O-Methylarenehydroxamates as *Ortho*-Lithiation Directing Groups. Ti(III)-Mediated Conversion of O-Methyl Hydroxamates to Primary Amides[1]

Lawrence E. Fisher,* Joan M. Caroon, Jahangir, S. Russell Stabler, Scott Lundberg, and Joseph M. Muchowski

Syntex Research, 3401 Hillview Avenue, P.O. Box 10850, Palo Alto, California 94304

Received February 18, 1993

Reaction of *O*-methyl benzohydroxamates **2a–c** with *sec*-butyllithium in the presence of TMEDA at −40 °C regiospecifically generates the highly reactive *N,ortho*-dilithiated species (e.g. **3**). These dilithio species react avidly with a wide spectrum of electrophilic reagents, including alkyl halides, giving adducts which on reduction with $TiCl_3$ are converted into *ortho*-substituted primary benzamides in excellent yields. *Ortho* lithiation of *O*-methyl benzohydroxamates is thus formally equivalent to *ortho* lithiation of primary benzamides themselves. The utility of these synthetic operations is enhanced by the well-known facility with which the primary amide moiety can be transformed into other useful functional groups. The conversion of *O*-methyl hydroxamates to primary amides is shown to be general, as exemplified by transformation of **14a–f** to **15a–f**.

O-Methyl 2-methylbenzohydroxamate (**4a**) undergoes regiospecific dilithiation on nitrogen and on the methyl group when treated with *sec*-butyllithium at −70 °C. These dilithio species react with DMF or "Weinreb-type" amides to give condensation products which cyclize to *N*-methoxyisoquinolin-1(2*H*)-ones under mildly acidic conditions. Removal of the *N*-methoxy moiety under conditions analogous to those used for *O*-methyl benzohydroxamate provides *N*-unsubstituted isoquinolin-1(2*H*)-ones with high overall efficiency. This process is exemplified by the synthesis of isoquinolin-1(2*H*)-one **9a**, its 3-*n*-butyl congener **9b**, and the tricyclic isoquinolin-1(2*H*)-ones **20a** and **20b** from *O*-methyl 2-methylbenzohydroxamate (**4a**).

Introduction

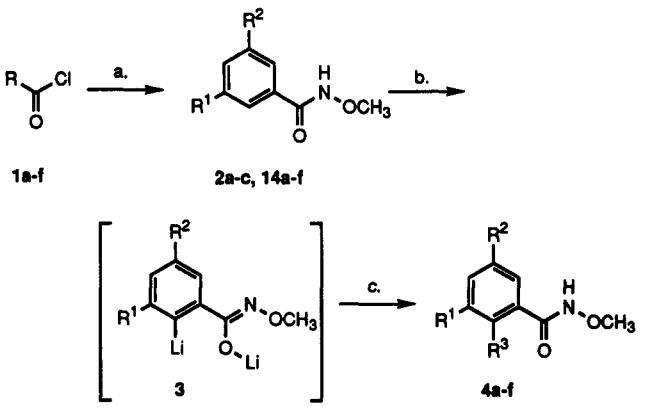
We have recently shown that *N*-propenylbenzamides undergo a regiospecific *N,ortho* dilithiation which, because of the facile removal of the propenyl moiety, is formally equivalent to *ortho* lithiation of the corresponding benzamides.[2] We now report that methyl benzohydroxamates and methyl 2-alkylbenzohydroxamates are readily lithiated at the *ortho* position and in the side chain, respectively, and that these lithiated species react with a variety of electrophilic reagents. Further, the products so obtained are efficiently converted by Ti(III) chloride into the primary benzamides which are themselves precursors of other useful functional groups.[3]

Results and Discussion

The lithiation of methyl benzohydroxamate (**2a**, Scheme I), readily synthesized from benzoyl chloride and methoxylamine hydrochloride in the presence of potassium carbonate (Table I), was more difficult than that of *N*-propenylbenzamide,[2] but could be accomplished efficiently with 2.5 mol equiv of *sec*-butyllithium in the presence of 2.5 equiv of tetramethylethylenediamine (TMEDA) in a THF solution (30–45 min at −40 °C). The dianion **3a** thus obtained reacted with a variety of electrophilic reagents (Table II). Substituted congeners of **3a** could be generated in an analogous manner (Scheme I, Table II).

It is noteworthy that the 2-*n*-octyl compound **4e** was formed directly from **3a** and *n*-octyl iodide. This suggests that **3a**, like dilithiated *N*-propenylbenzamides,[2] is more nucleophilic and/or less basic than the monolithio species derived from metalation of *N,N*-diethylbenzamide.[4]

Scheme I[a]



[a] (a) CH_3ONH_2–HCl, K_2CO_3, EtOAc/H_2O; (b) 2.4 equiv *sec*-butyllithium, 2.4 equiv TMEDA, −70 °C, warm to −30 °C (20 min), cool to −70 °C; (c) E^+, NH_4Cl, Et_2O.

The conditions to lithiate methyl 2-methylbenzohydroxamate (**4a**) were much milder than those required to form **3a**. Treatment of **4a** with 2.1 mol equiv of *sec*-BuLi in THF at −70 °C instantaneously dilthiated **4a**, as judged by the immediate reaction of the dianion with DMF. Acidic workup of the DMF adduct gave *N*-methoxyisoquinolone (**9a**) in good yield (Scheme II, Table III). *N*-Methoxy-*N*-methylamides **10a–c** also reacted with dianion **8**, and the products were cyclized and dehydrated readily to 3-substituted *N*-methoxyisoquinolones **9b–d** (Scheme II). Substituents on the *ortho* group of **7** decrease the yields of isolated isoquinolones **9f** and **13** (Scheme II, Table III), reflecting the incomplete formation or lack of reactivity

(1) Dedicated to John A. Edwards on the occasion of his retirement from Syntex Research. Contribution No. 870 from the Institute of Organic Chemistry.

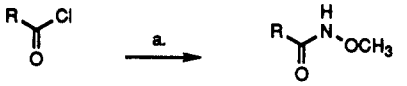
(2) Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 2700.

(3) (a) Wade, L. G., Jr.; Silvey, W. B. *Org. Prep. Proc. Int.* **1982**, *14*, 357. (b) Campagna, F.; Carotti, A.; Casini, G. Tetrahedron Lett. **1977**, 1813.

(4) Snieckus, V. *J. Heterocycl. Chem.* **1984**, 95.

0022-3263/93/1958-3643$04.00/0

Table I. Syntheses of Methyl Hydroxamates



1a-k 2a-c, 14a-f, 7, 11

reactant	R group	method[a]	product	yield (%)	mp °C (solvent)	lit.[b] mp °C
1a	C_6H_5	A	2a	87	62–64 (Et_2O–hex)	63–65[5]
1b	3-FC_6H_4	A	2b	99	62–63 (EtOAc–hex)	
1c	3,5-$(Ch_3O)_2C_6H_3$	A	2c	77	94–96 (EtOAc–hex)	
1d	3-CH_3O-C_6H_4	A	2d	98	oil	
1e	cC_6H_{11}	A	14a	83	62–62 (EtOAc)	
1f	CH_2C36H_5	A	14b	81	70–72 (EtOAc)	
1g	$CH(C_6H_5)_2$	A	14c	94	118–119 (EtOAc–hex)	
1h	$C_{16}H_{33}$	A	14d	67	65–66 (EtOAc–hex)	
1l	2-$CH_3O_2CC_6H_4$	A	14e	68	136–137 (EtOAc–hex)	142–144[6]
1j	$C_2H_5O_2C(CH_2)_3$	A	14f	89	oil	
1k	*c*	B	7	94	94–97 (EtOAc–hex)	
1l	*d*	B	11	92	120–121 (EtOAc–hex)	

[a] See Experimental Section for details. [b] If known. [c]

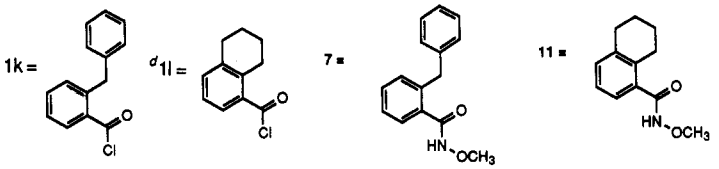
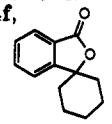
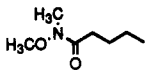
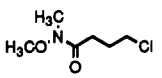
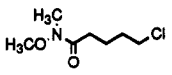


Table II. Conversion of 2 to 4 by *Ortho*-Lithiation and Electrophilic Quench

substrate	E+	R^1	R^2	product, R^3=	yield (%)	mp °C (solvent)	lit.[a] mp °C
2a	CH_3I	H	H	4a, CH_3	91	102–104 (Et_2O–hex)	–
2b	CH_3I	F	H	4b, CH_3	95	109–110 (Et_2O–hex)	–
2c	CH_3I	OCH_3	OCH_3	4c, CH_3	87	152–154 (Et_2O–EtOAc)	–
2a	CH_2=$CHCH_2Br$	H	H	4d, CH_2CH=CH_2	47	110–113 (EtOAc–hex)	–
2a	n-$C_8H_{17}I$	H	H	4e, C_8H_{17}	64	91–93 (EtOAc–hex)	–
2a		H	H	4f, 	35	77–78 (hex)	63–65[19]

[a] Given where known.

Table III. Lithiation and Quench of *O*-Methyl-*o*-Alkylbenzohydroxamates

substrate	R^1	R^2	R^3		electrophile	product	R^1	R^2	R^3	R^4	yield (%)	mp °C (solvent)
4a	H	H	H		DMF	9a	H	H	H	H	60	177–179 (EtOAc–hex)
4a	H	H	H	10a		9b	H	H	H	C_4H_9	75	197–199 (EtOAc–hex)
4a	H	H	H	10b		9c	H	H	H	C_3H_6Cl	64	69–72 (EtOAc–hex)
4a	H	H	H	10c		9d	H	H	H	C_4H_8Cl	81	46–52 (EtOAc–hex)
4b	F	H	H		DMF	9e	F	H	H	H	36	129–130 (EtOAc–hex)
7a	H	H	C_6H_5		DMF	9f	H	H	C_6H_5	H	49	92–94 (EtOAc–hex)
11	–	–	–		DMF	13	–	–	–	–	0	

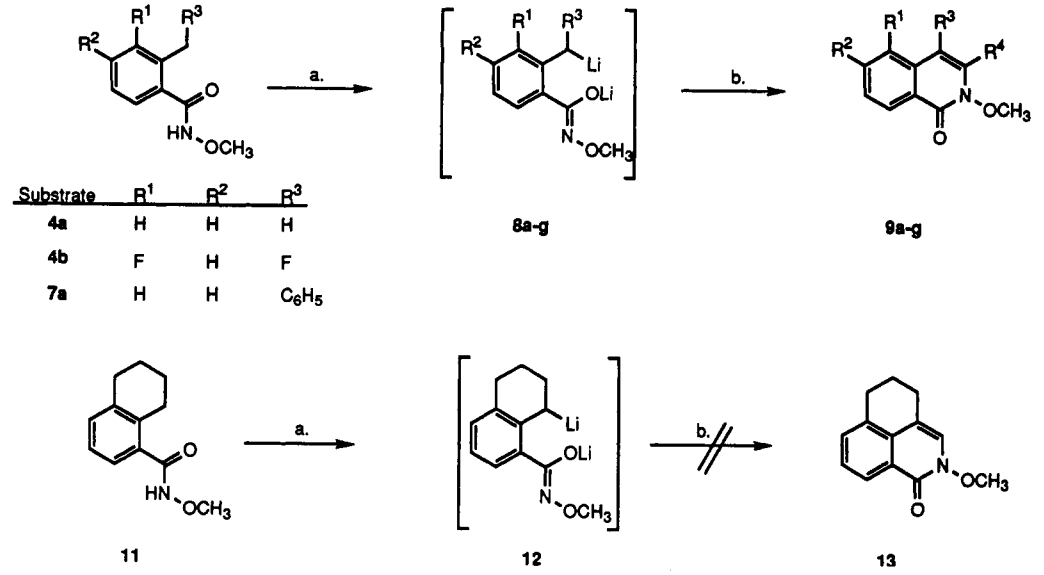
of the dianions **8f** and **11**, respectively, or perhaps a combination of both.

Alkyl hydroxamates have been reduced to the corresponding amides with Raney nickel or by the action of zinc in acetic acid.[2a] These methods are mild but suffer from a lack of chemoselectivity. Since Ti(III) chloride is reported to reduce hydroxylamines to amines,[5d] it seemed reasonable to us to attempt to reduce alkyl hydroxamates to amides with this reagent. Indeed, buffered titanium trichloride ($TiCl_3$) is stated to be effective in the reduction of *O*-benzyl hydroxamates but is ineffective on methyl hydroxamates.[5,6]

(5) (a) Mattingly, P. G.; MIller, M. J. *J. Org. Chem.* **1980**, *45*, 410. Titanium trichloride has also been shown to reduce *N*-oxides and oximes: (b) Timms, G.; Wildsmith, E. *Tetrahedron Lett.* **1971**, 195; and nitro groups: (c) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367; McMurry, J. *Acc. Chem. Res.* **1974**, 281. (d) Murahashi, S.; Kodena, Y. *Tetrahedron Lett.* **1985**, *26*, 4633.

(6) Kushner, D. J.; Landry, T. A.; Tyrell, M. C.; Akers, H. A. *Anal. Biochem.* **1983**, *133*, 116.

Scheme II[a]



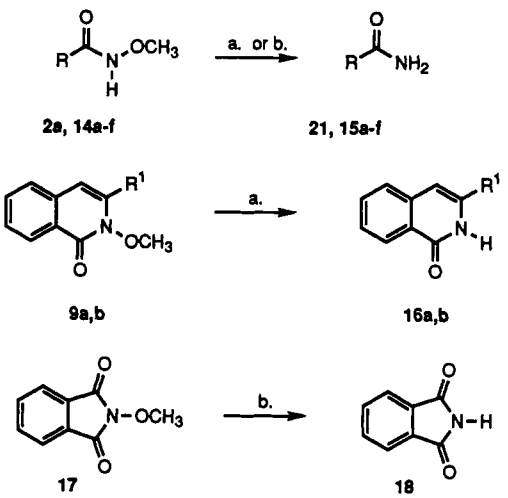
Substrate	R^1	R^2	R^3
4a	H	H	H
4b	F	H	F
7a	H	H	C_6H_5

8a-g 9a-g

11 12 13

[a] (a) 2.1 equiv *sec*-butyllithium, −70 °C, THF, TMEDA; (b) (1) electrophile (see Table III), (2) HCl, THF, 25–50 °C.

Scheme III[a]



[a] (a) (1) 2.0–2.4 equiv $TiCl_3$ (aqueous), ROH, (2) air, NaOH (aqueous), Et_2O; (b) (1) 2.1–2.5 equiv $TiCl_3$ (anhyd), EtOH, (2) H_2O, EtOAc, or Et_2O.

In contrast, we find that not only is methyl benzohydroxamate (**2a**) reduced to benzamide (**21**) using ≥2 mol equiv of Ti(III) chloride (aqueous or anhyd) in ethanol at reflux, methyl hydroxamates in general are transformed into the corresponding amides (Table IV) in moderate to excellent yields. In view of the emerging importance of methyl hydroxamates in organic synthesis,[23] this reduction takes on added significance.

To highlight the versatility of the hydroxamate dianions and the facile N–O bond cleavage of the derived products, tricyclic isoquinolones **20a,b** (Scheme IV) were synthesized from **9c,d** (Scheme II) and reductively demethoxylated to **19a,b** which were then converted into **20a,b** by a straightforward procedure (NaH, DMF, 0 °C to rt).[7]

Conclusions

In conclusion, this study has shown that the methyl hydroxamate moiety is an easily prepared, efficient, *ortho*-metalation directing group for aryl and toluyl systems. It has the advantage of simpler, more efficient preparation than the *N*-propenylamide directing group,[2] but requires higher (−40 vs −70 °C) temperatures and TMEDA as a cosolvent when used as an *o*-aryl lithiation directing group. When used as an *o*-toluyl lithiation directing group, the methyl hydroxamate moiety shows approximate equivalence with the *N*-propenylamide functional group. In addition, we have demonstrated that alkyl hydroxamates are converted into the corresponding amides by Ti(III)-mediated reduction. This fact indicates that the *N*-methoxy moiety could be used as an NH protecting group for *N*-alkylamides in certain instances. Extensions of the manipulation of the methyl hydroxamate functional group are ongoing in our laboratory and will be reported upon in due course.

Experimental Section

Proton magnetic resonance spectra were recorded at 300 or 500 MHz and are reported in ppm (δ) down field from an internal standard of tetramethylsilane. The infrared spectra were measured neat as liquid films or as solid dispersions in KBr. Melting points are uncorrected. Elemental analyses were obtained from the Syntex analytical department.[22]

Synthesis of *O*-Methyl Hydroxamates. Procedure A. To a solution of 2 parts of EtOAc and one part of H_2O containing K_2CO_3 (2 mol equiv) was added methoxylamine hydrochloride

(7) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippen, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.

(8) Johnson, J. E.; Nalley, E. A.; Kunz, Y. K.; Springfield, J. R. *J. Org. Chem.* **1976**, *41*(2), 252.

(9) Bowie, J. H.; Hearn, M. T. W.; Ward, A. T. *Aust. J. Chem.* **1969**, *22*(1), 175.

(10) Aldrich: mp 211–214 °C.

(11) Hall, J. H.; Gisler, M. R. *J. Org. Chem.* **1977**, 1135.

(12) Aschan, O. *Ann. Chem.* **1892**, *271*, 264.

(13) Meldrum, A. N.; Turner, W. E. S. *J. Chem. Soc.* **1910**, *97*, 1607.

(14) Hellerman, L.; Cohn, M. L.; Hoen, R. E. *J. Am. Chem. Soc.* **1928**, *50*, 1725.

(15) Krafft, F.; Stauffer, B. *Chem. Ber.* **1882**, *15*, 1730.

(16) Dyer, E.; Scott, H. *J. Am. Chem. Soc.* **1957**, *79*, 672.

(17) Graham, D. W.; Ashton, W. T.; Barash, L.; Brown, R. D.; Canning, L. F.; Chen, A.; Springer, J. P.; Rogers, E. F.; *J. Med. Chem.* **1987**, *30*, 1074.

(18) Noyes, W. A.; Porter, P. K. *Organic Syntheses*; Wiley: New York, 1932; Collect. Vol 1, p 457.

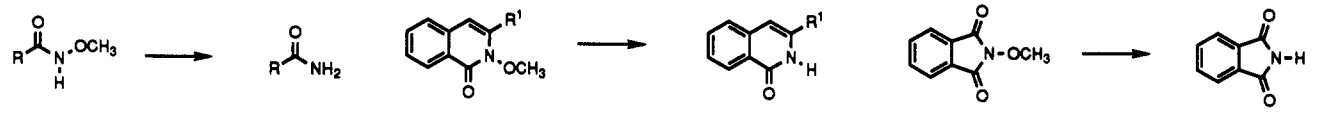
(19) Cannone, P.; Belanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091.

(20) Moriconi, E. J.; Creegan, F. J. *J. Org. Chem.* **1966**, *31*, 2090.

(21) Coppola, G. M. *J. Heterocycl. Chem.* **1981**, 767.

(22) For analytical and general experimental protocol see: Jahangir; Fisher, L. E.; Clark, R. D.; Muchowski, J. M. *J. Org. Chem.* **1989**, *54*, 2992.

Table IV. N-O Bond Cleavage by the Action of $TiCl_3$

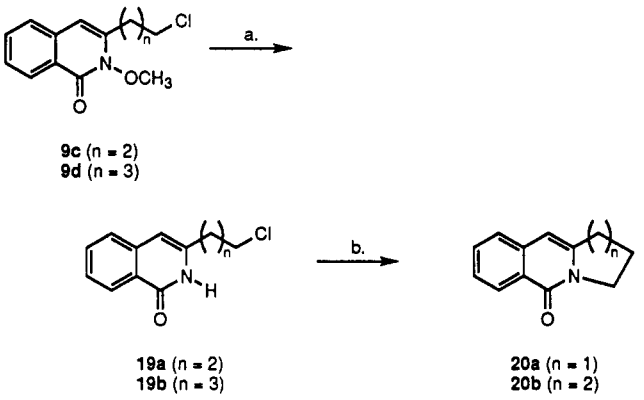


2a, 14a-f 21, 15a-f 9a-d 16a,b, 19a, b 17 18

reactant	method	T (°C)	time (h)	product	R	yield (%)	mp °C (solvent)	lit.[a] mp °C
2a	1[b]	25	48	**21**	C_6H_5	73	127–129 (Et_2O–hex)	129[8]
14a	1	40	0.75	**15a**	cC_6H_{11}	72	184–187 (EtOAc–hex)	186–188[9]
14b	1	40	3	**15b**	$CH_2C_6H_5$	74	157–158 (EtOAc)	157[10]
14c	1	40	0.5	**15c**	$CH(C_6H_5)_2$	47	166–169 (EtOAc)	167.5–168.5[11]
14d	2[b]	25	1	**15d**	$C_{16}H_{33}$	78	95–98 (EtOAc–Et_2O)	103–105[12]
14e	2	25	16	**15e**	2-$CH_3O_2CC_6H_4$	91	205–207 (CH_3CN)	205–206[13]
14f	2	45	9	**15f**	$C_2H_5O_2C(CH_2)_3$	67	52–54 (Et_2O)	51–52[14]
9a	1	45	11	**16a**	H	81	210–212 (H_2O)	211–214[24]
9b[c]	1	45	10	**16b**	C_4H_9	79	140–141 (Et_2O)	139–140[20]
9c[c]	2	60	12	**19a**	C_4H_8Cl	71	107–109 (Et_2O–hex)	–
9d[c]	2	60	14	**19b**	C_3H_6Cl	64	104–106 (Et_2O–hex)	–
17[c]	2	25	16	**18**	see above	55	228 (H_2O)	236[15]

[a] Given where known. [b] Methanol was used as a solvent instead of ethanol. [c] mp (solvent) **9a**: 177–179 (Et_2O–hex). **9b**: 197–199 (Et_2O–hex). **9c**: 89–91 (Et_2O–hex). **9d**: 88–89 (Et_2O–hex). **17**: commercially available.

Scheme IV[a]



9c (n = 2)
9d (n = 3)

19a (n = 2)
19b (n = 3)

20a (n = 1)
20b (n = 2)

[a] (a) 1.0 equiv $TiCl_3$, EtOH, reflux; (b) 1.3 equiv NaH, DMF, 0 °C to rt.

(1 mol equiv). The mixture was cooled in an ice–NaCl–H_2O bath and an acyl halide (1 mol equiv) dissolved in a minimum amount of EtOAc was added dropwise. After stirring for 2 h at 0 °C, the organic layer was separated from the aqueous layer, washed once with H_2O, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The solid amide was recrystallized from the indicated solvent. Starting materials, products, yields, melting points, and solvents of recrystallization for compounds prepared using this method are in Table I. Analytical data can be found in the supplementary material.

Procedure B. To a solution of the carboxylic acid in CH_2Cl_2 containing a catalytic amount of dry DMF at 0 °C was added dropwise 1.2 mol equiv of oxalyl chloride. After the addition was complete, the reaction was allowed to warm to room temperature and stirred for 12–16 h. The solvent and excess oxalyl chloride was removed *in vacuo*. Traces of remaining oxalyl chloride were removed by codistillation with toluene. To this acyl halide, dissolved in an appropriate amount of CH_2Cl_2 at −10 °C, was added a suspension of 2 mol equiv of methoxylamine hydrochloride and 2.5 mol equiv of triethylamine. After stirring at 0 °C for 2 h, the reaction mixture was allowed to warm to room temperature and washed successively with cold 5% HCl, H_2O, and brine. The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The residue was then crystallized from the appropriate solvent.

Typical Lithiation Conditions. Method A: *o*-Aryl Lithiation. To a cold (<−65 °C) solution of **2a** (freshly dried by toluene azeotrope) in THF containing 2.4 mol equiv of TMEDA (freshly distilled from CaH_2) was added dropwise 2.4 mol equiv of *sec*-BuLi (1.3 M in cyclohexane). After the addition of *sec*-BuLi, the reaction mixture was stirred at −20 °C for 45 min. The reaction was recooled to −65 °C, and 1.1 mol equiv of the appropriate electrophile in THF was added dropwise at a rate such that the reaction temperature did not exceed −55 °C. The reaction was allowed to warm to 0 °C and quenched with saturated NH_4Cl. The mixture was partitioned between Et_2O and brine. The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo* to give the product which was purified by MPLC and crystallized from the appropriate solvent. Starting materials, products, yields, melting points, and solvents of recrystallization for compounds prepared using this method are in Table II. Analytical data can be found in the supplementary material.

Method B: *o*-Alkyl Lithiation. To a cold (<−65 °C) solution of *O*-methyl *o*-alkylbenzohydroxamate in THF was added dropwise *sec*-BuLi (2.1 mol equiv, 1.3 M in cyclohexane). After the addition of *sec*-BuLi, the reaction mixture was stirred at <−60 °C for 5 min. The appropriate electrophile (1.1 mol equiv in THF) was added dropwise at a rate such that the reaction temperature did not exceed −55 °C. The reaction was allowed to warm to 0 °C and quenched with saturated NH_4Cl. The mixture was partitioned between Et_2O and brine. The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo* to give the product which was purified by MPLC and crystallized from an appropriate solvent. Starting materials, products, yields, melting points, and solvents of recrystallization for compounds prepared using this method are in Table III. Analytical data can be found in the supplementary material.

***N*-Methoxyisoquinolin-1(*2H*)-one (9a).** Prepared using typical lithiation conditions (method B) with the following addition: after addition of DMF in TMF, quench with saturated NH_4Cl, and workup as above; the residue was dissolved in 50 mL of THF and treated with 2 mL of concd HCl. The resulting mixture was stirred at 25 °C for 30 min and then diluted with EtOAc and washed successively with H_2O and brine. The organic layer was separated, dried with Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to give, after chromatography (7:3 hexanes–ethyl acetate, SiO_2). **9a**: yield 60%; mp 177–179 °C (EtOAc–hexane); IR (KBr) 1662 cm^{-1}; H^1 NMR ($CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 1H), 7.65–7.38 (m, 4H), 7.35 (d, J = 7.8 Hz, 1H), 6.49 (d, J = 7.5 Hz, 1H), 4.12 (s, 3H); MS m/z (rel inten) 175 (80), 144 (52). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.47; H, 5.26; N, 7.65.

***N*-Methoxy-3-butylisoquinolin-1(*2H*)-one (9b).** Prepared using typical lithiation conditions (method B) with the following addition: after addition of *N*-methoxy-*N*-methylvaleramide (**10a**) in THF, quench with saturated NH_4Cl, and workup as above; the residue was dissolved in 65 mL THF and treated with 3 mL

(23) (a) Kikugawa, Y.; Matsumoto, K.; Mitsui, K.; Sakamoto, T. *J. Chem. Soc., Chem. Commun.*, **1992**, (*12*), 921. (b) Kikugawa, Y.; Kawase, M. *J. Chem. Soc., Chem. Commun.*, **1992**, (*19*), 1354. (c) Kikugawa, Y.; Mitsui, K.; Sakamoto, T.; Kawase, M.; Tamiya, H. *Tetrahedron Lett.* **1992**, *31*(2), 243. (d) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, (*4*), 581.

(24) Robison, M. M.; Robison, B. L. *J. Org. Chem.* **1957**, *21*, 1337.

of concd HCl. The resulting mixture was stirred at 25 °C for 35 min and then diluted with EtOAc and washed successively with H_2O and brine. The organic layer was separated, dried with Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to give, after chromatography (3:1 hexanes–ethyl acetate, SiO_2). **9b**: yield 75%; mp 177–179 °C (EtOAc–hexane); IR (KBr) (IR KBr) 3100, 2820, 1610 cm^{-1}; NMR ($CDCl_3$) δ 8.35 (d, J = 7.9 Hz, 1H), 7.15 (m, 3H), 6.27 (s, 1H), 4.18 (s, 3H), 2.73 (m, 2H), 1.71, (m, 2H), 1.41 (m, 2H), 0.97 (t, J = 7.75 Hz, 3H); MS m/z (rel inten) 231 (15), 215 (80), 201, (17) 91 (44). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 69.08; H, 6.85; N, 7.32. Found: C, 68.85; H, 6.61; N, 7.02.

3-(3-Chloropropyl)-*N*-methoxyisoquinolin-1(*2H*)-one (9c). To a solution of 1.89 g of **2** (11.5 mmol) in THF (25mL) at –70 °C was added 18.5 mL (24.5 mmol) of 1.3 M *sec*-butyllithium in cyclohexane. After stirring at –70 °C for 5 min, the mixture was treated with a solution of 1.90 g (11.5 mmol) of 4-chloro-*N*,*O*-dimethylbutyric acid amide (**10b**) in THF (15 mL). The reaction mixture was allowed to warm to 0 °C and treated with saturated aqueous NH_4Cl. Ether (25 mL) was added and the organic layer was separated, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* to give crude **9c** as an oil. Chromatography (3:1 hexane–EtOAc on SiO_2) gave pure **9c** (1.84 g, 64%) as a solid: mp 69–72 °C (EtOAc–hexane); IR (KBr) (IR KBr) 3200, 2900, 1690 cm^{-1}; NMR ($CDCl_3$) 8.40 (d, J = 7.6 Hz, 1H), 7.64 (m, 1H), 7.45 (m, 2H), 6.33 (S, 3H), 4.11 (s, 3H), 3.64 (t, J = 6.04 Hz, 2H), 2.92, (t, J = 6.97 2H), 2.23 (m, J = 6.04, 6.97 Hz, 2H); MS m/z (rel inten) 251 (100), 189 (20), 159 (180). Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.04; H, 5.63; N, 5.56. Found: C, 62.02; H, 5.38; N, 5.65.

3-(4-Chlorobutyl)-*N*-methoxyisoquinolin-1(*2H*)-one (9d). To a solution of 1.32 g of **2** (8.0 mmol) in THF (30 mL) at –70 °C was added 12.9 mL (16.8 mmol) of 1.3 M *sec*-butyllithium in cyclohexane. After stirring at –70 °C for 5 min, the mixture was treated with a solution of 1.43 g (8.0 mmol) of 5-chloro-*N*,*O*-dimethylvaleric acid amide (**10c**) in THF (17 mL). The reaction mixture was allowed to warm to 0 °C and treated with saturated aqueous NH_4Cl. Ether (45 mL) was added and the organic layer was separated, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* to give crude **9d** as an oil. Chromatography (3:1 hexane–EtOAc on SiO_2) gave **9d** as a solid which was used without further purification: yield 81%; mp 46–52 °C (EtOAc–hexane); IR (KBr) (IR KBr) 3205, 2950, 1680 cm^{-1}; NMR ($CDCl_3$) δ 8.42 (d, J = 7.94 Hz, 1H), 7.62 (m, 1H), 7.45 (m, 2H), 6.39 (s, 1H), 4.10 (s, 3H), 3.61, (m, 2H), 2.77 (m, 2H), 1.91 (m, 4H); MS m/z (rel inten) 265 (8), 237 (100) 192 (98). Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.27; H, 6.07; N, 5.27. Found: C, 61.11; H, 6.54; N, 5.48.

***N*-Methoxy-5-fluoroisoquinolin-1(*2H*)-one (9f) from 4b.** Prepared using typical metalation conditions (method B) with the following addition: after addition of DMF in THF, quench with saturated NH_4Cl, and workup as above; the residue was dissolved in 50 mL of THF and treated with 2 mL of concd HCl. The resulting mixture was stirred at 25 °C for 30 min and then diluted with EtOAc and washed successively with H_2O and brine. The organic layer was separated, dried with Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to give, after chromatography (2:1 hexanes–ethyl acetate, SiO_2). **9f**: yield 36%; mp 129–130 °C (EtOAc–hexane); IR (KBr) 1652; ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8.1 Hz, 1H), 7.32–7.5 (m, 3H), 6.70 (d, J = 7.8 Hz, 1H), 4.12 (s,3H); MS m/z (rel inten) 193 (20), 163 (82), 134 (67), 107 (100). Anal. Calcd for $C_{10}H_8FNO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.22; H, 5.36; N, 5.53.

4-Phenyl-*N*-methoxyisoquinolin-1(*2H*)-one (9g) from 7. Prepared using the same reaction conditions that were used for **9f**: yield 49%; mp 92–94 °C (EtOAc–hexane); IR (KBr) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 8.7 Hz, 1H), 7.70–7.42 (m, 8H), 7.32 (s, 1H), 4.15 (s, 3H); MS m/z (rel inten) 251 (80), 221 (80), 220 (67), 192 (58, 165 (100). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.22; H, 5.36; N, 5.53.

Titanium(III) Chloride-Mediated Conversion of 2 to 21, 14a–f to 15a–f and 9a–d to 16a,b and 19a,b. Method I: Typical Procedure Using Aqueous Conditions. To a solution of hydroxamate (1 mol equiv) in EtOH (approximately 1 M in hydroxamate) was added aqueous $TiCl_3$ (2.2–3.0 mol equiv). The reaction mixture was then brought to the temperature specified for each entry in Table III for the specified amount of time. After cooling to room temperature, the reaction mixture was poured onto ice–H_2O and basified with 1 M NaOH to approximately pH 13. Air was bubbled through until the deep blue color disappeared. Acidification to pH 2, filtration, extraction with EtOAc, removal of water with Na_2SO_4, filtration again, and finally removal of solvent in vacuo gave the amide. The compounds were subjected to chromatography or recrystallization as needed; however, further purification in most cases was not necessary. Starting materials, products, yields, melting points, and solvents of recrystallization for compounds prepared using this method, with the exceptions of **19a** and **19b**, are in Table III. Analytical data can be found in the supplementary material.

3-(3-Chloropropyl)isoquinolin-1(*2H*)-one (19a). Prepared according to Method I from **9c**: yield 71%; mp 107–109 °C (hexane–ether); IR (KBr) 3260, 2980, 1685, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.12 (brs, 1H), 8.37 (d J = 7.98 Hz, 1H), 7.64 (m, 1H), 7.47 (m, 2H), 6.40 (s,1H), 3.64 (t, J = 6.04 Hz, 2H), 2.92, (t, J = 6.97 Hz, 2H), 2.23 (m, J = 6.04, 6.97 Hz, 2H); MS m/z (rel inten) 221 (58), 186 (6), 159 (100). Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.45; N, 6.32. Found: C, 64.78; H, 5.74; N, 6.58.

3-(4-Chlorobutyl)isoquinolin-1(*2H*)-one (19b). Prepared according to method I from **9d**: yield 64%; mp 104–106 °C (hexane–ether); IR (KBr) 3200, 2890, 1670, 1630 cm^{-1}; H^1 NMR ($CDCl_3$) δ 11.04 (brs, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.62 (m, 1H), 7.48 (m, 2H), 3.61, (m, 2H), 2.77 (m, 2H), 1.91 (m, Hz, 4H); MS m/z (rel inten) 159 (5), 114 (99), 87 (52), 59 (70). Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.17; H, 6.00; N, 5.94. Found: C, 65.95; H, 6.36; N, 5.76.

Method II: Conversion of 3 to 4. Typical Procedure Using Anhydrous Conditions. Solid $TiCl_3$ (2.5 mol equiv) was added to a stirred solution of hydroxamate in anhyd EtOH (approximately 0.3 M) and the solution was stirred for the period of time and at the temperature indicated in Table III. The solvent was then removed *in vacuo*, and the residue was treated with a volume of H_2O approximately equal to that of the ethanol used in the reaction itself. The pH of the mixture was adjusted to 9 with 10% Na_2CO_3 and the aqueous solution was then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and filtered, and the solvent removed *in vacuo*. The residue was crystallized from the appropriate solvent or chromatographed if necessary. Starting materials, products, yields, melting points, and solvents of recrystallization for compounds prepared using this method are in Table III. Analytical data can be found in the supplementary material.

Cyclization of 19a to 20a and 19b to 20b. Typical Reaction Conditions. To a cold (0 °C) solution of 3-(ω-chloroalkyl)-isoquinolin-1-one in dry DMF was added, in one portion, NaH (1.25 mol equiv, 60% in mineral oil). The reaction mixture was allowed to warm to room temperature over 1 h. After the evolution of H_2 had ceased, the mixture was treated with saturated aqueous NH_4Cl. Ether was added and the organic layer was separated, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* to give the crude product as an oil. Purification via SiO_2 chromatography or crystallization was performed as necessary.

2,3-Dihydropyrrolo[1,2-*b*]isoquinolin-5-(1*H*)-one (20a): yield 75%; mp 94–97 °C (hexanes) (lit.[21] mp 94–96 °C).

1,2,3,4-Tetrahydro-6*H*-benzo[*b*]quinolizin-6-one (20b): yield 71%; mp 99–102 °C (hexanes) (lit.[21] mp 100–103 °C).

Acknowledgment. We thank Professor E.J. Corey for helpful discussions and suggestions during the course of this work.

Supplementary Material Available: 300- or 500-MHz ^1H NMR and IR spectra, mass spectral data, and elemental analyses of **2a–d, 4a–f, 5, 6, 7, 9g, 11,** and **14a–f** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.