at 0 °C over a period of 5 min. The reaction was stirred for 15 min and then washed twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent and chromatgraphy on silica gel (ethyl acetate/hexane, 1:99) afforded 0.41 g (93%) of a clear liquid: bp 100–107 °C (0.8 mm); ^1H NMR ($CDCl_3$) 9.93 (1 H, s), 2.50–2.35 (2 H, m), 2.35–2.15 (2 H, m), 2.24 (3 H, s), 1.85–1.60 ppm (4 H, m); ^{13}C NMR ($CDCl_3$) 189.2 (d, J_{C-H} = 178 Hz), 168.6 (s), 164.2 (s), 126.7 (s), 28.8 (t), 22.1 (t), 21.2 (t), 21.1 (t), 20.7 ppm (q); IR 2750, 1760, 1675, 1650, 1365, 1205, 1125 cm^{-1}; mass spectrum, m/e M^+ 168, 126 (100).

Oxidation of 3 to 4. To a solution of **3** (285 mg, 1.70 mmol) in 10 mL of CH_2Cl_2 was added *m*-chloroperbenzoic acid (300 mg, ~1.8 mmol) in one portion. The flask was swirled and allowed to stand at room temperature for 2 h. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent afforded 0.28 g (91%) of a clear oil: ^1H NMR ($CDCl_3$) 8.01 (1 H, s), 2.35–2.25 (4 H, m), 2.13 (3 H, s), 1.85–1.70 ppm (4 H, m); ^{13}C NMR ($CDCl_3$) 168.3 (s), 158.6 (d, J_{C-H} = 229 Hz), 137.2 (s), 136.1 (s), 26.8 (t), 26.6 (t), 22.3 (t), 22.3 (t), 20.7 ppm (q); IR 1760 (br), 1370, 1220, 1120 cm^{-1}; mass spectrum, m/e M^+ 184, 43 (100). A sample for analysis was prepared by GLC (200 °C 10 ft × 0.25 in., 15% Carbowax). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.53; H, 6.77.

Oxidation of 1 to 3. To a solution of **1** (0.53 g, 3.87 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added dropwise with stirring a solution of *m*-chloroperbenzoic acid (1.3 g ~7.7 mmol) in 30 mL of CH_2Cl_2 over a period of 1.5 h. The reaction was washed with 5% NaOH (two times) and brine and dried over K_2CO_3. Removal of solvent and chromatography on silica gel (ethyl acetate/hexane, 1:99) afforded 0.521 g (80%) of **3** as a clear oil; spectral properties as above.

Oxidation of 1 to 4. To a solution of **1** (0.3 g, 2.19 mmol) in 20 mL of CH_2Cl_2 was added in small portions with swirling *m*-chloroperbenzoic acid (2.3 g, 7.7 mmol) over a period of 1 h. The flask was stored at 0 °C for 12 h. The reaction mixture was washed twice with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent afforded 0.26 g (64%) of **4** as a clear oil; spectral properties as above.

Preparation of ^{18}O-Labeled 2-Methyl-4,5,6,7-tetrahydrobenzofuran (1-^{18}O). A solution of **1b** (603 mg, 4.0 mmol), 75 μL of H_2O (99% ^{18}O, Stohler Isotope Co.), and 2 μL of concentrated HCl in 3 mL of THF (sufficient to solubilize materials) was allowed to stand at room temperature for 12 h. The reaction mixture was poured into H_2O and extracted several times with hexane. The combined hexane extracts were washed with 5% $NaHCO_3$ and brine and dried over K_2CO_3. Removal of solvent afforded 650 mg (95%) of **1b** as a clear oil: ^1H NMR as above; ^{13}C NMR—the resonance at 210.8 ppm could be resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.053 ppm. Comparison of relative intensities of these peaks showed 38% incorporation of ^{18}O. Mass spectral analysis showed 37% ^{18}O. The IR spectrum showed peaks at 1705 ($C^{16}O$) and 1675 ($C^{18}O$) cm^{-1}. **1b** (0.64 g, 3.7 mmol) was cyclized as above by using 1.2 mL of 90% H_2SO_4 (prepared by using 97% $H_2{}^{18}O$, MSD Isotopes). Workup afforded 0.37 g (75%) **1** as a clear oil: ^1H NMR and IR as above; mass spectral analysis showed 14% incorporation of ^{18}O; ^{13}C NMR—the resonance at 149.8 ppm could be resolved into two lines with the upfield line shifted by 0.041 ppm (12% ^{18}O). Similarly, the resonance at 149.0 ppm could be resolved with the upfield resonance shifted 0.039 ppm (12% ^{18}O).

Oxidation of 1-^{18}O to 2-^{18}O. The oxidation was carried out as above with 0.461 g of *m*-chloroperbenzoic acid (~2.7 mmol) in 45 mL of CH_2Cl_2 being added to 0.370 g (2.72 mmol) of 1-^{18}O in 100 mL of CH_2Cl_2. The reaction was worked up to yield 0.37 g of a yellow oil. ^{13}C NMR analysis showed the resonance for carbon 2 (204.6 ppm) to be a single line, while that for carbon 1 (200.1 ppm) could be resolved into two lines with the upfield resonance shifted by 0.050 ppm. Comparison of peak intensities showed 9% retention of ^{18}O. It was assumed the remainder of the ^{18}O was lost by exchange in workup.

Oxidation of 2-^{18}O to 3-^{18}O. To a solution of 2-^{18}O (350 mg, 2.30 mmol) in 20 mL of CH_2Cl_2 was added in one portion *m*-chloroperbenzoic acid (435 mg, 2.6 mmol). The flask was swirled and then allowed to stand for 15 min. Workup afforded 0.369 mg of a yellow oil: ^1H NMR as above; ^{13}C NMR showed that the resonance at 168.6 ppm (carbonyl of ester) could be resolved into two peaks with the upfield peak shifted by 0.037 ppm (9% ^{18}O); mass spectral analysis revealed 10% ^{18}O incorporation.

Acknowledgment. We express our gratitude for financial support of this research by Montana State University and the National Science Foundation Grant CHE 7826160.

Registry No. 1, 17392-08-4; 1-^{18}O, 86014-41-7; **1a**, 10468-40-3; **1a**·Mg, 86014-42-8; **1b**, 17392-07-3; **2**, 86014-43-9; 2-^{18}O, 86014-44-0; **3**, 14713-97-4; 3-^{18}O, 86014-45-1; **4**, 86014-46-2; cyclohexanone, 108-94-1; cyclohexylamine, 108-91-8; 2,3-dichloropropene, 78-88-6.

Convenient Ketone Synthesis by the Reaction of Organocuprate Reagents with 2-Pyridyl Esters

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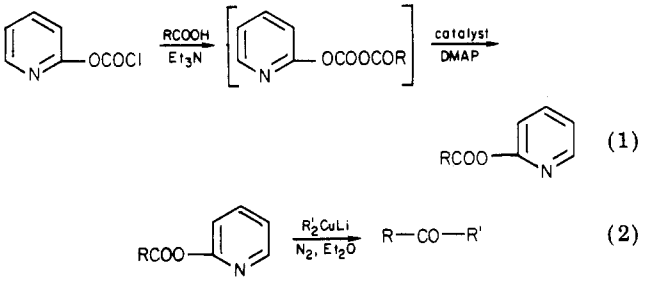
Many reports on the synthesis of ketones from organometallic reagents and carboxylic acid derivatives have appeared.[1] Among many available synthetic methods on the synthesis of ketones, reaction of Grignard reagents with acid chlorides[2] or *S*-2-pyridyl thioates[3] and of organocuprate reagents with acid chlorides[4] or thiol esters[5] are the most efficient and the most convenient. However, each method suffers from operational problems and limits with regard to scope.

It has been reported that reaction of Grignard reagents[6] and (π-allyl)nickel halides[7] with 2-pyridyl esters affords ketones and β,γ-unsaturated ketones, respectively. However, reaction of organocuprate reagents with 2-pyridyl esters has not been investigated.[8]

We now report the use of a new reagent, 2-pyridyl chloroformate, for conversion of acids to 2-pyridyl esters (eq 1) and our results for the reaction of lithium dialkylcuprates with 2-pyridyl esters, which gives the corresponding ketones in high yields (eq 2).



2-Pyridyl esters were prepared by a modification of a known method.[9] 2-Pyridyl chloroformate was conven-

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Table I. Preparation of Ketones from 2-Pyridyl Esters and Lithium Dialkylcuprates at −78 °C

R	yield RCOO-2-py,[a] %	amt, molar equiv R′	amt, molar equiv R'_2CuLi	time, h	yield RCOR′,[b] %	^1H NMR and IR spectral data of RCOR′
C_6H_5	92	Me	0.55	2.5	76 (15)	2.50 (s, 3 H), 7.20–8.00 (m, 5 H); 1685
		Me	0.7	1	84	
		Me	1.0	0.5	92	
		n-Bu	0.55	2.5	82[d] (13)	0.72–1.92 (m, 7 H), 2.96 (t, 2 H, J = 7), 7), 7.20–8.00 (m, 5 H); 1685
		n-Bu	0.7	2	91	
		n-Bu	1.0	0.5	95	
		t-Bu[e]	1.0	0.5	74[f]	1.36 (s, 9 H), 7.30–7.80 (m, 5 H); 1680
$CH_3CH_2CH_2$	93	*n*-Bu	1.0	0.5	84[g]	0.70–1.90 (m, 12 H), 2.20–2.35 (m, 4 H); 1715
$(CH_3)_2CH$	87	*n*-Bu	1.0	1	87[h]	1.10 (d, 1 H, J = 7), 0.70–1.82 (m, 7 H), 2.20–2.83 (m, 3 H); 1710
$(CH_3)_3C$	83	*n*-Bu	0.7	3	76[i] (7)	1.20 (s, 9 H), 0.72–1.82 (m, 7 H), 2.43 (t, 2 H, J = 7); 1705
mesitoic	92	Me	1.0	3	62[j] (36)	2.22 (s, 6 H), 2.27 (s, 3 H); 2.37 (s, 3 H), 6.70 (s, 2 H); 1695
		n-Bu	1.0	3	87[k] (11)	0.70–1.82 (m, 7 H), 2.07 (s, 6 H), 2.16 (s, 3 H), 2.46 (t, 2 H, J = 6), 6.62 (s, 2 H);[m] 1695
$C_6H_5COCH_2CH_2$	80	Me	1.0	0.5	82[l]	2.25 (s, 3 H), 2.66–3.40 (m, 4 H), 7.15–8.06 (m, 5 H);[m] 1685, 1715
		n-Bu	1.0	0.5	80[n]	0.70–1.83 (m, 7 H), 2.56 (t, 2 H, J = 6), 2.73–3.46 (m, 4 H), 7.26–8.10 (m, 5 H); 1685, 1715
$MeOOC(CH_2)_4$	85	*n*-Bu	0.7	0.5	89	0.76–1.86 (m, 1 H), 2.12–2.62 (m, 6 H), 3.62 (s, 3 H); 1715, 1740
$Br(CH_2)_5$	89	*n*-Bu	1.0	0.5	90[o]	0.76–2.20 (m, 3 H), 2.26–2.62 (m, 4 H), 3.42 (t, 2 H, J = 6); 1715
$C_6H_5CH{=}CH$	86	*n*-Bu	0.55	0.5	63[p] (27)	0.76–1.92 (m, 7 H), 2.66 (t, 2 H, J = 6), 6.66 (d, 1 H, J = 16), 6.98–7.66 (m, 6 H); 1700
		n-Bu	2.0	3	78[q]	0.70–2.84 (m, 16 H), 2.16 (t, 2 H, J = 7), 2.56 (d, 2 H, J = 7), 2.80–3.32 (m, 1 H), 7.16 (br s, 5 H); 1715

[a] The numbers indicate the isolated yields of 2-pyridyl esters from acids by using 2-pyridyl chloroformate. [b] The yields are based on 2-pyridyl esters and determined by isolation. The numbers in parentheses indicate the yields of recovered 2-pyridyl esters. [c] The chemical shifts are given in δ, J values are given in hertz, and the frequencies are given in cm^{-1}. See also ref 13. [d] Levine, R.; Karten, M. J.; Kadunce, W. M. *J. Org. Chem.* **1975**, *40*, 1770. [e] $(t\text{-Bu})_2CuLiPBu_3$ was used. [f] Posner, G. H.; Whitten, C. E. *Org. Synth.* **1976**, *55*, 122. [g] Smith, R. F. *J. Org. Chem.* **1960**, *25*, 453. [h] Cason, J.; Chang, M. P. *Ibid.* **1956**, *21*, 449. [i] Floey, W. M.; Welch, F. J.; LaCombe, E. M.; Mosher, H. S. *J. Am. Chem. Soc.* **1959**, *81*, 2779. [j] Pines, H.; Arrigo, J. T. *Ibid.* **1958**, *80*, 4369. [k] Gore, P. H.; Hoskins, J. A.; Thorburn, S. *J. Chem. Soc. B* **1970**, *7*, 1343. [l] Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641. [m] The spectra was taken in $CDCl_3$. [n] Setter, H.; Jones, F. *Chem. Ber.* **1981**, 114, 564. [o] Yamamoto, Y.; Kondo, K.; Moritani, I. *Tetrahedron Lett.* **1974**, 793. [p] Iwai, I.; Okajima, Y. *Yakukaku Zasshi* **1959**, *79*, 1284. [q] The structure of isolated product is 7-phenylundecan-5-one. Jensen, S. R.; Kristiansen, A. M.; Munch-Petersen, J. *Acta. Chem. Scand.* **1970**, *24*, 2641.

iently prepared from phosgene, 2-hydroxypyridine, and triethylamine. Treatment of it with equimolar amounts of an acid and triethylamine in methylene chloride at 0 °C for 30 min afforded the mixed anhydride along with a small amount of 2-pyridyl esters, unlike the case of facile formation of *S*-pyridyl thioates described by Corey.[9] Ester formation occurred to some extent from thermal decomposition of the mixed anhydride at 40 °C for 2 h, but quite sluggishly.[10] We found that the addition of 0.2 equiv of 4-(dimethylamino)pyridine (DMAP)[11] to the mixed anhydride was exceedingly effective in the conversion of the mixed anhydride into 2-pyridyl ester. As shown in Table I, a variety of 2-pyridyl esters including the highly hindered mesitoic acid were easily prepared at room temperature within 3 h in high yields without column chromatographic separation by this procedure.

Reaction of lithium dialkylcuprate with 2-pyridyl esters in diethyl ether proceeded smoothly under nitrogen at −78 °C. As shown in Table I, the reaction was usually complete within 2 h and the ketones were generally obtained in high yields without the formation of side products. However, reaction of 2-pyridyl esters with organocuprate reagents in the presence of oxygen afforded the corresponding esters.[5b] Thus, complete exclusion of oxygen is required for the ketone synthesis.

Although a small amount of starting material was recovered when 0.55 equiv of lithium dialkylcuprate was added, of special synthetic significance is essentially complete utilization of both the alkyl groups of organocuprate reagents. This observation is in marked contrast to the results obtained from the reaction of organocuprate reagents with acid chlorides where 3 equiv of R_2CuLi (6 equiv of R′) are required for optimal yields of ketones.[4] Presumably the intermediate complex, lithium alkyl(2-pyridyloxy)cuprate, also reacts with 2-pyridyl esters to afford ketones.

Reaction of lithium dialkylcuprates with 2-pyridyl esters having other functional groups such as bromide, ketone, and ester afforded ketones without damage to these functional groups. Furthermore, the selectivity of this method was demonstrated by the addition of $n\text{-}Bu_2CuLi$ to 2-pyridyl cinnamate.[12] Conversion of 2-pyridyl cin-

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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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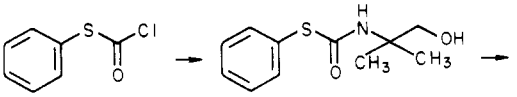
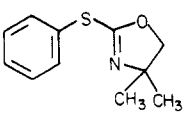
It is well-known that an oxazoline group directly attached to an aromatic nucleus is useful in directing ortho lithiation.[1] In contrast, the effectiveness of the oxazoline functionality in directing metalation reactions when separated from a phenyl group by one or more atoms has scarcely been addressed. 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

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