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# The Oxidation of 2-Oxazolines to 1,3-Oxazoles

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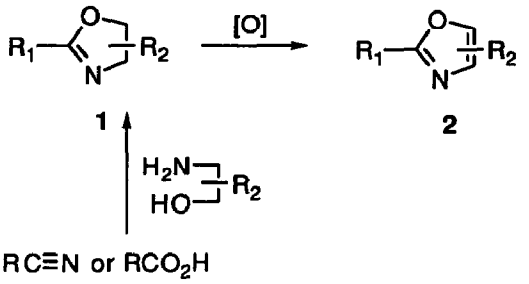
***Summary:*** *Oxazolines are readily oxidized to 1,3-oxazoles using NBS/peroxide or light or, more efficiently, by the Kharasch-Sosnovsky Reaction.*

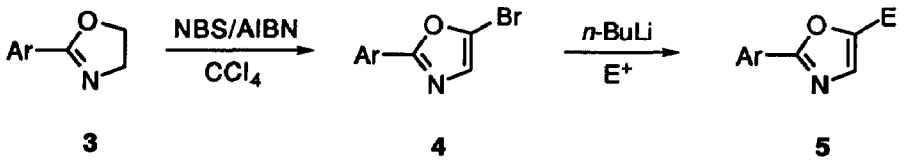
The presence of the 1,3-oxazole **2** in a variety of natural products of current interest[1,2] has spurred a number of synthetic efforts to reach them. These efforts have centered mainly around ring syntheses from acyclic precursors[3] however, several methods have been reported[4a,4b,4c] wherein direct oxidation or selenium-mediated olefination[4d] of oxazolines **1** have led to the oxazoles **2**. The latter approach to 1,3-oxazoles is particularly attractive since oxazolines are readily prepared from nitriles or carboxylic acids and amino alcohols.[5]




The recent report[4c] that a variety of 4-carbalkoxy-2-oxazolines are efficiently oxidized using $CuBr_2$-DBU-hexamethylenetetramine prompts us to describe our own results which involve radical processes.

During the course of a synthetic program to reach oxazole and thiazole-containing natural products[6] we have also initiated an effort to search for alternative and more efficient methods to oxidize 2-oxazolines containing a wide variety of substituents.

We now wish to describe our preliminary findings wherein two different procedures hold promise to affect the transformation, **1** to **2**. The first method involves a variation of a previously described[4b] route to 1,3-oxazoles by treating 2-aryl-2-oxazoline (**3**) with N-bromosuccinimide-AIBN to give the 5-bromo-1,3-oxazoles **4** in ca 50% yield. Halogen metal exchange and electrophilic quench of the latter provided the oxazoles **5** in 70-88% yield. The extra step required

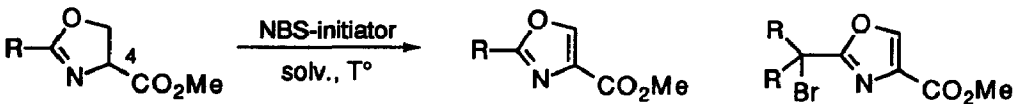



**3** **4** **5**

(Ar = Ph, p-ClPh, p-*t*-BuPh) (E = H, Alkyl)

to remove the bromo substituent detracts from the efficiency of this method and we, therefore, sought to completely avoid the bromo intermediate, **4**. Furthermore, this study dealt with a single ring derivative (**3**) and we were more concerned with oxazoles containing a 4-carboxy substituent,

**Table 1.**




**8** **6** **7**

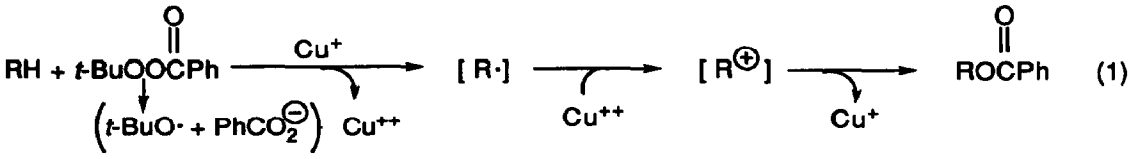
| | | Oxazole (%)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| Entry | R in **8** | **6** | **7** | Solvent | T°C | Equiv NBS (initiator)[b] | Rxn time (h) |
| 1 | Ph | 83 | <1 | benzene | 80 | 1.2 ($Bz_2O_2$) | 2 |
| 2 | Me | 62 | <1 | $CH_2Cl_2$ | -15 to -10 | 1.5 (hυ) | 7 |
| 3 | *n*-$C_5H_{11}$ | 65 | <1 | $CH_2Cl_2$ | -40 to -25 | 5.0 (hυ) | 12 |
| 4 | *i*-Pr | <1 | 76 | $CH_2Cl_2$ | 0 | 2.6 (hυ) | 10 |
| 5 | cyclohexyl | <1 | 66 | $CH_2Cl_2$ | 0 | 2.6 (hυ) | 12 |

a) Yields are of purified material obtained by radial chromatography (silica gel, hexane-ethyl acetate, 90:10). b) Irradiation to initiate the bromination was carried out under argon, at the indicated temperature using 450 W lamp. The reaction was performed by adding NBS and oxazoline to a pyrex test-tube, evacuated, purged with argon, solvent added, cooled, and irradiated for the indicated time.

**6** (derived from serine). Experiments were conducted using NBS with either benzoyl peroxide or light as the radical initiator and performing the oxidations by varying temperatures and stoichiometry. The results are presented in Table 1. Although the first three entries were successful in generating the desired oxazole, **6**, the last two entries gave essentially pure α-brominated products, **7**. Obviously, the 3°-radical in the last two entries was readily formed giving rise to bromination by the excess NBS present. Unfortunately, use of 1.0-1.2 equiv of NBS gave mixtures of **6** and **7** thus indicating that the radicals at C-4 and the side chain were competitively formed.

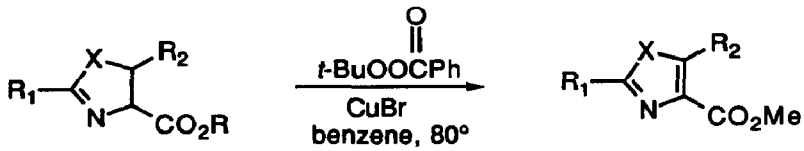
Since the latter method lacked the generality we sought, we next turned to an older reaction which has not been employed in this area - namely the Kharasch-Sosnovsky reaction.[7] The

process is generally considered to involve a copper-ion catalyzed decomposition of a peroxyester and reaction with a C-H substrate to generate a carbon radical which is oxidized to a cation and trapped by the carboxylate anion (eq 1). This process was found to be quite successful when




applied to the oxazolines and thiazolines, **9**. After some experimental trials it was necessary to utilize 1-1.1 equiv of Cu(I)Br and 1.5 equiv *t*-butyl perbenzoate in benzene at reflux. The yields of four examples are given in Table 2. The oxazolines containing the isopropyl or cyclohexyl susbstituent (entries 1,4) gave only the oxazole **10** devoid of any side chain bromination as

**Table 2.** Oxidation of Oxazolines, Thiazolines *via* the Kharasch-Sosnovsky Reaction.

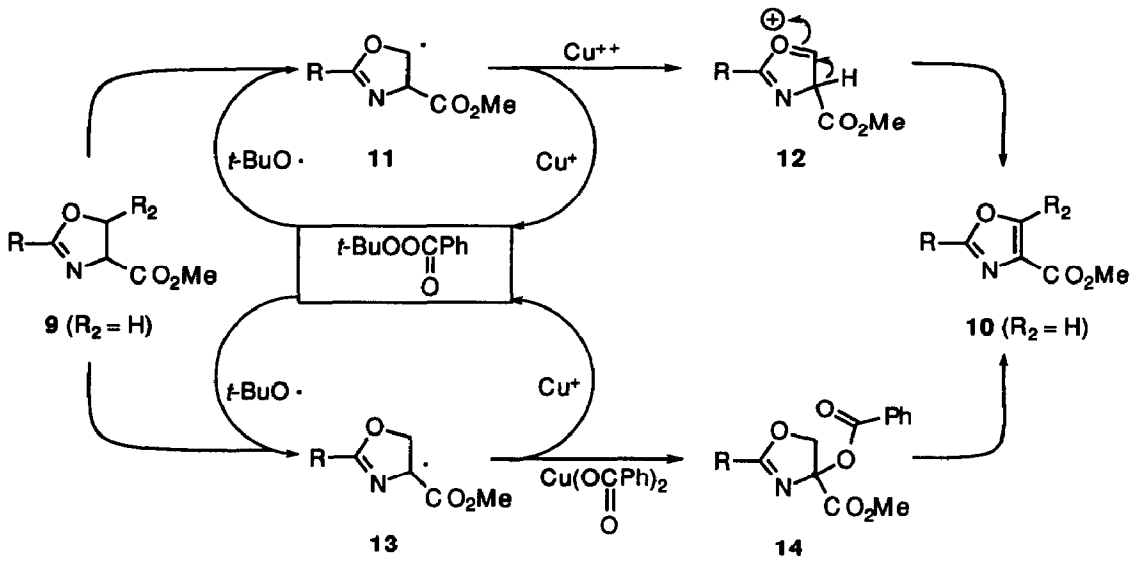



**9** **10**

| Entry | R | $R_1$ | $R_2$ | X | Rxn time[a] | Yield, %[b] |
|---|---|---|---|---|---|---|
| 1 | Me | *i*-Pr | H | O | 12 h | 60 |
| 2 | Et | Et | Me | O | 12 h | 63 |
| 3 | Et | *n*-Pr | H | S | 4.5 h | 83 |
| 4 | Me | Cyclohexyl | H | O | 12 h | 55 |

a) 1.1 equiv of Cu(I)Br and 1.5 equiv of *t*-butyl perbenzoate were employed. b) Products are chromatographed and pure.

observed earlier using NBS (Table 1). The thiazoline ester **9** (X = S) gave the corresponding thiazole (entry 3) in good yield while the presence of a 5-methyl group in the oxazoline **9** ($R_2$ = Me, X = O) (entry 2) did not interfere with the oxidation. It is of interest to note that the Bristol-Myers Squibb group[4c] which performed oxidations of 2-oxazolines utilizing Cu(II)Br suggested that the mechanism proceeded *via* an ionic pathway involving a copper enolate. The present oxidation process, although not yet confirmed, proceeds *via* a radical pathway possibly involving **11** or **13**. The intermediate **11** has precedent in Kharasch-Sosnovsky reactions[7] involving tetrahydrofurans and thiophenes, which are oxidized by Cu(II) *via* oxonium salt to their dihydro derivatives. In the case of **11** this would lead readily to **12** and rapid proton loss would provide the observed




oxazoles, **10**. On the other hand, hydrogen atom abstraction may be more favored to give **13** which could undergo a ligand transfer[8] with Cu(II) benzoate to give **14**. The latter would suffer elimination to the oxazole, **10**. Which of these processes is responsible for the oxidation of oxazolines to oxazoles will be further scrutinized and reported in due course.

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