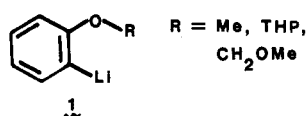


Communications

The Directed Ortho Lithiation of *O*-Aryl Carbamates. An Anionic Equivalent of the Fries Rearrangement

Summary: Ortho-lithiated *O*-aryl carbamates **3** constitute new synthetic intermediates which by treatment with a variety of electrophiles lead to ortho-substituted carbamates **4** and by rearrangement provide salicylamides **6**.

Sir: Within the scope of the aromatic directed ortho metalation reaction,¹ a strategy which is enjoying increasing utility in organic synthesis, masked phenol metalation (1)²



is feasible via the methyl ether,^{1,3} tetrahydropyran (THP),¹ or, most effectively, the CH₂OMe^{1,3,4} group. We report on the new directed metalation reaction of *O*-aryl carbamates,^{5,6} **2** → **3**, and demonstrate its utility for the regiospecific synthesis of ortho-substituted carbamates **4** and phenols **5** (Scheme I). We further describe the unprecedented⁷ O → C 1,3-carbamoyl migration of the ortho-lithiated species **3** to give salicylamides **6**. Thus, aside from providing synthetic complementarity to known ortho-metalation directors **1**, the carbamate **2** serves as a "carrier" of the tertiary amide, one of the most powerful ortho-metalation groups,⁸ into an ortho site from which it may

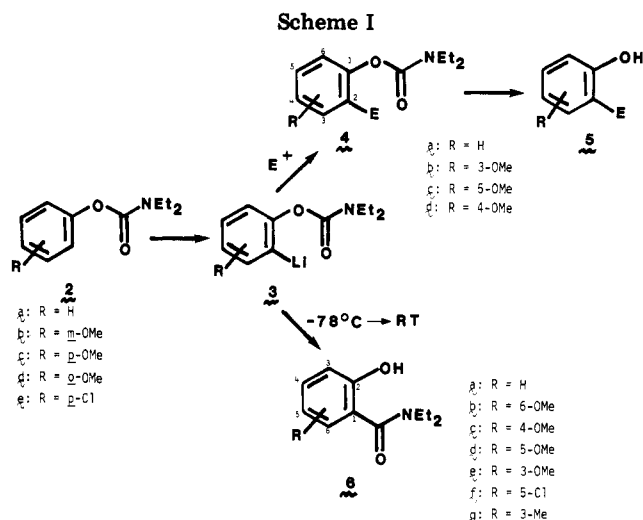


Table I. Synthesis of Ortho-Substituted Aryl Carbamates (**4**)

substrate	electrophile	product ^a	yield, ^b %	mp (bp), ^c °C
2a	MeI	4a, E = Me	80	(94-98/ 0.1 mm)
2a	DMF	4a, E = CHO	73 ^d	(99-103/ 0.25 mm)
2a	CO ₂	4a, E = CO ₂ H	73	(145-150/ 0.2 mm)
2a	ClCONEt ₂	4a, E = CONEt ₂	86	(132-136/ 0.1 mm)
2a	Me ₃ SiCl	4a, E = SiMe ₃	79	(106-110/ 0.2 mm)
2b	CO ₂	4b, E = CO ₂ H ^e	63	140-141
		4c, E = CO ₂ H ^f	20	(125-130/ 9.35 mm)
2c	MeI	4d, E = Me	72	(92-96/ 0.15 mm)
2c	DMF	4d, E = CHO	88 ^g	(115-120/ 0.2 mm)
2c	CO ₂	4d, E = CO ₂ H	69	112-113
2c	Me ₃ SiCl	4d, E = SiMe ₃	62	(119-122/ 0.2 mm)

^a All new compounds show analytical and spectral (IR, NMR, MS) data in accord with the assigned structures.

^b Based on purified (crystallized or distilled) materials.

^c bp refer to oven temperature of Kugelrohr bulb-to-bulb distillation. ^d 42% of this product was isolated as salicylaldehyde.

^e Converted by base hydrolysis (see text) into the known 2-hydroxy-6-methoxybenzoic acid, mp 132-133 °C (lit. mp 135 °C) (Limaye, D. B.; Kelkar, G. R. *Rasayanam* 1936, 1, 24; *Chem. Abstr.* 1937, 30, 2213^s). ^f Converted by base hydrolysis into the known 2-hydroxy-4-methoxybenzoic acid, mp 159-160 °C (lit. mp 160-161 °C) (Nierenstein, M. *J. Am. Chem. Soc.* 1930, 52, 4012). ^g 57% of this product was isolated as 5-methoxysalicylaldehyde characterized by comparison with spectral data reported for the authentic material (see ref 12).

promote further metalation chemistry. Both reactions offer new and general tactics for the regiospecific con-

(1) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (N.Y.) 1979, 26, 1.

(2) The formation of the ortho-lithiated lithium phenoxide species by direct dimetalation of phenol occurs in low yields: Santucci, L.; Gilman, H. *J. Am. Chem. Soc.* 1958, 80, 4537. For a highly substituted phenol exception, see: Schafer, W.; Leute, R.; Schlude, H. *Chem. Ber.* 1971, 104, 3211. The aliphatic equivalent of such species has been recently generated: Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* 1982, 104, 1777.

(3) Recent use in total synthesis. OMe: van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc.* 1982, 104, 1785. Guthrie, A. E.; Semple, J. E.; Jouilleé, M. M. *J. Org. Chem.* 1982, 47, 2369. OCH₂OMe: Corey, E. J.; Das, J. *J. Am. Chem. Soc.* 1982, 104, 5551. Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *Ibid.* 1981, 103, 6885. See also the related OCH(Me)OEt group: Kraus, G. A.; Pezzanite, J. O. *J. Org. Chem.* 1979, 44, 2480.

(4) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* 1982, 47, 2101. (b) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* 1981, 22, 3923 and references therein.

(5) Although ortho-metalated secondary *N*-aryl carbamates have been described (Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* 1980, 45, 4798), our work constitutes the first report of ortho metalation of tertiary *O*-aryl carbamates. Implicit in this observation is the inertness of these species to nucleophilic attack by organolithium base, the synthetic consequence of which has been amply demonstrated for ortho-metalated tertiary benzamides.⁸

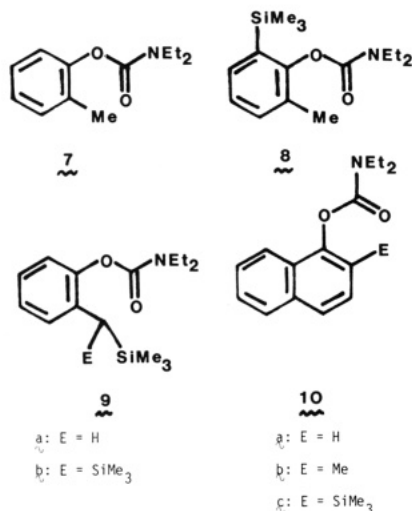
(6) Carbamates constitute an important class of insecticides (Kuh, R. J.; Dorrough, H. W. "Carbamate Insecticides: Chemistry, Biochemistry, and Toxicology"; CRC Press: Cleveland, OH, 1976) and useful pharmacological agents (Brezonoff, H. E.; Giuliano, R. *Annu. Rev. Pharmacol. Toxicol.* 1982, 22, 341).

(7) Ortho anion induced O → C 1,3-migrations of silicon and phosphorus functions are known. Silicon: Habich, D.; Effenberger, F. *Synthesis* 1979, 841. Billedeau, R.; Snieckus, V., unpublished results. Phosphorus: Cambie, R. C.; Plamer, B. D. *Aust. J. Chem.* 1982, 35, 827 and references therein. A solitary case of a corresponding C → C 1,3-acyl migration has been reported: Dyllick-Brenzinger, R. A.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* 1979, 108. The silicon 1,3-shift excepted, the intramolecularity of these migrations, including our carbamate rearrangement, has not been demonstrated.

(8) Snieckus, V. *Heterocycles* 1980, 14, 1649. Beak, P.; Snieckus, V. *Acc. Chem. Res.* 1982, 15, 306.

struction of polysubstituted aromatics.

Selected results of the reactions of ortho-lithiated carbamates **3** with a variety of electrophiles are presented in Table I. Treatment of carbamates **2a-c**⁹ under the standard conditions for metalation of tertiary amides,⁸ (1.1 equiv *sec*-BuLi/TMEDA/THF/-78 °C/1 h) followed by quenching with electrophiles, warming to room temperature (8–12 h), and NH₄Cl workup afforded compounds **4a-c** in synthetically useful yields. On the basis of quenching experiments with carbon dioxide, the *m*-methoxycarbamate **2b** undergoes metalation at both available ortho sites to give the isomeric acids **4b** (63%) and **4c** (25%). Thus the carbamate behaves analogously but not as decisively as the tertiary amide⁸ and the methoxy-methoxy⁴ groups in directing metalation in between the two substituents. For the *o*-methylcarbamate **7**, aromatic



vs. *o*-methyl proton abstraction selectivity was observed as a function of the base employed. Treatment with *sec*-BuLi under the standard conditions followed by Me₃SiCl quench gave a mixture of the silylated products **8** and **9a** in a ratio of 2:1. On the other hand, metalation with LDA (THF/-78 °C/1 h) and subsequent reaction with Me₃SiCl resulted in the formation of **9a** as the major product (66%) together with the bis(silylated)carbamate **9b** (12%).

The results of the base-induced 1,3-acyl migration of carbamates **2** into the salicylamides **6** are summarized in Table II. Typically, the carbamates **2a-e**⁸ are metalated with *sec*-BuLi under the standard conditions,⁸ and the solutions of the resulting lithiated species are allowed to warm to room temperature over 10–12 h to give, after normal workup, compounds **6a-g** in good yields. Rearrangement of the *m*-methoxycarbamate **2b** leads to a 3:1 mixture of salicylamides **6b** and **6c**, indicating again the predominance of metalation between the two groups. In spite of the evidence that carbamate **7** undergoes partial metalation with *sec*-BuLi at the *o*-methyl group (\rightarrow **9a**), subjection of **7** to the migration conditions provided the 3-methylsalicylamide **6g** in good yield. These results presumably reflect thermodynamic stability of the respective metalated species. Advantage can be taken of the deuterium isotope effect¹⁰ to synthesize specifically deuterated benzene derivatives. For example, the sequential

(9) Carbamates were prepared in 80–95% yields by treatment of the corresponding phenols with ClCONEt₂ in pyridine (Lustig, E.; Benson, W. R.; Dut, N. *J. Org. Chem.* 1967, 32, 851) and show spectral (IR, NMR, MS) data consistent with their assigned structures.

(10) On the basis of this principle, 2,6-dideuterated benzamides have been prepared: Beak, P.; Brown, R. A. *J. Org. Chem.* 1982, 47, 34.

Table II. Synthesis of Salicylamides (**6**) by 1,3-Carbamoyl Migration

substrate	product ^a	yield, %	mp/bp, °C (lit. mp, °C)
2a	6a	75	101–102 (104) ^b
2b	6b	48	139–140
	6c	18	120–121 (121–122) ^c
2c	6d	60	100–101 (103–104) ^c
2d	6e	68	82–83 ^d
2e	6f	65	151–153
7	6g	70	100–105/0.15 mm

^a See footnote a, Table I. ^b Couturier, P. C. R. *Hebd. Seances Acad. Sci.* 1936, 202, 1994; *Chem. Abstr.* 1936, 30, 6725⁸. ^c Canonica, L.; Botta, B.; Bonati, A.; Tedeschi, C. *Ann. Chim. (Rome)* 1955, 45, 205; *Chem. Abstr.* 1955, 49, 13939a. ^d Known compound, see: Roussel-UCLAF, French Patent Add. 0302; *Chem. Abstr.* 1973, 78, P58093.

one-pot lithiation–deuteration (EtOD)–lithiation of the parent carbamate **2a** leads in 55% yield to 3-deuterio-salicylamide (95% *d*₁ by MS and 400-MHz NMR).

The directed ortho metalation reaction is not restricted to *O*-phenyl carbamates. Thus the 1-naphthyl carbamate **10a**⁹ affords the 2-substituted products **10b** (90%) and **10c** (90%) under the standard lithiation conditions followed by treatment with MeI and Me₃SiCl,¹¹ respectively.¹²

Carbamate removal from **4** to give phenols **5** was effected in 90% yields by reduction (LAH/THF/reflux; H⁺) or hydrolysis (NaOH/aqueous MeOH or HO(CH₂)₂OH/reflux),¹³ depending on the type of electrophile introduced. Compound **4a**, E = CHO, suffered hydrolysis to salicylaldehyde during the reaction or in the workup, presumably owing to an anchimerically assisted mechanism.

The carbamate function is a versatile addition to the directed ortho metalation repertoire. In comparison with the methoxymethoxy substituent, the carbamate appears to be a more powerful directing group (*sec*-BuLi/-78 °C vs. *t*-BuLi or *n*-BuLi/0 °C or higher),¹⁴ shows parallel but somewhat lower regioselectivity in metalation of non-equivalent ortho sites,^{4a} and provides complementary, base-catalyzed hydrolytic procedures for conversion to phenols **5**. Its supplementary feature, the anionic equivalent of the Fries rearrangement¹⁴ (**3** \rightarrow **6**), allows access to alkoxybenzamides whose metalation in turn is of demonstrated utility in organic synthesis.⁸ The two reactions, separately or combined, suggest new avenues for the regiospecific elaboration of polysubstituted aromatics. Studies to develop the scope, to define the relative metalation efficacy vis-à-vis other groups,^{4,15} and to establish application in synthesis are in progress.¹⁶

(11) We are grateful to R. J. Mills for this experiment.

(12) 10b: IR (neat) ν_{max} 1710 cm⁻¹; NMR (CDCl₃) δ 1.3 (m, 6 H), 2.3 (s, 3 H), 3.5 (m, 4 H), 7.1–8.0 (m, 6 H); MS, *m/e* 257 (M⁺). Base hydrolysis (see text) gave 2-methyl-1-naphthol, mp 61–62 °C (lit. mp 64–66 °C); spectral data identical with those reported (Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra", 1974. Pouchert, C. J.; "The Aldrich Library of Infrared Spectra", 3rd ed.; 1981). 10c: IR (neat) ν_{max} 1705 cm⁻¹; NMR (CDCl₃) δ 0.39 (s, 9 H), 1.28 (t, 3 H), 1.45 (t, 3 H), 3.65 (m, 4 H), 6.3–7.0 (m, 6 H).

(13) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley-Interscience: New York, 1982; p 236.

(14) Olah, G. A., Ed. "Friedel-Crafts and Related Reactions", Vol. III, pt. 2, Interscience, New York, 1964, p 499. Recent examples: Lewis, J. R.; Paul, J. G. *J. Chem. Soc., Perkin Trans. 1*, 1981, 770. Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* 1981, 103, 4251. For a photo-Fries rearrangement of a secondary carbamate, see: Trecker, D. J.; Foote, R. S.; Osborn, C. L. *Chem. Commun.* 1968, 1034.

(15) Beak, P.; Brown, R. A. *J. Org. Chem.* 1979, 44, 4463. Meyers, A. I.; Lutomski, K. *Ibid.* 1979, 44, 4464.

(16) Note added in proof: Ortho metalation of secondary carbamates is also feasible as evidenced from treatment of phenyl methylcarbamate with 2 equiv of *sec*-BuLi followed by a CO₂ quench to give, after hydrolysis, salicylic acid.

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Registry No. 2a, 65009-00-9; 2b, 85630-17-7; 2c, 85630-18-8; 2d, 85630-19-9; 2e, 85630-20-2; 3a, 85630-42-8; 3b (3-OMe), 85630-43-9; 3b (5-OMe), 85630-44-0; 3c, 85630-45-1; 3d, 85630-46-2; 3e, 85630-47-3; 4a (E = CHO), 85630-21-3; 4a (E = CO₂H), 85630-22-4; 4a (E = CONEt₂), 82819-70-3; 4a (E = SiMe₃), 85630-23-5; 4b (E = CO₂H), 85630-24-6; 4c (E = CO₂H), 85630-25-7; 4d (E = Me), 85630-26-8; 4d (E = CHO), 85630-27-9; 4d (E = CO₂H), 85650-28-8; 4d (E = SiMe₃), 85630-28-0; 5a (E = Me), 95-48-7; 5a (E = CHO), 90-02-8; 5a (E = CO₂H), 69-72-7; 5a (E = CONEt₂), 19311-91-2; 5a (E = SiMe₃), 15288-53-6; 5b (E = CO₂H), 3147-64-6; 5c (E = CO₂H), 2237-36-7; 5d (E = Me), 5307-05-1; 5d (E = CHO), 672-13-9; 5d (E = CO₂H), 2612-02-4; 5d (E = SiMe₃), 85630-29-1; 6a, 19311-91-2; 6b, 85630-30-4; 6c, 85630-31-5; 6d, 85630-32-6; 6e, 19351-20-3; 6f, 85630-33-7; 6g, 85630-34-8; 7, 85630-35-9; 8, 85630-36-0; 9a, 85630-37-1; 9b, 85630-38-2; 10a, 85630-39-3; 10b, 85630-40-6; 10c, 85630-41-7; 2-methyl-1-naphthol, 7469-77-4.

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Novel Diterpenes with a Cyclobutenone Moiety from the Brown Alga *Pachydictyon coriaceum*

Summary: The structures of acetylcoriacenone and isoacetylcoriacenone, new diterpenes possessing a cyclobutenone moiety, have been elucidated as 4a and 4b, respectively, by spectral and chemical means.

Sir: Brown algae of Dictyotaceae have attracted recent interest because of their variety of unique components that are not found in terrestrial plants. *Pachydictyon coriaceum* of this family, which grows along the California coast, has been reported to produce the unusual diterpenes acetoxycrenulatin¹ and pachydictyol A.² The same species, collected on the Japanese coast, has been shown to contain a different diterpene, sanadaol.³ This communication reports that two new compounds isolated from the same alga have the novel structures 4a and 4b, possessing a cyclobutenone moiety.

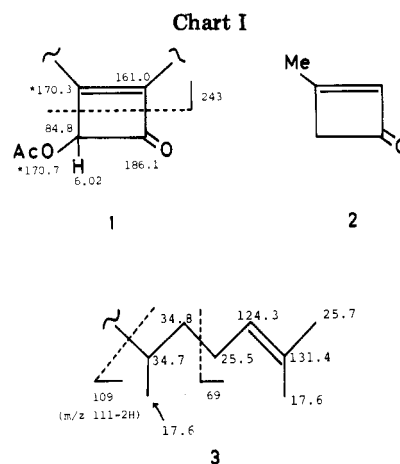
The methanol extract of *P. coriaceum* (collected at Izu-Shimoda beach, Japan, in July 1981) was fractionated chromatographically, giving a fraction containing a pair of isomers. These isomers were separated by preparative TLC (Merck, Kieselgel 60 F-254, hexane-ethyl acetate, 95:5, 11 developments) as viscous oils, which were designated as acetylcoriacenone (0.09% of the methanol extract) and isoacetylcoriacenone (0.07%).

High-resolution mass spectral analysis of acetylcoriacenone⁴ showed a molecular ion at *m/e* 344.233 corresponding to C₂₂H₃₂O₃. An intense IR absorption at 1770 cm⁻¹ and a weak but sharp signal at 1610 cm⁻¹ suggested

Table I. Nuclear Magnetic Resonance Data for Acetylcoriacenone (4a) and the Epoxide 6a

position no.	carbon-13 chemical shift ^a of 4a	proton chemical shift ^b	
		4a	6a
1	161.0		
2	170.3 ^c		
3	28.5	2.79 (dt, 12, 3) 2.3 ^d	2.67 (ddd, 14, 13, 4) 2.88 (br d, 14)
4	25.2	1.98 ^d 2.28 ^d	1.18 (ddd, 15, 13, 10) 2.28 (br dd, 15, 4)
5	122.8	5.13 (dd, 11, 3)	2.88 (br d, 10)
6	140.4		
7	40.2	1.9 ^d 2.25 ^d	2.22 ^d
8	31.6	<i>e</i> <i>e</i> <i>e</i>	1.85 ^d <i>e</i> <i>e</i>
9	43.4		
10	34.7	1.7 ^d	1.7 ^d
11	34.8	1.3 ^d	<i>e</i>
12	25.5	1.85 ^d	1.85 ^d
13	124.3	5.01 (br t, 7)	5.01 (br t, 7)
14	131.4		
15	25.7	1.67 (br s)	1.67 (br s)
16	17.6	1.57 (br s)	1.57 (br s)
17	17.6	0.91 (d, 7)	0.93 (d, 7)
18	186.1		
19	84.8	6.02 (s)	6.07 (s)
20	16.3	1.41 (br s)	1.07 (s)
AcO	20.8	2.11 s	2.08 (s)
	170.7 ^c		

^a Determined by off-resonance and selective decoupling experiments at 22.5 MHz. ^b Based on double and triple resonance experiments at 400 MHz. ^c Assignments may be reversed. ^d These chemical shifts were deduced on the basis of double resonance experiments. However, coupling patterns were not clarified, because of overlapping on other signals. ^e Undetermined.



the existence of a highly strained enone system, which was assumed to be included in a cyclobutane ring because these IR absorptions were reasonably close to those reported for 3-methylcyclobutenone (2).⁵ A short-wavelength absorption maximum (229 nm) with a small molar absorptivity (ϵ 6500) in the UV spectrum was also compatible with the reported value (219 nm, ϵ 6300) of 2.⁵ The unusual downfield chemical shifts of the olefinic carbons, 170.3 (or 170.7) and 161.0 ppm, together with the upfield chemical shift of the carbonyl carbon (186.1 ppm) in the ¹³C NMR spectrum (Table I) were characteristic of a cyclobutenone moiety.⁶

(5) Dowd, P.; Sachdev, K. *J. Am. Chem. Soc.* 1967, 89, 715.

(1) McEnroe, F. J.; Robertson, K. J.; Fenical, W. H. "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum Press: New York, 1977; pp 179-189.

(2) Hirschfeld, D. R.; Fenical, W. H.; Lin, G. H. Y.; Wing, R. M.; Radlick, P. *J. Am. Chem. Soc.* 1973, 95, 4049.

(3) Ihitsuka, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* 1982, 23, 3179.

(4) 4a: mass spectrum (relative intensity, %), *m/z* 344 (M⁺, 1), 302 (5), 274 (14), 243 (100), 163 (48), 147 (60), 109 (60), 69 (24).