namate to the α,β-unsaturated ketone was accomplished by the addition of 0.55 equiv of n-Bu_2CuLi. Addition of 2 equiv of n-Bu_2CuLi converted 2-pyridyl cinnamate to the saturated ketone, resulting from conjugate addition of n-Bu_2CuLi to the α,β-unsaturated ketone.

The present method offers advantages over other reported methods with respect to (i) lower cost of 2-hydroxypyridine over 2-mercaptopyridine, (ii) stability of 2-pyridyl esters over other carboxylic acid derivatives used for the ketone synthesis, (iii) the functional group specificity, (iv) an efficient high-yield ketone synthesis, and (v) the mildness of the reaction conditions.

Reaction of organocuprate reagents with 2-pyridyl esters thus appears to be a highly useful method for the synthesis of ketones.

Experimental Section[13]

The following experiments illustrate the procedures utilized.

General Procedure for Preparation of 2-Pyridyl Esters. Phosgene (60 mmol) was dissolved in a mixture of toluene (20 mL) and methylene chloride (20 mL) at −20 °C. A solution of 2-hydroxypyridine (1.14 g, 12 mmol) and triethylamine (1.28 g, 12.6 mmol) in methylene chloride (40 mL) was added dropwise over 30 min. The resulting solution was stirred for 20 min at −20–0 °C. The excess phosgene and solvents were removed under reduced pressure, and the residue was dissolved in methylene chloride (30 mL). A solution of benzoic acid (1.22 g, 10 mmol) and triethylamine (1.06 g, 10.5 mmol) in methylene chloride (20 mL) was poured into the stirred solution of 2-pyridyl chloroformate in methylene chloride at 0 °C. After the mixture was stirred for 30 min, 4-(dimethylamino)pyridine (245 mg, 2 mmol) was added, and the resulting solution was stirred at room temperature for 1 h. The solution was washed with 10% $NaHCO_3$ (20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$. The product (1.83 g, 92%, pure by NMR and TLC) was isolated on solvent removal under vacuum. The product could be recrystallized from hexane–cyclohexane to afford 2-pyridyl benzoate; mp 40–41 °C (lit.[6] mp 41–42 °C); ^1H NMR ($CDCl_3$) δ 7.1–7.7 and 8.0–8.4 (m); IR (KBr) 1740 cm^{-1}.

General Procedure for Preparation of Ketones. Lithium di-n-butylcuprate was prepared by addition of n-butyllithium (1.5 M, 2.7 mL, 4.1 mmol) in hexane to cuprous iodide (398 mg, 2.1 mmol) in diethyl ether (5 mL) at −30 °C under nitrogen. To a solution of lithium di-n-butylcuprate in diethyl ether–hexane at −78 °C under nitrogen was added a solution of 2-pyridyl benzoate (400 mg, 2 mmol) in diethyl ether (5 mL). After being stirred for 30 min at −78 °C, the reaction mixture was quenched with 10% NH_4Cl (0.5 mL). The reaction mixture was allowed to attain room temperature, poured into 10% NH_4Cl (20 mL), and extracted with methylene chloride (30 mL) three times. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum. The crude product was purified by filtration through a short column of silica gel by using methylene chloride as an eluant to afford valerophenone (307 mg, 95%) as a colorless oil.

Acknowledgment. We are grateful to the Korea Science and Engineering Foundation for financial support.

Registry No. C_6H_5COOH, 65-85-0; $CH_3CH_2CH_2COOH$, 107-92-6; $(CH_3)_2CHCOOH$, 79-31-2; $(CH_3)_3CCOOH$, 75-98-9; $C_6H_5COCH_2CH_2COOH$, 2051-95-8; $MeOOC(CH_2)_4COOH$, 627-91-8; $Br(CH_2)_5COOH$, 4224-70-8; $C_6H_5CH{=}CHCOOH$, 621-82-9; C_6H_5COO-2-Py, 5005-35-6; $CH_3CH_2CH_2COO$-2-Py, 19337-30-5; $(CH_3)_2CHOO$-2-Py, 86014-54-2; $(CH_3)_3CCOO$-2-Py, 59658-05-8; $C_6H_5COCH_2CH_2COO$-2-Py, 86014-55-3; $MeOOC(CH_2)_4COO$-2-Py, 86014-56-4; $Br(CH_2)_5COO$-2-Py, 86014-57-5; $C_6H_5CH{=}CHCOO$-2-Py, 86014-58-6; Me_2CuLi, 15681-48-8; n-Bu_2CuLi, 24406-16-4; $(t\text{-}Bu)_2CuLiPBu_3$, 24743-96-2; C_6H_5COMe, 98-86-2; C_6H_5CO-n-Bu, 1009-14-9; C_6H_5CO-t-Bu, 938-16-9; $CH_3CH_2CH_2CO$-n-Bu, 589-63-9; $(CH_3)_2CHCO$-n-Bu, 13019-20-0; $(CH_3)_3CCO$-n-Bu, 19078-97-8; $C_6H_5COCH_2CH_2COMe$, 583-05-1; $C_6H_5COCH_2CH_2CO$-n-Bu, 77588-52-4; $MeOOC(CH_2)_4CO$-n-Bu, 61820-00-6; $Br(CH_2)_5CO$-n-Bu, 53174-50-8; $C_6H_5CH{=}CHCO$-n-Bu, 4071-84-5; 2-hydroxypyridine, 72762-00-6; phosgene, 75-44-5; 2-pyridyl chloroformate, 86014-59-7; mesitoic acid, 480-63-7; 2-pyridyl mesitoate, 63540-63-6; 2-acetyl-1,3,5-trimethylbenzene, 1667-01-2; 1-(2,4,6-trimethylphenyl)-1-pentanone, 23351-71-5; 7-phenylundecan-5-one, 30242-38-7.

(13) ^1H NMR spectra were recorded in CCl_4 with a Varian T-60A spectrometer, unless otherwise specified. Chemical shifts are expressed as δ units relative to tetramethylsilane. Infrared spectra were determined as a neat film on a Perkin-Elmer Model spectrometer 267 unless otherwise specified, and the frequencies are given in reciprocal centimeters. Melting points were taken on an electrothermal apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated silica gel glass plates (0.25 mm, 60F-254, E. Merck), and silica gel (activity III, 04526, ICN) was used for column chromatography.

Synthesis and Chemistry of 2-(Arylthio)oxazolines†

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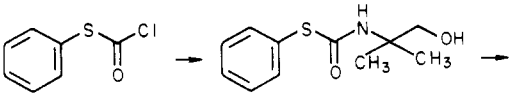
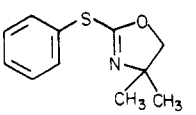
It is well-known that an oxazoline group directly attached to an aromatic nucleus is useful in directing ortho lithiation.[1] In contrast, the effectiveness of the oxazoline functionality in directing metalation reactions when separated from a phenyl group by one or more atoms has scarcely been addressed. In the case of a one-carbon-atom separation (2-benzyl-4,4-dimethyloxazoline), only benzylic lithiation occurs.[2] The introduction of a heteroatom joining the oxazoline to the phenyl ring would remove the competing metalation reaction and allow the assessment of the more distant directing effect, assuming the heteroatom did little to direct metalation itself. Divalent sulfur seemed to offer the desired properties for the connecting unit as it was inefficient in directing ring metalation in thioanisole and thiophenetole.[3] Furthermore, the selectivity of ortho over meta and para metalation was not very good. With diphenyl sulfide the ortho selectivity was better, but the overall yield was still somewhat low.[4] In this report, we describe a convenient synthesis of the previously unknown 2-(arylthio)-4,4-dimethyloxazolines and present some novel reactions of 2-(phenylthio)-4,4-dimethyloxazoline (1) with organolithium reagents.

Results and Discussion

The initial approach to 1 was based on Meyers' oxazoline synthesis.[5] Thiophenyl chloroformate[6] reacted with 2-amino-2-methylpropanol to give 2 in only 21% isolated



2



1

yield. Cyclization of 2 was effected by the standard conditions[5] to afford 1 in 66% yield. Because of the low

† Contribution No. 3148.

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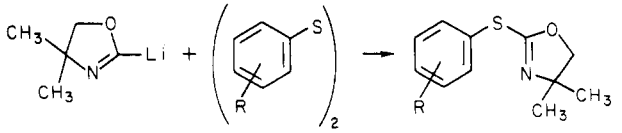
Table I. Synthesis of 2-(Arylthio)-4,4-dimethyloxazolines



R	product (yield, %)[a]
H	1 (69)
4-CH_3	4 (40)
4-Cl	5 (53)
3,4-Cl_2	6 (33)
2-Br	7 (39)
2-CH_3, 4-Cl	8 (24)

[a] All yields are for chromatographed product. Except for 1, yields are not optimized.

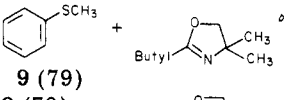
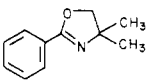
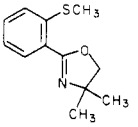
overall yield[7] for this sequence, an alternative synthesis was desired.

The ready availability of 4,4-dimethyloxazoline (3) from inexpensive reagents made it an ideal starting material,[8] but the chemistry of the lithium salt of 3 was not at all predictable since it can behave as either an oxazoline anion or an isonitrile alkoxide.[9] However, when 3 was reacted sequentially with *n*-butyllithium at 0 °C and diphenyl disulfide at reflux in glyme, it cleanly gave 1. A solvent that boils at least as high as glyme was required since little 1 was formed at lower temperatures. (For example, even after prolonged heating in tetrahydrofuran (THF), less than 10% of 1 was formed.) Several 2-(arylthio)-4,4-dimethyloxazolines prepared by this procedure are shown in Table I.

n-Butyllithium reacted with 1 in THF at −78 °C to give thioanisole (9) in 79% yield after quenching with methyl iodide (Table II). The other product is presumably 2-butyl-4,4-dimethyloxazoline, but it was not isolated. The addition of tetramethylethylenediamine (TMEDA) did not alter the outcome of this experiment. Phenyllithium behaved similarly, affording after methylation 2-phenyl-4,4-dimethyloxazoline (10) and 9 in 66% and 70% respective yields. When the methyl iodide quench was omitted, the side product, thiophenol, could be washed away in the workup, providing a facile route to phenyloxazolines that nicely complements Meyers' synthesis.[5]

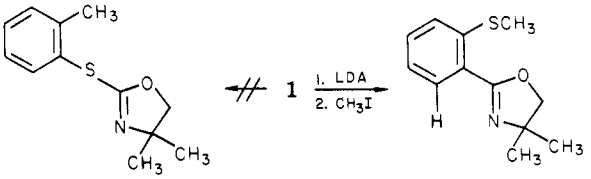
The *n*-BuLi and PhLi reactions with 1 appear to involve straightforward nucleophilic carbanion attack on the oxazoline ring. That phenyllithium reacted at all with 1 was somewhat surprising in light of a recent report that aryl Grignard reagents required a nickel catalyst to react with 2-(methylthio)-4,4-dimethyloxazoline.[9] In agreement with this observation, only starting material was recovered from the reaction of 1 with phenylmagnesium bromide. The present work demonstrates that no catalyst is required if the nucleophile is changed from a Grignard reagent to an organolithium species.

Table II. Reaction of 1 with Organometallic Reagents

reagent	products[a] (isolated yield, %)
n-BuLi	 9 (79)
PhLi	9 (70) +  10 (66)
PhMgBr	no reaction
LDA	 11 (76)
t-BuLi	9 (46) + 10 (31)

[a] Products were isolated after quenching with methyl iodide. [b] Not isolated.

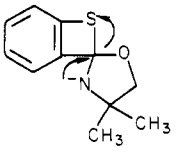
The reaction of 1 with lithium diisopropylamide (LDA) was quite different. At −78 and 0 °C, only 1 was recovered after workup with methyl iodide; however, when 1 and LDA were refluxed in THF followed by methylation, a new product (11) was obtained in 76% yield.[10] That 11 was



12 11

the rearrangement product and not the desired product 12 was suggested from its NMR spectrum, which showed H as a doublet of doublets centered at δ 7.78. In comparison, the ortho protons in 1 resonate as a multiplet centered at δ 7.6. Conclusive proof for 11 was obtained when the product was hydrolyzed to the known 2-(methylthio)benzoic acid in 85% yield.[11]

Apparently with a nonnucleophilic base, the oxazoline group effectively directs ortho lithiation, although the resulting anion rapidly rearranges. The susceptibility of the oxazoline ring in 1 to nucleophilic attack suggests that the rearrangement proceeds via 13, although other possibilities cannot be excluded at this time.



13

n-Butyllithium lithiated 11 at 0 °C to give 2-(2-butylphenyl)-4,4-dimethyloxazoline, the product of nucleophilic substitution. This is analogous to the chemistry observed with 2-(2-methoxyphenyl)-4,4-dimethyloxazoline.[12]

(1) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158–9.
(2) Hansen, J. F.; Wang, S. *J. Org. Chem.* **1976**, *41*, 3635–7. For a similar reaction, see: Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567–76.
(3) Shirley, D. A.; Reeves, B. J. *J. Organomet. Chem.* **1969**, *16*, 1–6.
(4) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
(5) Meyers, A. I.; Temple, D. L.; Haidukewyeh, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787–93.
(6) Rivier, M. H. *Bull. Soc. Chim. Fr.* **1907**, *1*, 733.
(7) Rivier's procedure[6] calls for use of the lead salt of thiophenol. We attempted to use sodium thiophenolate or thiophenol and triethylamine to prepare thiophenyl chloroformate and could only achieve a 23% yield of product.
(8) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676–8.
(9) For a summary of the ambident chemistry of the 2-lithio derivative of 3 and similar compounds, see: Pridgen, L. N.; Killmer, L. B. *J. Org. Chem.* **1981**, *46*, 5402–4.
(10) It should be noted that the transformation of 1 to 11 was not general. A multitude of products was formed when 5 was subjected to LDA.
(11) Hinsberg, O. *Chem. Ber.* **1910**, *43*, 653.

tert-Butyllithium reacted with **1** in yet a different fashion. In this case, reaction at −78 °C followed by quenching with methyl iodide yielded **10**, the product of sulfur extrusion (31%), along with **9** (46%). To our knowledge, this is the first example of the desulfurization of an organic compound effected by *tert*-butyllithium.[13] We intend to explore the scope of this reaction as well as the mechanistic questions raised by this novel chemistry.

Experimental Section

General Procedures. Melting points were taken with a Thomas-Hoover or a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 7199 FT infrared spectrometer and are reported in reciprocal centimeters. Only strong bands are reported unless otherwise stated. Routine proton NMR were obtained at either 80 or 90 MHz with a Varian EM390 or an IBM NR80 FT instrument. NMR data are reported in parts per million (δ) downfield from tetramethylsilane in deuteriochloroform. Analyses were determined by either Micro-Analysis Inc., Wilmington, DE, or our own analysis group. Dry THF and glyme were stored under nitrogen over a sodium chip. *n*-Butyllithium (1.6 M) was from Foote Mineral Co. Phenyllithium and *tert*-butyllithium were from Aldrich. All were used without titration. Workup as usual refers to washing the organic phase with water and saturated brine solution followed by drying over calcium sulfate or sodium sulfate and removal of the solvent in vacuo. Removal of solvent at reduced pressure implies the use of a rotary evaporator.

Preparation of 2. Triethylamine (7.12 mL, 51.19 mmol) and 2-amino-2-methylpropanol (4.88 mL, 51.19 mmol) were dissolved in methylene chloride (100 mL) under a nitrogen atmosphere and cooled to 0 °C. Thiophenyl chloroformate (8.83 g, 51.19 mmol) in methylene chloride (50 mL) was added dropwise over 25 min followed by 2 h of stirring at ambient temperature. The turbid solution was poured into water (200 mL), and the phases were separated. The organic layer was washed with 5% hydrochloric acid, water, 5% sodium bicarbonate, water, and brine and then dried over calcium sulfate. Concentration left 7.92 g of pale yellow oil from which a solid separated. The solid was triturated with 3:1 hexane–ether to give **2** (2.5 g, 21%). This intermediate was characterized by its melting point (82–85 °C) and ^{1}H NMR spectrum [(90 MHz) δ 7.65–7.3 (m, 5 H), 5.6 (br s, 1 H), 3.5 (br s, 2 H), 3.3 (br s, 1 H), 1.23 (s, 6 H)].

Preparation of 2-(Arylthio)-4,4-dimethyloxazolines. The synthesis of **1** serves as a general example. A three-neck flask equipped with a mechanical stirrer, condenser, pressure-equalizing addition funnel, and nitrogen inlet was charged with **3** (20.0 g, 0.202 mol) and glyme (900 mL) and cooled to 0 °C. *n*-Butyllithium (139 mL, 0.222 mol) was added with stirring dropwise via an addition funnel over 20 min followed by stirring 15 min at 0 °C. Diphenyl disulfide (48.4 g, 0.222 mol) was added all at once neat, then the ice bath was replaced with a heating mantle, and the slurry was refluxed for 20 h. During this time the mixture darkened and became homogeneous. The solution was cooled to ambient temperature, and the glyme was removed at reduced pressure. The residue was partitioned between ether (500 mL) and water (200 mL). Workup as usual gave a brown oil, which was chromatographed on silica gel (1 kg). Elution with 10% ether–hexane gave unreacted diphenyl disulfide. Continued elution with 20% ether–hexane gave **1** as a pale yellow oil that crystallized on standing: 28.8 g, 69%; ^{1}H NMR (90 MHz) δ 7.68–7.5 (m, 2 H), 7.45–7.2 (m, 3 H), 3.96 (s, 2 H), 1.27 (s, 6 H); IR (KBr) 1610, 1110, 962 (m), 755 cm^{-1} (m). The analytical sample was recrystallized from hexane; mp 47–48 °C. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; O, 7.72; S, 15.45. Found: C, 63.46; H, 6.29; N, 6.61; O, 7.82; S, 15.45.

2-[(4-Methylphenyl)thio]-4,4-dimethyloxazoline (4): 40%; mp 56–58 °C (hexane); ^{1}H NMR (90 MHz) δ 7.32 (AA′BB′q, $\Delta\nu_{1-3}$ = 26 Hz, J = 7.5 Hz, 4 H), 3.95 (s, 2 H), 2.35 (s, 3 H), 1.28 (s, 6 H); IR (KBr) 1612, 1116, 1093 (m), 962 (m), 806 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 64.99; H, 6.75; N, 6.29.

2-[(4-Chlorophenyl)thio]-4,4-dimethyloxazoline (5): 53%; mp 77.5–79 °C (ether–hexane); ^{1}H NMR (80 MHz) δ 7.45 (AA′BB′q, $\Delta\nu_{1-3}$ = 17.5 Hz, J = 8.5 Hz, 4 H), 4.0 (s, 2 H), 1.3 (s, 6 H); IR (KBr) 1611, 1478 (m), 1118, 1092, 1015, 821 cm^{-1}. Anal. Calcd for $C_{11}H_{12}ClNOS$: C, 54.65; H, 5.00; N, 5.79. Found: C, 54.88; H, 5.12; N, 5.98.

2-[(3,4-Dichlorophenyl)thio]-4,4-dimethyloxazoline (6): 33%; mp 65–67 °C (hexane); ^{1}H NMR (80 MHz) δ 7.75 (m, 1 H), 7.45 (m, 2 H), 4.02 (s, 2 H), 1.3 (s, 6 H); IR (KBr) 1621, 1612, 1112, 1099 cm^{-1}. Anal. Calcd for $C_{11}H_{11}Cl_2NOS$: C, 47.84; H, 4.01; N, 5.07. Found: C, 48.01; H, 4.21; N, 5.03.

2-[(2-Bromophenyl)thio]-4,4-dimethyloxazoline (7): 39%, oil; Kugelrohr bp 79–90 °C (0.15 mm); ^{1}H NMR (80 MHz) δ 7.8–7.5 (m, 2 H), 7.4–7.15 (m, 2 H), 3.96 (s, 2 H), 1.31 (s, 6 H); IR 1608, 1447, 1108, 960, 750 cm^{-1}. Anal. Calcd for $C_{11}H_{12}BrNOS$: C, 46.16; H, 4.23; N, 4.89. Found: C, 46.41; H, 4.41; N, 4.72.

2-[(4-Chloro-2-methylphenyl)thio]-4,4-dimethyloxazoline (8): 24%; mp 92–94 °C; ^{1}H NMR (90 MHz) δ 7.55 (d, J = 8 Hz, 1 H), 7.27 (d, J = 2 Hz, 1 H), 7.16 (dd, J = 8, 2 Hz, 1 H), 3.95 (s, 2 H), 2.42 (s, 3 H), 1.28 (s, 6 H); IR (KBr) 1616, 1115, 1099 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClNOS$: C, 56.35; H, 5.52; N, 5.48. Found: C, 56.14; H, 5.47; N, 5.39.

2-Phenyl-4,4-dimethyloxazoline (10). A solution of **1** (0.5 g, 2.41 mmol) in THF (10 mL) was cooled to −78 °C under an inert atmosphere, and phenyllithium (1.21 mL, 2.65 mmol, 2.2 M) was added via syringe over 5 min. The light yellow solution was warmed to ambient temperature and stirred for 1 h (red-brown solution), and then methyl iodide (0.187 mL, 3.0 mmol) was added. The mixture was stirred for 1 h more, then THF was removed at reduced pressure, and ether (75 mL) and water (25 mL) were added. Workup as usual gave 0.64 g of light yellow oil. Chromatography on silica gel (50 g) proceeded as follows: 10% ether–hexane (200 mL) gave 0.21 g (70%) of **9** as a colorless oil identical with an authentic sample in NMR and IR spectral properties. Continued elution with 20% ether–hexane (400 mL) gave 0.28 g (66%) of **10** as a clear colorless oil identical with an authentic sample in NMR and IR spectral properties.

2-[2-(Methylthio)phenyl]-4,4-dimethyloxazoline (11). A three-neck flask fitted with septum, nitrogen inlet, condenser, and mechanical stirrer charged with THF (200 mL) and diisopropylamine (5.35 mL, 38.5 mmol). After the solution was cooled to 0 °C, *n*-butyllithium (22.5 mL, 36 mmol) was added via syringe over 5 min. A solution of **1** (5.0 g, 24.1 mmol) in THF (40 mL) was added after 5 min, and the mixture was heated to reflux for 6 h and then cooled to ambient temperature and treated with methyl iodide (2.0 mL, 32 mmol). After the mixture was stirred overnight, the THF was removed at reduced pressure and the residue partitioned between ether (300 mL) and water (50 mL). Workup as usual gave 5.44 g of orange solid that was chromatographed on silica gel (100 g). Elution proceeded as follows: 5% ether–hexane, 500 mL, trace amount of **9**; 20% ether–hexane, 200 mL, nil; 500 mL, 4.07 g (76%) of **11** as a white solid [mp 89–92 °C; ^{1}H NMR (90 MHz) δ 7.71 (dd, J = 7.5, 2 Hz, 1 H), 7.43–6.95 (m, 3 H), 4.02 (s, 2 H), 2.41 (s, 3 H), 1.4 (s, 6 H); IR (KBr) 1642, 1034 cm^{-1}]. The analytical sample was recrystallized from hexane; mp 92–93 °C. Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 64.93; H, 6.74, N, 6.33.

2-(Methylthio)benzoic Acid. A mixture of **11** (0.90 g, 4.07 mmol) and 3 M hydrochloric acid (25 mL) was heated to reflux for 30 h during which time a tan solid precipitated. The mixture was cooled and filtered to give 0.68 g of dried solid. The solid was dissolved in methylene chloride (warming required) and treated with activated carbon, and then the mixture was filtered and concentrated. The residue was dissolved in boiling water (100 mL) and filtered to remove a tan impurity. Concentration to 65 mL and cooling gave long white needles of the known 2-(methylthio)benzoic acid: 0.58 g, 85%; mp 168–169 °C (lit.[11] mp 169 °C).

Reaction of 1 with *tert*-Butyllithium. A three-neck flask equipped with septum, nitrogen inlet, and magnetic stirring bar was charged with THF (10 mL) and **1** (0.5 g, 2.41 mmol) and cooled to −78 °C. To this mixture was added *tert*-butyllithium (1.4 mL, 2.66 mmol, 1.9 M) dropwise via syringe over 3 min. The resulting light yellow solution was stirred for 25 min at −78 °C,

(12) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.

(13) Shirley and Reeves observed phenyl–sulfur bond cleavage in the reaction of thiophenetole with *n*-butyllithium. See ref 3.

and then methyl iodide (0.168 mL, 2.7 mmol) was added all at once via syringe. The solution was warmed to ambient temperature, and then the solvent was removed at reduced pressure. The residue was partitioned between ether (75 mL) and water (25 mL) followed by workup as usual to leave 0.34 g of a pale yellow oil. Chromatography on silica gel (50 g) proceeded as follows: 10% ether–hexane, 100 mL, nil; 125 mL, 0.14 g, 46% of **9** as a colorless oil. Elution continued as follows: 10% ether–hexane, 125 mL, nil; 20% ether–hexane, 70 mL, nil; 175 mL, 0.13 (31%) of colorless oil, **10**, identical with an authentic sample in NMR and IR spectral properties; mass spectrum, *m/e* 175.

Acknowledgment. I thank Thomas Miller for technical assistance.

Registry No. **1**, 86064-95-1; **2**, 86064-96-2; **3**, 30093-99-3; **4**, 86064-97-3; **5**, 86064-98-4; **6**, 86064-99-5; **7**, 86065-00-1; **8**, 86065-01-2; **10**, 19312-06-2; **11**, 86065-02-3; *n*-BuLi, 109-72-8; PhLi, 591-51-5; *t*-BuLi, 594-19-4; LDA, 4111-54-0; diphenyl disulfide, 882-33-7; di-*p*-tolyl disulfide, 103-19-5; di-*p*-chlorophenyl disulfide, 1142-19-4; di-3,4-dichlorophenyl disulfide, 4235-78-3; di-*O*-bromophenyl disulfide, 71112-91-9; di-4-chloro-2-methylphenyl disulfide, 86065-03-4; 2-amino-2-methylpropanol, 124-68-5; thiophenyl chloroformate, 13464-19-2; lithium, 7439-93-2.

Preparation of 1,2-Benzisoxazoles from Salicylaldoximes via Trichloroacetyl Isocyanate

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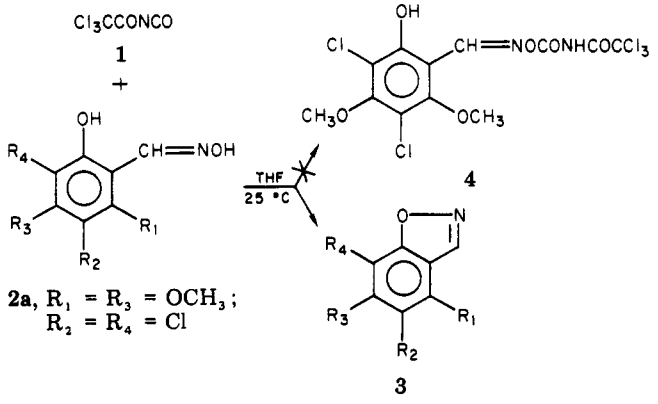
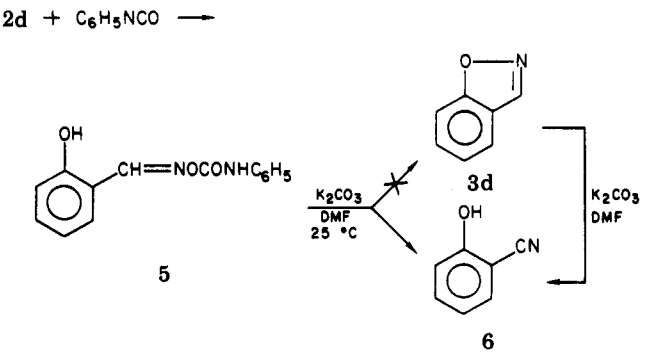
Trichloroacetyl isocyanate (**1**)[1,2] has been used since 1965[1] as a derivatization reagent for the classification of alcohols. In this regard, we recently attempted to identify unequivocally the phenolic proton and the hydroxylimine proton in the ^1H NMR spectrum of **2a** (br s at δ 11.6 and 11.8) by treatment with **1**. Instead of the expected carbamoylaldoxime **4**, the only product obtained was the 1,2-benzisoxazole **3a** in 81% yield. A limited study was initiated in order to assess the scope and generality of this reaction as a means for preparation of 1,2-benzisoxazoles.



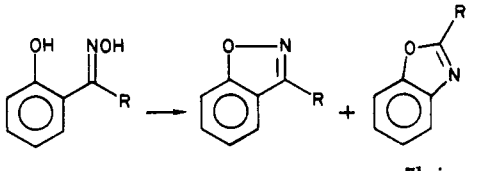
Compound **2a** was the only oxime in this study (see Tables I and II), which, on treatment with **1** in THF, spontaneously cyclized in greater than trace amouts without the addition of a base (K_2CO_3).[3] Replacement of THF by Et_2O or MeCN resulted in lower yield, while substitution by DMF resulted in a violent exothermic reaction.

Chlorosulfonyl isocyanate, recently demonstrated by Olah to be a mild and effective dehydrating agent for aldoximes,[4] provided a slightly lower yield than **1** in this reaction. Only a trace (TLC) of **3a** was observed with the use of *n*-propyl, *n*-butyl, or *tert*-butyl isocyanates or 4-nitrophenyl isothiocyanate in THF with or without the addition of K_2CO_3. Substitution of phenyl isocyanate for **1** resulted in a lower yield (56%) of **3a**, although this could be increased to 76% by the addition of 1 equiv of K_2CO_3. Upon treatment of **2d** with phenyl isocyanate, intermediate **5** precipitated before the base was added.[5] When **5** was subsequently dissolved in DMF and treated with K_2CO_3, and exothermic reaction ensued to yield **6** in 66% yield instead on the expected **3d**. 2-Hydroxy nitrile **6** was also obtained from **3d** when it was reacted similarly with K_2CO_3 in DMF at 25 °C.



On standing several months at ambient temperature in the dark, **3e** was found to have undergone ring opening and concomitant prototropic rearrangement, even in the solid state, to provide the corresponding 2-hydroxy nitrile.[6] The only other 1,2-benzisoxazoles in this study to display this tendency, albeit to a much lesser extent, were **3c** and **3f**, as judged by the emergence of the CN peak (2220–2230 cm^{-1}) in the IR and slight broadening of the melting point.

Two 2-hydroxy ketoximes (**2h–i**) were also studied, and in each case the yields of the expected isoxazoles were lower than from the aldoximes and were accompanied by formation of the corresponding oxazole resulting from a Beckmann rearrangement of the intermediate carbamoyl oxime[7] and subsequent ring closure.



2h, R = CH_3

i, R = 

(1) Goodlett, V. W. *Anal. Chem.* **1965**, *37*, 431.
(2) Meyer zur Heyde, M. *Fresenius Z. Anal. Chem.* **1979**, *295* (*2/3*), 125.
(3) The explanation for the ability of **2a** to spontaneously form **3a** without the addition of a base was originally thought to be a functon of its pK_a (7.65 in 30% EtOH). However, the reason must be more complex than the mere acidity of the salicylaldoximes for **2g** is more acidic (pK_a = 6.8), while **2c** is of equivalent acidity (pK_a = 7.60) and the remaining salicylaldoximes are less acidic (pK_a values, 8.95–9.70).
(4) Olah, G. A.; Vankar, Y. D.; Garcia-Luna, A. *Synthesis* **1979**, 227.
(5) Collected by cooling to −20 °C, 50% yield, mp 148–149 °C dec; ^1H NMR (Me_2SO-d_6) δ 6.8–8.0 (9 H, m), 8.8 (H, s, CH=N), 9.9 (H, s), 10.3 (H, s).
(6) Mp 86–86.5 °C from hexane; ^1H NMR ($CDCl_3$), δ 1.30 (9 H, s), 7.46 (H, d, J = 3 Hz), 7.56 (H, d, J = 3 Hz); IR (Nujol) 3500–3050 (OH), 2220 (C≡N) cm^{-1}; Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.88; H, 5.93; N, 6.41.
(7) Kuhara has previously demonstrated that benzenesulfonyl esters of diaryl oximes rearranged spontaneously at 20 °C and further that the rate of rearrangement was proportional to the strength of the esterifying acid as cited by Smith, P. A. S. In "Molecular Rearrangements"; deMayo, P., Ed.; Interscience: New York, 1963; pp 488–489.

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