Table I[a]

Entry	Sulfamic acid (salt)	Registry no.	% yield	Sulfamoyl chloride	Ref	% yield	Registry no.
1	CH_3NHSO_3H	4112-03-2	58	CH_3NHSO_2Cl	5	84	10438-96-7
2	$C_2H_5NHSO_3H$	4626-94-2	86	$C_2H_5NHSO_2Cl$	4	89	16548-07-5
3	n-$C_4H_9NHSO_3H$	39085-61-5	65	n-$C_4H_9NHSO_2Cl$	4	65	10305-43-8
4	i-$C_3H_7NHSO_3H$	42065-76-9	65	i-$C_3H_7NHSO_2Cl$	8	94	26118-67-2
5				c-$C_6H_{11}NHSO_2Cl$[b]	5	65	10314-35-9
6	t-$C_4H_9NHSO_3^- \cdot H_3N^+$-$t$-$C_4H_9$	60260-48-2	c	t-$C_4H_9NHSO_2Cl$	g	34[d]	33581-95-2
7				$C_6H_5NHSO_2Cl$[e]		f	60260-49-3

[a] All compounds had boiling points consistent with those in the literature, or satisfactory elemental analysis. Ed. [b] Starting sulfamic acid commercially available. [c] The salt was not isolated. [d] Yield based on starting amine. [e] From the sodium salt of phenylsulfamic acid; see ref 9. [f] Simple workup provided 90% material recovery. Attempts to purify further were attended by considerable decomposition. Immediate use of this crude material afforded adequate yields of products. [g] W. L Matier, W. T. Comer, and D. Deitchman, *J. Med. Chem.*, **15**, 538 (1972).

amine.[9] Treatment of a benzene slurry of these salts with PCl_5 as described above provides the desired compounds.[10]

$$3RNH_2 + ClSO_3H \rightarrow RNHSO_3^- \cdot H_3N^+R$$

$$RNHSO_3^- \cdot H_3N^+R \xrightarrow{PCl_5} RNHSO_2Cl$$

The previously unreported phenylsulfamoyl chloride thus obtained had limited stability. Bulb-to-bulb distillation of the crude reaction mixture resulted in considerable decomposition but did afford a product which recrystallized from carbon disulfide to afford an analytical sample. Treatment of the crude reaction mixture with excess isopropylamine provided N-isopropyl-N'-phenylsulfamide, identical with the product obtained from aniline and isopropylsulfamoyl chloride. Allowing the crude acid chloride to stand for any length of time resulted in significantly lower yields of products.

In summary, the method described above provides a synthesis of sulfamoyl chlorides that is fast, efficient, economical, and uncomplicated by side reactions. The starting materials are readily available and the conditions employed are quite mild, thereby allowing synthesis of more functionally diverse compounds than was previously possible.

Experimental Section[11]

General Procedure for the Preparation of Sulfamic Acids.[7] To a stirred solution of 100 g of 15% fuming sulfuric acid in 250 ml of nitromethane was added dropwise 1 mol of the appropriate isocyanate. An ice bath maintained the temperature at 25–30 °C. After addition the resulting suspension was refluxed for 0.5 h, then cooled and filtered. The collected crystalline acid was washed with ether and air dried.

General Procedure for the Preparation of Sulfamoyl Chlorides. To a stirred suspension of 1 molar equiv of the appropriate sulfamic acid in a suitable amount of benzene was added 1 molar equiv of phosphorus pentachloride. After gentle warming initiated a vigorous reaction, an ice bath was used to control the rate of reaction. After gas evolution had ceased the resulting solution was refluxed for 0.5 h, cooled, and concentrated in vacuo. Distillation at reduced pressure afforded the product.

***N*-*tert*-Butylsulfamoyl Chloride.** To a stirred solution of 43.8 g (0.6 mol) of *tert*-butylamine in 500 ml of methylene chloride, cooled to 0 °C in an ice/salt bath, was cautiously added 23.3 g (0.2 mol) of chlorosulfonic acid. After addition was complete, the resulting suspension was stirred for 0.5 h at room temperature and then filtered. The collected solids were air dried, then slurried in a convenient amount of benzene and treated with 41.6 g (0.2 mol) of phosphorus pentachloride. After the mildly exothermic reaction subsided, the solution was refluxed for 1 h. After cooling the mixture was filtered, and the filtrate was concentrated in vacuo. Distillation afforded the product as a colorless oil which crystallized on standing, bp 76–78 °C (0.6 mm).

***N*-Phenylsulfamoyl Chloride.** A slurry of 14.95 g (0.077 mol) of sodium N-phenylsulfamate and 15.95 g (0.077 mol) of phosphorus pentachloride in 250 ml of benzene was refluxed for 21 h. After cooling, the reaction mixture was cooled and filtered. The filtrate was concentrated in vacuo to afford 13.8 g (94%) of a crude yellow oil. A 1-g portion of this oil was subjected to evaporative bulb-to-bulb distillation (0.05 mm, oven temperature 110 °C) and provided 0.42 g of a yellow solid. Recrystallization from CS_2 gave pale yellow crystals, mp 69–70 °C.

Anal. Calcd for $C_6H_6ClNO_2S$: C, 37.60; H, 3.16; N, 7.31. Found: C, 37.82; H, 3.25; N, 7.41.

Registry No.—RNCO (R = CH_3), 624-83-9; RNCO (R = C_2H_5), 109-90-0; RNCO (R = n-C_4H_9), 111-36-4; RNCO (R = i-C_3H_7), 1795-48-8; cyclohexylsulfamic acid, 100-88-9; sodium phenylsulfamate, 15790-84-8; sulfuric acid, 7664-93-9; phosphorus pentachloride, 10026-13-8; *tert*-butylamine, 75-64-9; chlorosulfonic acid, 7790-94-5.

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(8) A report of a conceptually similar transformation has been made: G. Hamprecht, D. Mangold, and K. Koenig, German Patent 2 164 176 (1973). Although PCl_5 was included in a long list of similar reagents alleged to effect this type of conversion, emphasis was given to the fact that thionyl chloride was the reagent of choice. In our hands this reagent was of little or no value.
(9) L. F. Audrieth and M. Sveda, *J. Org. Chem.*, **9**, 89 (1944).
(10) This transformation parallels the synthesis of sulfonyl chlorides: R. Adams and C. S. Marvel, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 394.
(11) Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on Varian T-60 and EM-360 spectrometers. Combustion analyses were performed by Atlantic Microlabs.

Ortho Lithiation of Thiobenzamides

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Received June 16, 1976

Access to ortho-substituted derivatives of benzoic acids, in particular to those bearing one or more additional ring substituents, has been rather limited and was largely based on oxidative degradation, or Sandmeyer-type reactions of the

Table I

Registry no.	Starting thioamide	Lithiation conditions	Electrophile[c]	Product[d]	R	Yield, % (isolated)	Mp, °C
60253-29-4	**1a**	−45 to 10 °C	$(C_6H_5S)_2$	**3**	SC_6H_5	90.6	112–115
	1a	−45 to 10 °C	*t*-BuNCO	**4**	CONH-*t*-Bu	61	178–179
	1a	−45 to 10 °C	DMF	**5**	(CHO)[a]	76.5	175–178
	1a	−45 to 10 °C	CH_3CHO	**6 (9)**	$HOC(—)HCH_3$	68[b]	94–96[b]
5310-14-5	**1b**	0 °C, 4 h	$(CH_3)_3SiCl$	**7**	$Si(CH_3)_3$	48.5	121–123
32872-35-8	**1c**	25 °C, 8.5 h	$(CH_3S)_2$	**8**	SCH_3	77.6	79–81

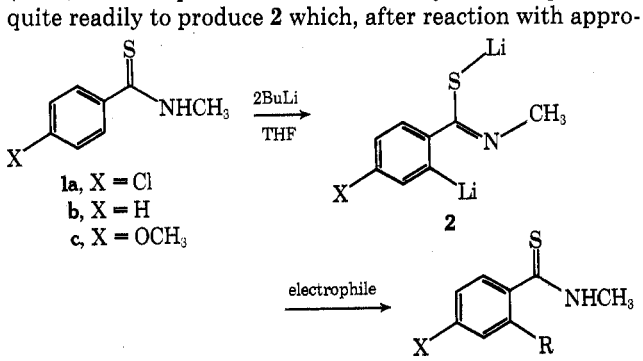
[a] This compound exists exclusively as the cyclic tautomer **5**. [b] Compound isolated as phthalide **9**. [c] Registry no. are, respectively, 882-33-7, 1609-86-5, 68-12-2, 75-07-0, 75-77-4, 624-92-0. [d] Registry no. are, respectively, 96-32-2, 60253-31-8, 60253-32-9, 60253-33-0 (60253-34-1), 60253-35-2, 60253-36-3.

appropriate anthranilic acids. With the discovery that certain derivatives of aromatic carboxylic acids, such as benzamides[1,2] and aryloxazolines,[3,4] can be lithiated directly in their ortho position, a useful, reliable, and simple new method for the regiospecific introduction of virtually any substituent became available.

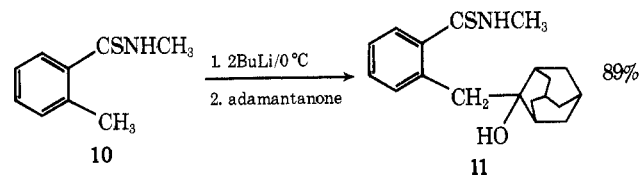
In the search for new ortho-directing groups which would be more easily amenable to further transformation, ideally without the need to protect other functionalities, our attention turned to thioamides. In particular, the secondary thioamides and lactams are known to serve as excellent precursors for the subsequent elaboration to β-keto or β-enamino ketone systems via sulfur extrusion.[5] Although the ortho metalation of numerous benzamides and arylsulfonamides[6] has been studied extensively, the analogous reaction with *N*-alkylthio benzamides has hitherto not been reported.

Although thioamides are generally prepared by sulfurization of the corresponding amides, we find it more convenient to treat the appropriate aryllithium reagent with methyl isothiocyanate. Thioamides **1a–c** and **10** are obtained in 40–60% yield.

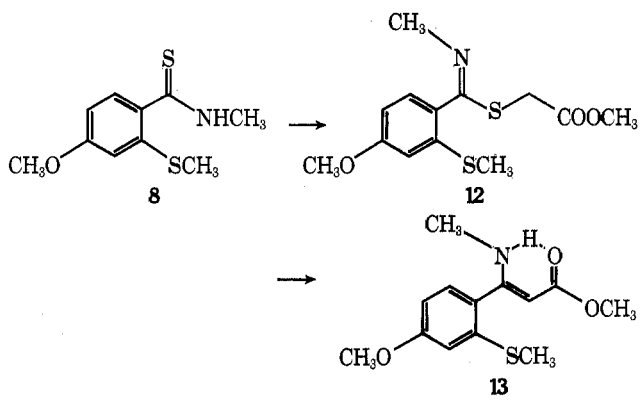
As expected, the dilithiation of *N*-methylthiobenzamides (**1a–c**) with 2 equiv of *n*-BuLi in tetrahydrofuran proceeds quite readily to produce **2** which, after reaction with appropriate electrophiles, gives access to a variety of ortho-substituted derivatives, as indicated in Table I. The effect of para substituents on the ease of metalation parallels quite closely the observations made with regular benzamides, i.e., the rate increases in the following order: $OCH_3 < H < Cl$. Analogous to the results in the lithiation of *p*-methoxy-*N*-methylbenzamide,[7] metalation of **1c** was found to occur exclusively ortho to the thiocarboxamide function.



The lithiation of the *N*-methylthio-*o*-toluamide **10** proceeds rapidly to give, by analogy with the *o*-toluamides,[8,9] the deep red benzylic anion which reacts with adamantanone to give the carbinol **11** in high yield.



To illustrate the potential for further transformation, the thioamide **8** was alkylated with methyl bromoacetate. The crude product **12** of this reaction was then directly desulfurized[5] with triphenylphosphine to give the enamino ester **13**.



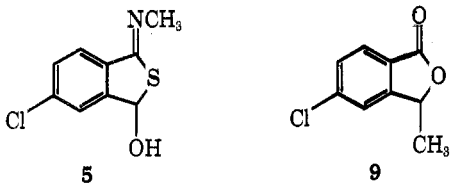
Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; mass spectra on a AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as internal standard. The following abbreviations are used: (b) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

4-Chloro-*N*-methyl-2-phenylthiothiobenzamide (3). A solution of 2.8 g (15 mmol) of thioamide **1a** in 40 ml of dry THF was cooled to −45 °C under N_2. Then 20 ml (32 mmol) of a 1.6 *m* solution of *n*-BuLi in hexane was added dropwise. The reaction mixture was stirred at room temperature until the internal temperature reached 10 °C. It was then recooled to −70 °C, and a solution of 3.5 g (15 mmol) of phenyl disulfide in 15 ml of THF added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with brine, and dried over Na_2SO_4. The residue from the organic layer crystallized from ether to give 3.99 g (90.6%) of compound **3**: mp 112–115 °C; ir (CH_2Cl_2) 3386, 1565, 1510, 1340 cm^{-1}; NMR ($CDCl_3$) δ 3.21 (d, 3 H), 7.00–7.58 (m, 8 H), 7.87 (b, 1 H, ex).

Anal. Calcd for $C_{14}H_{12}ClNS_2$: C, 57.23; H, 4.12; N, 4.77. Found: C, 57.49; H, 4.11; N, 4.68.

***N*-(*tert*-Butyl)-3-chloro-6-(*N*-methylthiocarbamoyl)benzamide (4).** A solution of 2.8 g (15 mmol) of thioamide **1a** in 50 ml of dry THF was cooled to −50 °C and 20 ml of a 1.6 *m* solution of *n*-BuLi/hexane was added. The mixture was allowed to reach 10 °C and was cooled again to −70 °C, then 1.7 g of *t*-BuNCO in 5 ml was added and the reaction mixture was stirred at ambient temperature overnight. After diluting with ether and washing with water and brine, the



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.

Acknowledgment. We wish to acknowledge the support of these studies by Dr. Neville Finch and the carefully executed work of Ms. Ruth Behnke (NMR) and Mrs. Barbara Warren (MS).

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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Received May 10, 1976

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