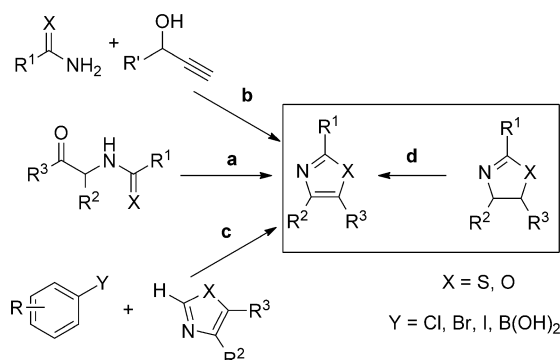


DDQ-Induced Dehydrogenation of Heterocycles for C–C Double Bond Formation: Synthesis of 2-Thiazoles and 2-Oxazoles

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Thiazoles and oxazoles represent a predominant structural motif in many natural compounds, organic dyes, and pharmaceuticals.^[1–3] In recent years, thiazoles and oxazoles that are monosubstituted at the C2 position have been widely used in organic synthesis as building blocks owing to their versatile reactivity.^[4] However, a potential limitation for the application of 2-substituted thiazoles and oxazoles could be the lack of practical methods to produce these important heterocycles. There are some synthetic strategies available for the synthesis of 2-thiazoles and 2-oxazoles (Scheme 1).^[5–8] Among these methods, oxidation of 2-thiazo-



Scheme 1. Strategies for the synthesis of 2-thiazoles and 2-oxazoles.

lines and 2-oxazolines (Scheme 1 d) is of great importance, and various approaches have been reported for this transformation.^[8] Based on the literature precedent, C4 (R²) and/or C5 (R³) substituents on 2-thiazolines and 2-oxazolines have significant influence on the oxidation reaction, and 2-thiazolines and 2-oxazolines without substituents at C4 and C5 are inert to oxidation. For instance, Meyers and Tavares have developed a Cu^I/Cu^{II}/peroxide oxidation for the synthesis of 2-thiazoles and 2-oxazoles, however, the main limitation of this method was that oxidation was unsuccessful with 2-thiazolines and 2-oxazolines that were lacking a substituent at

the C4 and C5 positions.^[9] Barrish and co-workers demonstrated a Cu^{II}/DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) system for synthesis of 2-oxazoles-4-carboxylate, however, oxidation of 2-monosubstituted oxazolines using this method did not afford the desired products.^[10] Wang et al. also reported that the Cu(OAc)₂/O₂ system did not afford the desired 2-thiazoles when 2-thiazolines bearing an inactive group at the C4-position were employed.^[11] Therefore, the oxidation of 2-thiazolines and 2-oxazolines without substituents at C4 and C5 is considered to be challenging, and few methods are reported for this transformation. Recently, we have reported a convenient and efficient copper-catalyzed tandem reaction to form a wide range of 2-thiazolines and 2-oxazolines,^[12] and this allowed us to further study the oxidation of 2-thiazolines and 2-oxazolines.

DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is a highly effective oxidant. In the past decades, DDQ has been widely used in chemical transformations, including protecting-group removal, cross-coupling reactions, cyclizations, and biaryl construction.^[13] Encouraged by extensive investigations on DDQ-induced dehydrogenation reactions,^[14] herein, we report a convenient and efficient approach for 2-thiazoles and 2-oxazoles from the oxidation of 2-thiazolines and 2-oxazolines, respectively, using DDQ as the oxidant. To the best of our knowledge, this is the first system for the synthesis of 2-monosubstituted thiazoles and oxazoles through dehydrogenation. Furthermore, metals are not required in this study, thus making this method attractive for pharmaceutical purposes.

As shown in Table 1, 2-phenyl-2-thiazoline (**1a**) was chosen as the model substrate for optimization studies. Firstly, a variety of common oxidants were screened (Table 1, entries 1–6), but no desired product **2a** was obtained. To our delight, DDQ was proved to be an efficient oxidant for the transformation (Table 1, entry 7). Solvent effects were also investigated, and it was found that CH₂Cl₂ performed better than any other solvent (Table 1, entries 7–12). Furthermore, catalysts were screened, which showed no improvement in the efficiency of the transformation (Table 1, entries 13–15). Finally, different additives and reaction temperatures were examined, and optimal results were obtained with molecular sieves (5 Å) at room temperature (Table 1, entries 16–20).

The optimal reaction conditions were DDQ, CH₂Cl₂, 5 Å MS, at room temperature. With these conditions in hand, studies on the substrate scope were carried out, and the results are summarized in Table 2. We initially investigated

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