organic layer was evaporated. The residue was crystallized from AcOEt/hexane to give 2.6 g (61%) of product **4**: mp 178–179 °C; ir (Nujol) 3250, 3180, 1635, 1545, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 9 H), 3.33 (d, J = 5 Hz, 3 H/singlet after exchange), 6.5 (s, ex, 1 H), 7.0 (s, broad, 1 H), 7.35 (s, broad, 2 H).

Anal. Calcd for $C_{13}H_{17}ClN_2OS$: C, 54.83; H, 6.02; N, 9.83. Found: C, 54.94; H, 6.07; N, 9.56.

6-Chloro-1,3-dihydro-3-methyliminobenzo[*c*]thiophen-1-ol (5). A solution of 2.8 g (15 mmol) of thioamide **1a** in THF was lithiated as described for **3**. After cooling to −70 °C, 5.48 g (75 mmol) of dimethylformamide was added and the reaction mixture stirred to room temperature for 18 h. The reaction mixture was quenched with water, washed with NaH_2PO_4 buffer, and dried over Na_2SO_4. Evaporation of the organic layer gave a residue that crystallized from ether/hexane, 2.45 g (76.5% yield) of compound **5**: mp 175–178 °C; ir (Nujol) 3230, 1585, 1303, 820 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) δ 3.38 (s, 3 H), 5.82 (s, 1 H), 6.80 (b, 1 H, ex), 7.33–7.91 (m, 3 H); MS m/e 213 (M^+).

Anal. Calcd for C_9H_8ClNOS: C, 50.59; H, 3.87; N, 6.57. Found: C, 50.64; H, 3.83; N, 6.42.

5-Chloro-3-methylphthalide (9). A solution of 2.8 g (15 mmol) of thioamide **1a** in THF was lithiated as described for **3**. After cooling to −70 °C, a solution of 750 mg (17 mmol) of acetaldehyde in 5 ml of THF was added. After stirring at room temperature for 18 h the mixture was quenched with water, washed with brine, and dried over Na_2SO_4. The residue from the organic layer, 3.5 g of compound **6**, was an oil: NMR ($CDCl_3$) δ 1.28 (d, 3 H), 3.1 (s, 3 H), 4.65–5.1 (m, 1 H), 7.02–7.68 (m, 3 H), 8.8 (b, 1 H, ex). It was dissolved in 25 ml of ethanol and 15 ml of 5.0 N HCl and refluxed for 24 h. The reaction mixture was evaporated and the residue partitioned between brine and ether. The residual oil from the ether layer crystallized from ether–hexane to give 1.86 g (68%) of compound **9**: mp 94–96 °C; ir (CH_2Cl_2) 1765, 1620, 1055 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (d, 3 H), 5.57 (q, 1 H), 7.40–8.0 (m, 3 H).

Anal. Calcd for $C_9H_7ClO_2$: C, 59.20; H, 3.86. Found: C, 59.07; H, 4.11.

4-Methoxy-2-methylthio-*N*-methylthiobenzamide (8). A solution of 1.36 g (7.5 mmol) of thioamide **1c** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise and stirred for 8.5 h at room temperature. The reaction mixture was recooled in an ice bath and 800 mg (8.5 mmol) of methyl disulfide added. The mixture was stirred at 25 °C for 18 h, quenched with water, washed with brine, dried, and evaporated to give an oil residue. Crystallization from ether gave compound **8**: 1.32 g (77.6%); mp 79–81 °C; ir (CH_2Cl_2) 3395, 1592, 1351, 1040 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.29 (d, 3 H), 3.81 (s, 3 H), 6.58–7.66 (m, 3 H), 7.95 (b, 1 H, ex).

Anal. Calcd for $C_{10}H_{13}NOS_2$: C, 52.86; H, 5.77; N, 6.17. Found: C, 53.06; H, 5.76; N, 6.14.

***N*-Methyl-2-trimethylsilylthiobenzamide (7).** A solution of 1.13 g (7.5 mmol) of thioamide **1b** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After stirring for 4.0 h at 0 °C the reaction mixture was cooled to −70 °C and 920 mg (8.5 mmol) of chlorotrimethylsilane added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with brine, dried, and evaporated to give a crystalline residue. Recrystallization from ether–hexane gave 640 mg (48.5%) of compound **7**: mp 121–123 °C; ir (CH_2Cl_2) 3375, 1508, 1340, 828 cm^{-1}; NMR ($CDCl_3$) δ 0.30 (s, 9 H), 3.24 (d, 3 H), 7.25–7.70 (m, 4 H), 8.15 (b, 1 H, ex).

Anal. Calcd for $C_{11}H_{17}NSSi$: C, 59.14; H, 7.67; N, 6.27. Found: C, 59.06; H, 7.93; N, 6.23.

***o*-[(2-Hydroxy-2-adamantanyl)methyl]-*N*-methylthiobenzamide (11).** A solution of 1.24 g (7.5 mmol) of thioamide **10** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After 15 min at 0 °C, a solution of 1.2 g (8 mmol) of 2-adamantanone in 5 ml of THF was added. After 18 h at 25 °C the reaction mixture was quenched with water, washed with brine, dried, and evaporated to give a crystalline residue. Recrystallization from ether gave 2.11 g (89.4%) of compound **11**: mp 172–175 °C; ir (Nujol) 3370, 3190, 1555, 755 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.35 (m, 14 H), 2.98 (s, 2 H), 3.20 (d, 3 H), 6.82–7.81 (m, 5 H; 1 H, ex), 9.95 (b, 1 H, ex).

Anal. Calcd for $C_{19}H_{25}NOS$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.55; H, 7.93; N, 4.27.

***N*-Methylthio-*o*-toluamide (10).** A solution of o-tolyllithium was prepared from 17.1 g (0.1 mol) of o-bromotoluene and 1.4 g of lithium wire in 75 ml of ether. This solution was then cooled to −78 °C, diluted with 75 ml of dry THF, and then a solution of 7.3 g (0.1 mol) of methyl isothiocyanate in 10 ml of THF was added at once. The cold bath was removed and the reaction mixture stirred at ambient temperature for 4 h. Workup with cold water, then brine, provided 13.0 g of a dark oil which was crystallized from ether to give 6.1 g of **10**, mp 76–78 °C.

Anal. Calcd for $C_9H_{11}NS$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.83; H, 6.78; N, 8.19.

The thioamides **1a–c** were prepared analogously.

4-Methoxy-β-methylamino-2-methylthiocinnamic Acid Methyl Ester (13). A solution of 500 mg (2.2 mmol) of thioamide **8** in 10 ml of dry THF was cooled to −70 °C under N_2. Then 1.5 ml (2.4 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After 15 min, a solution of 340 mg (2.2 mmol) of methyl bromoacetate in 2 ml of THF was added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with $NaHCO_3$ solution (twice) and brine, dried, and evaporated to give 590 mg of compound **12**: NMR ($CDCl_3$) δ 2.42 (s, 3 H), 3.03 (s, 3 H), 3.32–3.88 (m, 2 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 6.50–7.35 (m, 3 H). To a solution of this residue in 20 ml of xylene, 2.07 g (7.89 mmol) of triphenylphosphine was added and refluxed for 24 h. The solvent was evaporated and the residue chromatographed over 15 g of silica gel set in hexane. Compound **13**, 160 mg (31%) of a solid, was eluted with benzene. Recrystallization from ether afforded the analytical sample: mp 100–102 °C; ir (CH_2Cl_2) 3300, 1645, 1595, 1170 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.67 (d, 3 H), 3.65 (s, 3 H), 3.82 (s, 3 H), 4.52 (s, 1 H), 6.57–7.29 (m, 3 H), 8.50 (b, 1 H, ex); MS m/e 267 (M^+); uv (CH_3OH) 216 nm (ϵ 20 870), 293 (19 740).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.65; H, 6.33; N, 4.91.

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Registry No.—**10**, 60253-37-4; **11**, 60253-38-5; **12**, 60253-39-6; **13**, 60253-40-9; 2-adamantanone, 700-58-3; o-tolyllithium, 6699-93-0; methyl isothiocyanate, 556-61-6; methyl bromoacetate, 590-97-6.

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The Chemistry of Carbanions. 29. The Nature of the Enolate Formed by Addition of Lithium Dimethylcuprate to Enones[1]

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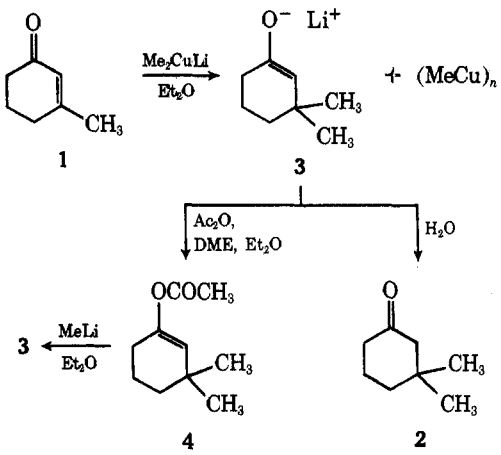
The conjugate addition of lithium diorganocuprates to α,β-unsaturated carbonyl compounds[2] produces, prior to hydrolysis, an intermediate with the properties of a metal enolate. Thus, reaction of this intermediate with Ac_2O yields an enol acetate,[3] reaction with Me_3SiCl yields a trimethylsilyl enol ether,[4] and reaction with a $ClPO(OEt)_2$ yields an enol phosphate.[5] Furthermore, this reaction intermediate reacts with carbonyl compounds to give aldol products,[6] with Michael acceptors to form Michael adducts,[7] and with reactive alkyl halides to form alkylated ketones.[4b,8] This reaction intermediate has been variously formulated as a lithium enolate,[2b] a copper(I) enolate,[7,8a,b] or as a species with the copper

bound either to the α carbon atom or to both the oxygen atom and the C=C of the enolate.[3b]

Several observations led us to believe that these reaction intermediates were best formulated as lithium enolates rather than copper derivatives. The addition of 1 equiv of the *soluble* copper(I) derivative $(n\text{-}Bu_2S)_2CuI$ to a solution of the enolate $PhC(OLi)=CH_2$ did not alter the reactivity of this enolate in a Michael reaction.[9] Also, the addition of 1 equiv of the same *soluble* copper(I) derivative did not alter the ^1H NMR spectrum of the lithium enolate $PhC(OLi)=CHCl$.[10] Furthermore, in typical reactions of lithium dialkylcuprates (e.g., Me_2CuLi) with enones, the reaction is accompanied by precipitation of the *insoluble* alkylcopper(I) derivative [e.g., $(MeCu)_n$] suggesting that the copper does not remain in solution with the intermediate enolate. However, all of the above observations leave some ambiguity about the nature of the reaction intermediate and yet this reaction intermediate is attaining increasing importance as a synthetic intermediate.[3-8] Consequently, it was clearly desirable to provide unambiguous information concerning this intermediate.

To provide this information in a typical reaction, the enone 1 was added to an Et_2O solution containing 1 equiv of Me_2CuLi. The resulting slurry was centrifuged to separate about 75% of the reaction mixture, a colorless, supernatant liquid, from the lower portion of the reaction mixture which contained all the yellow $(MeCu)_n$ precipitate. Analysis of aliquots of each portion of the reaction mixture indicated that more than 99% of all the copper employed in the reaction was in the lower portion containing the $(MeCu)_n$ precipitate. A second aliquot of the supernatant solution exhibited ^{13}C NMR absorption corresponding to an Et_2O solution of a lithium enolate.[11] After the remaining supernatant solution had been hydrolyzed, the amount of ketone 2 isolated corresponded to a 66% yield of this product from the supernatant solution.



In another experiment, the total reaction mixture from the enone 1 and Me_2CuLi was added to excess Ac_2O to form the expected[3] enol acetate 4 in 76% yield. Reaction of this enol acetate 4 with an ethereal solution containing 2 equiv of MeLi afforded an Et_2O solution of the lithium enolate 3 whose ^{13}C NMR spectrum corresponded to the spectrum of the solution obtained from the cuprate reaction. Therefore, it is clear that conjugate addition of ethereal Me_2CuLi to the enone 1 forms the lithium enolate 3 and not some other intermediate in which the enolate is associated with a copper(I) species. It is very probable that the same conclusion applies to any conjugate addition of a cuprate reagent R_2CuLi that yields a soluble metal enolate along with an insoluble RCu product. Even in cases where the organocopper product RCu remains in the reaction solution, our earlier NMR and reactivity studies[9,10] offer no evidence to support the view that lithium enolates interact with soluble copper(I) species to form copper(I) enolates.

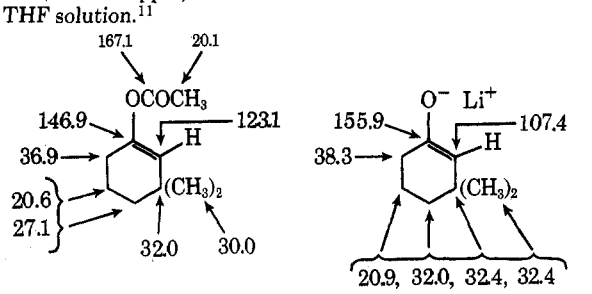
Experimental Section[12]

Preparation of the Enol Acetate 4 and the Lithium Enolate 3. After a solution of Me_2CuLi, prepared from 9.64 g (46.9 mmol) of Me_2SCuBr in 25 ml of Me_2S and 53 ml of an Et_2O solution containing 93.8 mmol of halide-free MeLi, had been stirred at 27 °C for 5 min, a solution of 3.93 g (35.8 mmol) of the enone 1 in 12 ml of Et_2O was added dropwise and with stirring during 10 min. The resulting mixture [containing solid $(MeCu)_n$] was stirred for 20 min and then added with stirring to a solution of 18.3 g (179 mmol) of freshly distilled Ac_2O in 35 ml of DME. After the resulting slurry had been stirred at 27 °C for 30 min, it was partitioned between pentane and saturated aqueous $NaHCO_3$ and the organic phase was separated, dried, and concentrated. After an aliquot of the crude product had been mixed with a known weight of *t*-BuPh, analysis (GLC, Carbowax 20M on Chromosorb P) indicated the presence of *t*-BuPh (retention time 3.8 min) and the enol acetate 4 (8.8 min, calculated yield 96%); neither the enone 1 (16.5 min) nor the ketone 2 (6.5 min) was detected in the GLC analysis. Distillation of the crude product separated 4.54 g (75.5%) of the enol acetate 4 as a colorless liquid: bp 35–37 °C (0.4 mm); $n^{25}D$ 1.4500; ir (CCl_4) 1754 (ester C=O) and 1689 cm^{-1} (C=C); uv (95% EtOH), end absorption with ϵ 1580 at 210 nm; NMR (CCl_4) δ 5.05 (1 H, broad, vinyl CH), 1.2–2.3 (9 H, m, aliphatic CH including a CH_3CO singlet at 1.99), and 1.02 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 168 (M^+, 5), 126 (12), 111 (100), 55 (13), 43 (30), and 41 (11).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.58.

To obtain an authentic sample of the enolate 3, 678 mg (4.04 mmol) of the enol acetate 4 was added, dropwise and with stirring, to 5.02 ml of a cold (10 °C) Et_2O solution containing 8.88 mmol of halide-free MeLi. After the resulting pale yellow solution had been stirred at 20 °C for 5 min, a 2.3-ml aliquot was mixed with 0.2 ml of Me_4Si and 0.2 ml of C_6D_6 (to provide a "lock" signal) and the natural abundance ^{13}C NMR signal was determined. For comparison the natural abundance ^{13}C NMR spectrum of the enol acetate 4 was also determined in Et_2O containing Me_4Si and C_6D_6. These ^{13}C NMR spectra (assignments consistent with off-resonance decoupling measurements and previous[11] analogous measurements) are summarized in the following structures. The ^{13}C NMR spectrum of the enolate 3 also exhibited a peak at 35.0 ppm attributable[11] to the Me groups of *t*-BuOLi; the second ^{13}C NMR signal for this material was not resolved from the Et_2O peak at 65.8 ppm.

It will be noted that the chemical shift difference ($\Delta\delta$) between the α-carbon atoms of the enol acetate 4 and the lithium enolate 3 in an Et_2O solution is 15.7 ppm, a value considerably smaller than the $\Delta\delta$ values (21.5–25.5 ppm) observed for similar lithium enolates in DME or THF solution.[11]



Reaction of the Enone 1 with Me_2CuLi. To 5.00 g (24.3 mmol) of Me_2SCuBr was added, dropwise with stirring and cooling to 18–20 °C, 27.5 ml of an Et_2O solution containing 48.7 mmol of halide-free MeLi. The enone 1 (2.55 g or 23.2 mmol) was added to this solution of Me_2CuLi dropwise and with stirring during 15 min. The reaction mixture, from which yellow $(MeCu)_n$ began to precipitate within a few seconds after addition of the enone began, was stirred at 20–25 °C for 20 min and then centrifuged. The colorless supernatant solution (23.2 ml) was separated and the residue [a mixture of solid $(MeCu)_n$ and the remaining reaction solution] was quenched in dilute aqueous HNO_3. Analysis of an aliquot of this aqueous solution by electrodeposition indicated the total copper content of the residue to be 24.3 mg-atoms. Three 1.00-ml aliquots of the supernatant solution were each quenched in dilute aqueous HNO_3 and then analyzed by electrodeposition; from these analyses, the copper content of the total supernatant solution was found to be 0.047 mg-atom. A 2.00-ml aliquot of the supernatant solution was mixed with 0.2 ml of C_6D_6 and 0.2 ml of Me_4Si in order to determine the ^{13}C NMR spectrum. This spectrum exhibited peaks corresponding to Et_2O (15.4 and 65.8 ppm), Me_2S (17.9 ppm), and to the previously described enolate 3. The positions of the "carbonyl" carbon and α-carbon ^{13}C signals of this en-

olate (156.2 and 105.4 ppm) differed slightly from the spectrum of the enolate 3 described above, reflecting the facts that the concentrations of the two solutions were different and that one solution contained an equimolar amount of *t*-BuOLi while the other solution contained equimolar amounts of LiBr and Me_2S. However, in all other respects, the two enolate ^{13}C NMR spectra were the same.

The remaining 18.2-ml aliquot of the supernatant liquid was partitioned between aqueous $NaHCO_3$ and pentane. After the organic layer had been dried and concentrated, distillation of the residual liquid separated 1.51 g (corresponding to a 66% yield of ketone 2 in the supernatant solution) of the pure (GLC) ketone 2 as a colorless liquid, bp 47–49 °C (5 mm), $n^{25}D$ 1.4454 [lit.[13] bp 74–74.5 °C (16 mm), $n^{25}D$ 1.4458], that was identified with an authentic sample[13] by comparison of ir and NMR spectra.

Registry No.—1, 1193-18-6; 2, 2978-19-3; 3, 57074-02-9; 4, 54200-64-5; Me_2CuLi, 15681-48-8.

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(12) All boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
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Organocopper Intermediates. Synthesis of 2-Isoxazoline *N*-Oxides and Cyclopropanes

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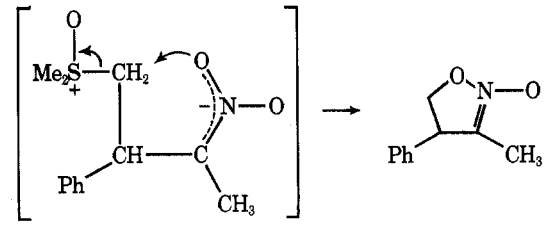
We had as a synthetic objective the preparation of the cyclopropane derived from β-methyl-β-nitrostyrene. Since palladium-catalyzed cyclopropanation has been effective for olefins bearing electron-withdrawing groups, this route was evaluated.[2] Upon treatment of the styrene with diazomethane and palladium nitrate, 60% of the starting material was recovered and there was no evidence of cyclopropane formation. An alternative route, employing a Me_2SO-derived ylide, was then investigated. Treatment of β-methyl-β-nitrostyrene with dimethylsulfoxonium methylide led to the immediate precipitation of an amorphous solid.[3,4] Noting that a transient red color appeared during this reaction and that electron transfer processes often display this behavior,[5] it was considered that the electron-donating characteristics of the ylide might be altered by complexation with copper.[6] Thus, the ylide was prepared in the usual fashion and a copper halide was then added. In dimethylformamide (DMF), with copper(I) iodide, the reagent was red-brown; in methyl sulfoxide (Me_2SO) the same halide resulted in an intense orange-pink color.[7] Because of greater solubility, Me_2SO was typically employed as the solvent. Upon addition of the styrene to the ylide–copper complex no precipitate was formed and after 2 h the products were isolated and purified. Instead of finding the cyclopropane, we identified the product as a 2-isoxazoline



N-oxide. A likely intermediate in its formation is the ylide adduct, which O-alkylates instead of closing to form the cyclopropane.[8] To determine the generality of this reaction, other unsaturated compounds were treated with copper–ylide complexes (Table I).

The reaction has greater significance as a synthetic approach to 2-isoxazoline *N*-oxides than to cyclopropanes. The cyclopropanation yield from benzalacetophenone is comparable to that reported from the ylide without the use of copper.[3] By contrast, there is no cyclopropanation of ethyl cinnamate in the presence of the copper reagent.[3b,c] The yields from the α,β-unsaturated ester and ketones are lower than those obtained using (dimethylamino)methyloxosulfonium methylide.[3d]

The experimental results are consistent with the relationship between product formation and polarographic reduction potential reported initially by House.[9] In this study, compounds having reduction potentials less negative than −1.8 V vs. SCE react with the ylide–copper complex whereas compounds with reduction potentials more negative than −1.8 V vs. SCE are recovered unchanged. Thus, the utility of this reaction lies in those applications in which derivatives are desired of compounds having low reduction potentials.

Experimental Section

Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 710 infrared spectrometer. Proton magnetic resonance spectra were recorded on a Varian A-60A spectrometer using Me_4Si as the internal standard. The carbon-13 magnetic spectra were obtained with a Varian CFT-20. The mass spectrum was recorded on a Perkin-Elmer RMU7, ionizing voltage 70 and 10 eV.

3-Methyl-4-phenyl-2-isoxazoline *N*-Oxide. To 250 ml of dry deoxygenated (N_2) DMF were added 12.8 g (58.2 mmol) of trimethylsulfoxonium iodide and 2.6 g (50% in oil, 55 mmol) of sodium hydride. After stirring for 2 h, 3.00 g (15.8 mmol) of copper(I) iodide was added. Upon stirring for 0.5 h, during which the color changed from gray to red-brown, the solution was cooled in an ice bath and 8.00 g (49.2 mmol) of β-methyl-β-nitrostyrene dissolved in 60 ml of DMF was added dropwise over the course of 20 min. After addition was complete, the ice bath was removed. After stirring for 2 h, ice water was added, the organic products were extracted with methylene chloride, and 6.4 g (74%) of crude 3-methyl-4-phenyl-2-isoxazoline *N*-oxide was isolated, mp 45–54 °C. Recrystallization from anhydrous ethanol resulted in 5.6 g (64%) of the purified product: mp 63–64 °C; NMR (CCl_4) δ 1.82 (d, 3 H, CH_3), 4.12–4.93 (m, 3 H, CH and CH_2),