8	 <b>26</b>	<b>19</b>	 <b>27</b> (R = CHMe <sub>2</sub> )	82%
9	<b>26</b>	<b>21</b>	<b>28</b> (R = CH <sub>2</sub> OCH <sub>2</sub> Ph)	38%
10	 <b>29</b>	<b>19</b>	 <b>30</b> (R = CHMe <sub>2</sub> )	80%
11	<b>29</b>	<b>21</b>	<b>31</b> (R = CH <sub>2</sub> OCH <sub>2</sub> Ph)	35%
12	 <b>32</b>	<b>19</b>	 <b>33</b> (R = CHMe <sub>2</sub> )	75%
13	<b>32</b>	<b>21</b>	<b>34</b> (R = CH <sub>2</sub> OCH <sub>2</sub> Ph)	55%
14	 <b>35</b> (PMB = CH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> )	<b>19</b>	 <b>36</b> (PMB = CH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> )	70%

<sup>a</sup> Reactions were conducted in THF at 22 °C and quenched (aq 30% sodium potassium tartrate). <sup>b</sup> SmI<sub>2</sub> (2.5–3 equiv) was freshly prepared in THF by addition of a solution of 1,2-diiodoethane to Sm<sup>0</sup> powder under argon (stirring in the dark over 5 h). <sup>c</sup> Products were purified by flash silica gel chromatography and were fully characterized.

**29**, **32**, and **35** displayed similar reaction characteristics as their C-2 counterparts with model aldehydes **19** and **21**. Oxazole **35** led to 70% yield of adduct **36** despite small amounts of reductive degradation stemming from the presence of the C-2 *p*-methoxybenzyl ether.

In summary, a survey of reductive Barbier coupling reactions of substituted  $\alpha$ -iodomethyloxazoles and thiazoles with aliphatic aldehydes has been conducted using samarium diiodide. This method conveniently permits direct incorporation of the intact heterocyclic system. The iodomethylene



**Figure 2.** Mechanistic considerations for samarium Barbier coupling of aldehydes and 2- $\alpha$ -iodomethyloxazoles and thiazoles.

appendage may be positioned at C-2 or at C-4 of the heterocyclic nucleus. Reactions are compatible with the

presence of esters and common ether protecting groups, including allylic ethers. However,  $\alpha$ -alkoxyaldehydes have shown diminished yields owing to competing side reactions.

**Acknowledgment.** We thank the National Institutes of Health (GM-41560) for generous support of this work.

**Supporting Information Available:** Experimental procedures and complete characterization data for the compounds of Schemes 1 and 2; general procedures for preparation of  $\text{SmI}_2$  and for the Barbier reactions of Table 1; spectral data for the products of Table 1 including the ketone of **12**, **15**, **17**, **20**, **22**, **24**, **25**, **27**, **28**, **30**, **31**, **33**, **34**, and **36**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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