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SILICON IN BENZAMIDE DIRECTED ORTHO METALATION REACTIONS. CARBO- AND BROMO-DESILYLATIONS AND SYNTHESIS OF NATURALLY-OCCURRING ANTHRAQUINONES

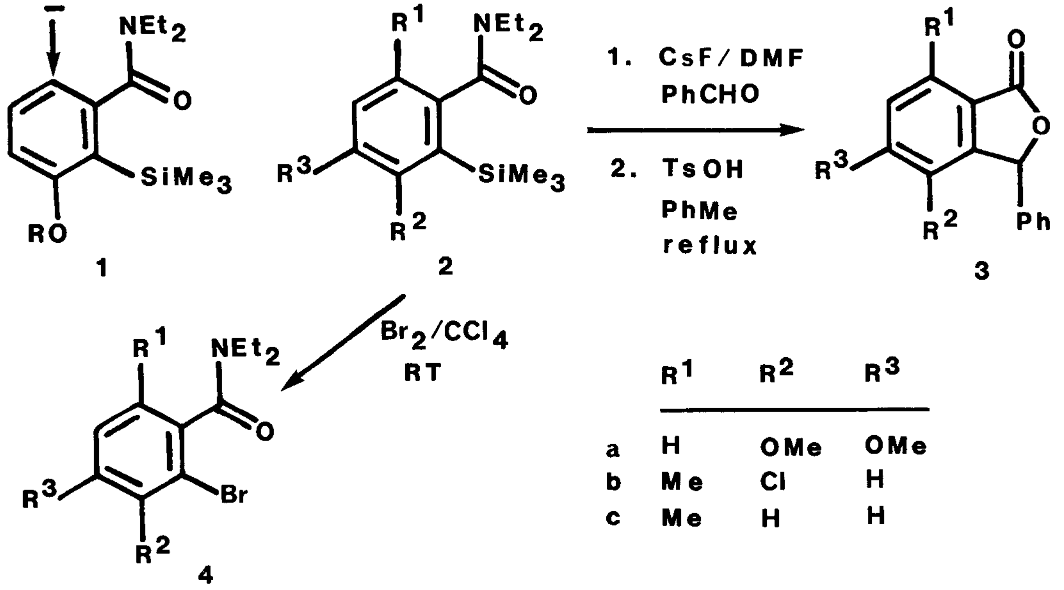
R.J. Mills and V. Snieckus*

The Guelph-Waterloo Centre for Graduate Work in Chemistry

University of Waterloo, Waterloo, Canada N2L 3G1

Summary: Silylated benzamides 2, available by directed ortho metalation, undergo fluoride-induced carbodesilylation and ipso bromodesilylation to give usefully-substituted aromatics 3 and 4; these reactions are utilized in a short and efficient synthesis of erythrolaccin tetramethyl ether 10.

Silicon protection of the more reactive directed ortho metalation site in benzamides 1 has been shown to be a highly expedient tactic for the preparation of diverse polysubstituted aromatics.[1] In this Letter, we demonstrate the utility of combining this concept with fluoride-induced carbodesilylation[2] and ipso bromodesilylation[3] to allow convenient access to aromatic substitution patterns (3,4) which are difficult to achieve by classical



	R^1	R^2	R^3
a	H	OMe	OMe
b	Me	Cl	H
c	Me	H	H

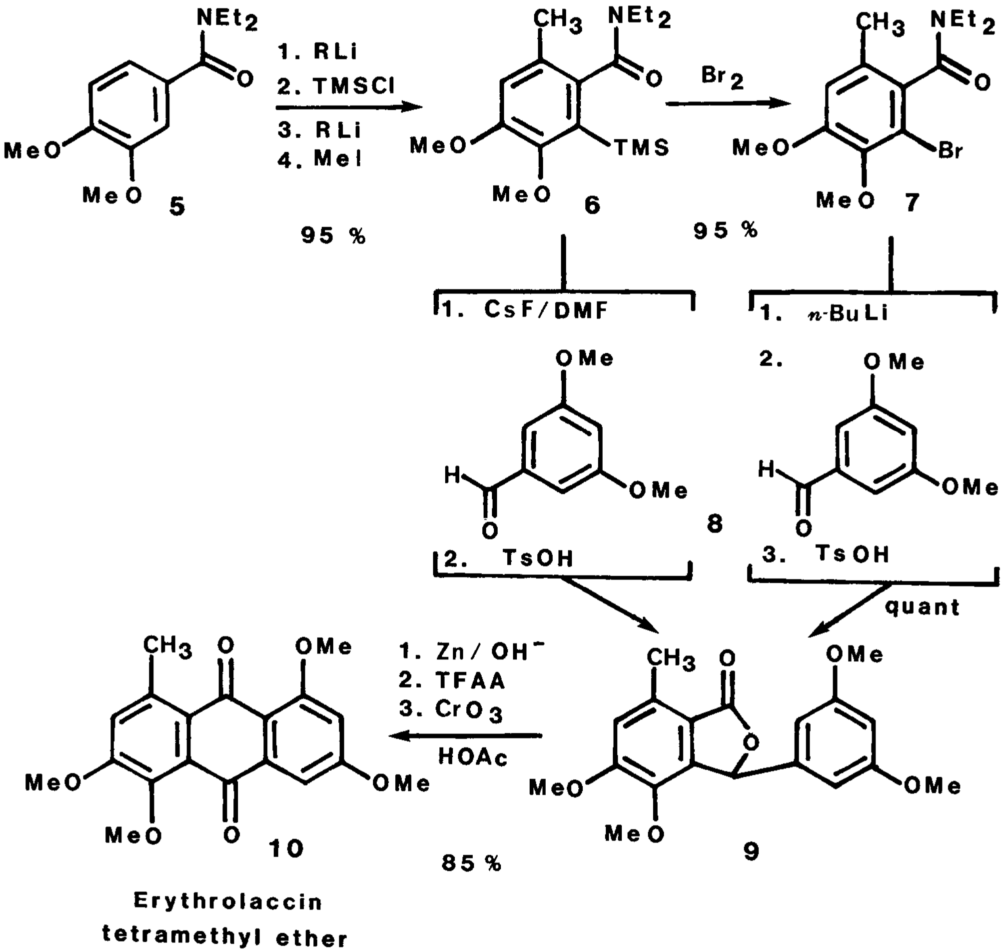
methodology. To illustrate methodological applications, we describe two concise syntheses of the anthraquinone, erythrolaccin tetramethyl ether 10.[4] These strategies promise to considerably enhance the synthetic utility of the aromatic directed metalation reaction.

In view of the report[2] that carbodesilylation is particularly sluggish for aryl silanes with electron-donating substituents, we tested substrates 2a and 2b. Reactions with benzaldehyde in the presence of CsF in anhydrous DMF (reflux/16h)[1] gave, after tosic acid-catalyzed cyclization, the phthalides 3a and 3b respectively in 40-60% yields.[5] The fluoride-silicon interaction is undoubtedly an important feature of this reaction.[2] In 2a and 2b, the electron-withdrawing effect of the amide function presumably overcomes the electron-donating properties of methyl, chloro, and methoxy groups in initiating the aryl carbon-silicon bond cleavage. The mild conditions and the ability to accommodate substituents which would be preferentially metalated (Me) or lead to benzynes (Cl) under strongly basic conditions are significant advantages of the carbodesilylation method over the normal directed ortho lithiation approach.[6,7]

Ipso bromodesilylations were examined for substrates 2b and 2c. Treatment with bromine in CCl_4 at room temperature or with warming led to regiospecific formation of the bromo benzamides 4b and 4c respectively in 55-80% yields.[5] Access to these substitution patterns are far from trivial problems by classical methodology.

The above results guided the approaches to erythrolaccin tetramethyl ether 10 (Scheme). Introduction of trimethylsilyl and methyl groups into 5 by a one-pot sequence gave the pentasubstituted benzene derivative 6. Compound 6, when subjected to reaction with benzaldehyde 8 in the presence of CsF followed by TsOH treatment gave the phthalide 9 in 40% unoptimized yield. On the other hand, bromination (CCl_4/0°C/1 h) of 6 cleanly afforded 7. Taking advantage of the extremely fast rate of metal-halogen exchange compared to base-catalyzed deprotonation,[9] compound 7 was metalated with *n*-BuLi (Et_2O/-100°C/15 min) and condensed with aldehyde 8 to provide, after acid-catalyzed cyclization as before, the same phthalide 9 in quantitative yield. Application of the standard[8] hydrogenolysis-cyclization-oxidation sequence afforded erythrolaccin tetramethyl ether 10.[10] This constitutes the most efficient synthesis (65% overall yield) of this penultimate precursor of the natural product.[11]

The use of silicon protection and regiospecific activation as described in this work should enhance the value of the directed metalation strategy in synthesis. The mild conditions



Scheme

of the fluoride-induced aromatic C-C bond forming reaction, the regiospecific ipso bromodesilylation, and the selective metal-halogen exchange in presence of reactive C-H groups hold promise for other innovative ramifications in preparative aromatic chemistry.[12,13]

References and Footnotes

1. Mills, R.J.; Snieckus, V. J. Org. Chem. 1983, 48, 1565.

2. The synthetic potential of this reaction has been greatly advanced by the systematic work of Effenberger: Effenberger, F.; Schollkopf, K. Angew. Chem. Int. Ed. Engl. 1981, 20, 265.

3. This mechanistically established reaction has not received adequate synthetic attention; see Colvin, E. "Silicon in Organic Synthesis" Butterworths, London **1982**, p. 125.
4. Thomson, R.H. "Naturally Occuring Anthraquinones", 2nd Ed., Academic Press: New York, **1971**.
5. Salient spectral features are: **3a**: mp 92.5-93°C (Et_2O); IR ($CHCl_3$) νmax 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ3.37 (s, 3H), 3.93 (s, 3H), 6.38 (s, 1H). **3b**: mp 132-133°C (Et_2O); IR ($CHCl_3$) νmax 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.73 (s, 3H) 6.32 (s, 1H). **4b**: IR (neat) νmax 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.28 (s, 3H). **4c**: mp 70-71°C (hexane); IR ($CHCl_3$) νmax 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.30 (s, 3H). **9**: mp 110-111.5°C (Et_2O-CH_2Cl_2); IR ($CHCl_3$) νmax 1735 cm^{-1}; ^1H NMR ($CHCl_3$) δ2.68 (s, 3H), 3.41 (s, 3H), 3.77 (s, 6H), 3.91 (s, 3H), 6.24 (s, 1H), 6.45 (s, 1H), 6.83 (s, 1H).
6. Beak, P.; Snieckus, V. *Accts. Chem. Research*, **1982**, *15*, 306.
7. The failure of the reaction between **2c** and 1-naphthaldehyde (CsF/DMF/reflux/10 h) dictated the development of the silicon protection method for the alternate route to peri-methyl substituted anthraquinones.[8]
8. Mills, R.J.; Snieckus, V. *Tetrahedron Lett.*, preceding communication in this issue.
9. Schollkopf, U. in *Methoden der Organische Chemie (Houben-Weyl)*, E. Muller, ed. Georg Thieme Verlag, Stuttgart, **1970**, Vol. 13/1, p. 148. The work of Gronowitz (Gronowitz, S. *Adv. Heterocyclic Chem.* **1963**, *1*, 1; Gronowitz, S. in "Organic Sulfur Chemistry", C.J.M. Stirling ed. Butterworths, London, **1975**, p. 203), and Parham and Bradsher (Parham, W.E.; Bradsher, C.K. *Accts. Chem. Research*, **1982**, *15*, 300) have indicated the greater possibilities of this reaction for the synthesis of polysubstituted heteroaromatic and aromatic systems.
10. Mp 155-156°C, lit[11] mp 155-156°C, shown to be identical (mixture mp, IR, NMR) with an authentic sample kindly provided by Professor P. Brassard.
11. Brassard, P.; Brisson, C.; *J. Org. Chem.* **1981**, *46*, 1810.
12. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with their assigned structures.
13. We are grateful to NSERC of Canada for continuing financial support and Professor Paul Brassard for a sample and Professor Yates for IR and NMR spectral data of **10**.

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