NOVEL DEHYDROGENATION OF 2,5-DIARYL SUBSTITUTED Δ^2-OXAZOLINES TO OXAZOLES

Robert F. X. KLEIN*, Václav HORÁK and Godfrey A. S. BAKER**

Department of Chemistry,
Georgetown University, Washington, DC 20057-0001, U.S.A.

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The dehydrogenation of various 2,5-diaryl substituted Δ^2-oxazolines with either Br_2/LiBr/$CaCO_3$ (molar ratio 1.05 : 2 : 3) or $CuBr_2$/LiBr/$CaCO_3$ (2 : 1 : 3) in refluxing *o*-dichlorobenzene gives the corresponding oxazole in up to 87% yield. Free radical benzylic bromination followed by dehydrobromination is the expected dehydrogenation mechanism. The successful application of the reagent combination for this transformation is in contrast to standard dehydrogenation reagents, including N-bromosuccinimide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, chloranil, NiO_2 and active γ-MnO_2.

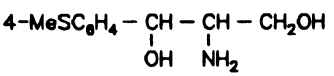
Δ^2-Oxazolines, readily prepared via a variety of synthetic routes[1], represent potential synthetic precursors for preparation of oxazoles via dehydrogenation. Prior to the introduction of nickel peroxide[2] (NiO_2), however, no dehydrogenation of any Δ^2-oxazoline to its corresponding oxazole had ever been reported[3]. NiO_2 was shown to be effective for dehydrogenation of a wide variety of Δ^2-oxazolines (and Δ^2-thiazolines); however, it was found to be unsatisfactory for 5-aryl substituted Δ^2-oxazolines, with a maximum reported yield of only 2%.

In our recent research involving thiomicamine (*I*), we became interested in generating a series of 2,5-diaryloxazole-4-acetic acids (e.g., *IV*, R^1 = 4-$MeSC_6H_4$, R^2 = CH_2COOH, R^3 = Ph) for investigation as potential non-steroidal anti-inflammatory[4], hypolipidemic[5], hypoglycemic[6] or anticholesteremic[7] agents. As preservation of the methylthio moiety was desirable for enhanced pharmacological activity in the final products, "classic" oxazole syntheses involving oxidation of the benzylic hydroxy group (i.e., via intramolecular condensation of the α-benzamidopropiophenone derivative *II*) proved to be unsuitable, commonly resulting in oxidation to the sulfoxide/sulfone or in retro-aldol loss of formaldehyde[8].

* Current address: Special Testing and Research Laboratory, 7704 Old Springhouse Road, McLean, VA 22102-3494, U.S.A.

** Current address: Department of Chemistry, University of Vermont, Burlington, VT 05405, U.S.A.

We therefore began investigation into an alternate oxazoline dehydrogenation route. Herein, we report the successful dehydrogenation of a series of 2,5-diaryl substituted Δ^2-oxazolines using either Br_2/LiBr/$CaCO_3$ (1.05 : 2 : 3) or $CuBr_2$/LiBr/$CaCO_3$ (2 : 1 : 3) in refluxing *o*-dichlorobenzene.



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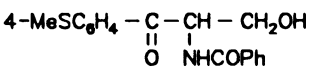


II

EXPERIMENTAL

Thiomicamine (*I*) was supplied by Zambon Farmaceutici S. P. A., Milano, Italy. Other Δ^2-oxazoline precursors were obtained from Aldrich and were used without further purification. All other chemicals utilized were reagent grade or better. The synthetic route to the Δ^2-oxazolines utilized in this study has been previously detailed[9].

Melting points were recorded on a Fisher–Johns melting point apparatus, and are uncorrected. Infrared spectra (wavelengths in cm^{-1}) were recorded on a Perkin–Elmer 727B and were calibrated using polystyrene. ^1H NMR were recorded at 300 MHz on a Bruker AM-300 WB NMR spectrometer and were calibrated using internal tetramethylsilane. Chemical shifts are given in ppm (δ-scale). Mass spectra were obtained at 70 eV on a Hewlett–Packard 5970 MSD interfaced with a Hewlett–Packard 5890 gas chromatograph equipped with a 15 m × 0.2 mm capillary column coated with 0.33 μm HP-1 (Hewlett–Packard). Helium was used as the carrier gas (linear velocity 60 cm/s). GC temperature conditions: injector 270 °C, column-initially 130 °C (1 min), programmed increase 8 °C/min to 240 °C. Thin layer chromatograms were run on unactivated Baker silica gel IB-F thin layer plates. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, U.S.A.

The following represents a typical reaction procedure using Br_2/LiBr/$CaCO_3$ (1.05 : 2 : 3).

4-(Cyanomethyl)-2-(4-fluorophenyl)-5-(4-methylthiophenyl)oxazole (IVc). Under nitrogen, 4-(cyanomethyl)-2-(4-fluorophenyl)-5-(4-methylthiophenyl)-Δ^2-oxazoline (*IIIc*) (2.5 g, 7.7 mmol) was dissolved in *o*-dichlorobenzene (250 ml) and LiBr (1.33 g, 15.3 mmol) and $CaCO_3$ (2.30 g, 23.0 mmol) suspended with vigorous stirring. The suspension was heated to reflux and 25 ml of the solvent was distilled off (for azeotropic removal of H_2O). The distillation column was replaced by a large reflux condenser and Br_2 (1.29 g, 8.0 mmol, 5% excess) dissolved in dry, nitrogen-saturated *o*-dichlorobenzene (25 ml) added over 10 s; a rapid color change from red-orange to green-brown was observed. After 2 min, TLC ($CHCl_3$) indicated complete conversion of *IIIc* to *IVc* (2,5-diaryloxazoles invariably displayed intense blue fluorescence under either 254 or 366 nm irradiation). The suspension was immediately cooled to 25 °C, the suspended salts removed by suction filtration, and the resulting brown-orange filtrate washed with H_2O (2 × 500 ml), dilute aqueous NH_4Cl (2 × 500 ml) and finally dried over anhydrous Na_2SO_4. Following high vacuum removal of the solvent (b.p. 55 – 75 °C at 13.3 Pa), the crude product was extracted with boiling cyclohexane (10 × 200 ml), the combined extracts evaporated to dryness on a rotary evaporator and the resulting solid recrystallized from cyclohexane–CCl_4 (5 : 1) to give pure *IVc* (2.16 g, 87%) as a crystalline yellow-orange powder, m.p. 139 – 141 °C. IR spectrum (KBr): 2 910 (m); 2 250 (w, C≡N); 1 600 (s); 1 490 (s); 1 415 (m); 1 220 (s); 1 155 (m); 1 095 (s); 845 (s); 735 (s). ^1H NMR spectrum ($CDCl_3$): 2.55 s, 3 H

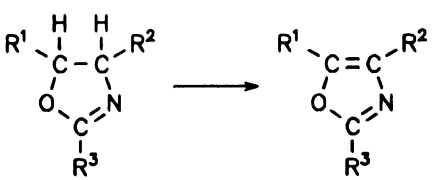
(SCH_3); 3.90 s, 2 H (CH_2CN); 7.15 – 8.20 m, 8 H (aromatic H). MS: M^+ calculated for $C_{18}H_{13}FN_2OS$: 324, found: 324.

Use of $CuBr_2$/LiBr/$CaCO_3$ (2 : 1 : 3) required a slightly longer reaction time (10 min), vigorous mechanical stirring (to keep the inorganic salts suspended) and more rigorous cleanup procedures (the crude product resulting from evaporation of the combined cyclohexane extracts was run through a short silica gel column). On 2.0 g scale, a final yield of 83% *IVc* was obtained.

The yields of the dehydrogenation of 2,5-diaryl-substituted Δ^2-oxazolines are given in Table I.

RESULTS AND DISCUSSION

Novel dehydrogenation of 2,5-diaryl-substituted Δ^2-oxazolines was developed and optimization studies were completed with 4-(cyanomethyl)-5-(4-methylthiophenyl)-2-phenyl-Δ^2-oxazoline *IIIa*. In agreement with the literature, only trace yields of the corresponding oxazole *IVa* resulted from attempted dehydrogenation of *IIIa* with N-bromosuccinimide, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, chloranil or similar "classic" dehydrogenation reagents. Furthermore, NiO_2, previously utilized successfully for dehydrogenation of a variety of Δ^2-oxazolines[2], and active γ-MnO_2, previously utilized successfully for dehydrogenation of a variety of isoxazolines[10], were similarly unsuccessful, giving only the corresponding sulfoxide of *IIIa*. In contrast, $CuBr_2$/LiBr (1 : 1) in refluxing CCl_4 or C_6H_6, previously utilized successfully for dehydrogenation of 2-cyclohexenones to phenols[11], gave approximately 2% yield of *IVa*.



III *IV*

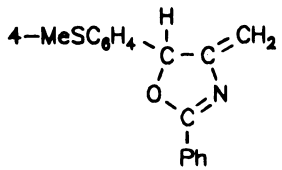
SCHEME 1

As no other reagent gave better than trace yields of *IVa*, a complete optimization study of the $CuBr_2$/LiBr reagent pair was undertaken. Significant improvements in overall yield were noted upon doubling the molar ratio of $CuBr_2$, adding an excess of an inorganic base ($CaCO_3$) to trap liberated HBr (noted to be deleterious in the dehydrogenation of 2-cyclohexenones to phenols[11]), using vigorous mechanical stirring and especially by using a non-nucleophilic, highly polar, high boiling halogenated aromatic solvent (*o*-dichlorobenzene). Following extensive variation of experimental parameters[9], *IVa* was eventually isolated in 58% yield ($CuBr_2$/LiBr/$CaCO_3$ (2 : 1 : 3), refluxing *o*-dichlorobenzene, 10 min).

Investigation into the possible role[12] of $CuBr_2$ suggested its substitution with Br_2; following additional variations utilizing Br_2, *IVa* was eventually isolated in 54% yield (Br_2/LiBr/$CaCO_3$ (1.05 : 2 : 3), refluxing *o*-dichlorobenzene, 2 min). The results

suggest that $CuBr_2/LiBr$ acts as an in situ source of molecular Br_2. Although either reagent combination was nearly equally effective, Br_2 was favored by virtue of a cleaner product workup, while $CuBr_2$ appeared to be a somewhat more "gentle" reagent giving a slower generation of a lower, steady state concentration of Br_2. Substitution of $CuCl_2$ for $CuBr_2$ or Cl_2 (or I_2) for Br_2 gave only trace yields and/or complex mixtures. (For a related dehydrogenation reaction utilizing $CuCl_2$, see ref.[13].)

Following completion of the optimization study, the general applicability of the reaction methodology was investigated (Table I). Although the data base is quite limited, it appears that both the presence of a 4-alkyl substituent (R^2) and electron lone pair donating substituents in both aromatic rings are important for obtaining high yields. In the two simplest substrates *IIIf* and *IIIg*, the principal reaction products are phenylbrominated oxazolines (no further reaction optimization was attempted for either *IIIf* or *IIIg*. Additional substrates analogous to *IIIa* (not reported in Table I) with good leaving groups located at the α-position of the 4-methyl substituent (e.g., R^2 = CH_2OH, CH_2OMs, CH_2OAc, CH_2F, CH_2Cl, CH_2Br or CH_2I) primarily undergo elimination to the methylidene compound *V* under the reaction conditions, generating (after allylic rearrangement) the 4-methyl substituted oxazole *IV*, R^1 = 4-$MeSC_6H_4$, R^2 = Me, R^3 =



V

TABLE I
Dehydrogenation of 2,5-diaryl substituted Δ^2-oxazolines *III* to oxazoles *IV*

Δ^2-Oxazoline	R^1	R^2	R^3	Oxazole yield[a], %
IIIa	4-$MeSC_6H_4$	CH_2CN	Ph	54
IIIb	4-$MeSC_6H_4$	CH_2OCOPh	Ph	40[b,c]
IIIc	4-$MeSC_6H_4$	CH_2CN	4-FC_6H_4	87
IIId	4-$MeSC_6H_4$	CH_2CN	2,4-$Cl_2C_6H_3$	79
IIIe	4-$MeSC_6H_4$	CH_2CN	2-thienyl	74
IIIf	Ph	Me	Ph	27[c]
IIIg	Ph	H	Ph	12[c]

[a] All reaction yields (except *IVb*) from reaction using $Br_2/LiBr/CaCO_3$ (1.05 : 2 : 3); listed yields are of isolated, recrystallized products. All compounds were fully characterized by ^1H NMR, IR and GC-MS, and gave satisfactory elemental analyses; [b] from reaction using $CuBr_2/LiBr/CaCO_3$ (2 : 1 : 3); [c] reaction at 140 °C.

Ph. In addition, substrates with various arylamino substituents in the 2 position (i.e., R^3 = NHC_6H_4X or $NHC_6H_3X_2$) give highly complex mixtures containing only trace amounts of the corresponding oxazoles. Finally, substrates containing methylsulfinyl groups (i.e., R^1 = 4-$MeSOC_6H_4$) are preferentially oxidized to complex mixtures containing (after workup) the corresponding sulfones and α-bromomethylsulfinyl compounds (i.e., R^1 = 4-$BrCH_2SOC_6H_4$).

In summary, the described methodology is highly successful for dehydrogenation of various 2,5-diaryl substituted Δ^2-oxazolines, especially those with electron donating substituents in the aromatic rings. This is not a serious practical limitation, however, since nearly all of the known pharmacologically active 2,5-diaryloxazole-4-acetic acids in fact have such substituents[4-7]. The most serious limitation appears to be the sensitivity towards leaving groups located in the α position on the 4-alkyl moiety (R^2).

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