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DIRECTED METALATION OF TERTIARY BENZAMIDES.

SHORT SYNTHESES OF HYDRANGENOL AND PHYLLODULCIN

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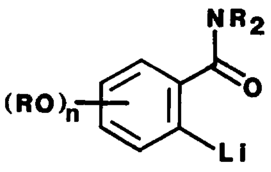
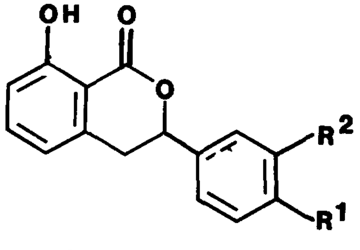
Summary: Brief syntheses of isocoumarin natural products hydrangenol (2) and phyllodulcin (3) via ortho-lithiated benzamide intermediates are described.

The directed metalation of tertiary benzamides has evolved as a useful strategy for the construction of polysubstituted aromatics, phthalides, several classes of biogenetically diverse alkaloids, naturally-occurring anthraquinones, condensed carbocyclic and heterocyclic benzoquinones, and polycyclic aromatic hydrocarbons (PAH's).[1,2] The regiospecific introduction of C_1-units at various oxidation states into substituted ortho-lithiated intermediates 1 allows subsequent chain extension and ring elaboration to systems not easily prepared by classical methods. In this Letter, we show that such methodology provides expedient syntheses of hydrangenol (2, major constituent of *Hydrangea opuloides* Stend var. *otakusa* Maxim)[3,4a] and phyllodulcin (3, sweet principle of *H. serrata* Seringe var. *thunbergii* Sugimoto) [3,4b-d,5] which offer advantages of brevity and efficiency to those previously reported.[3,4]



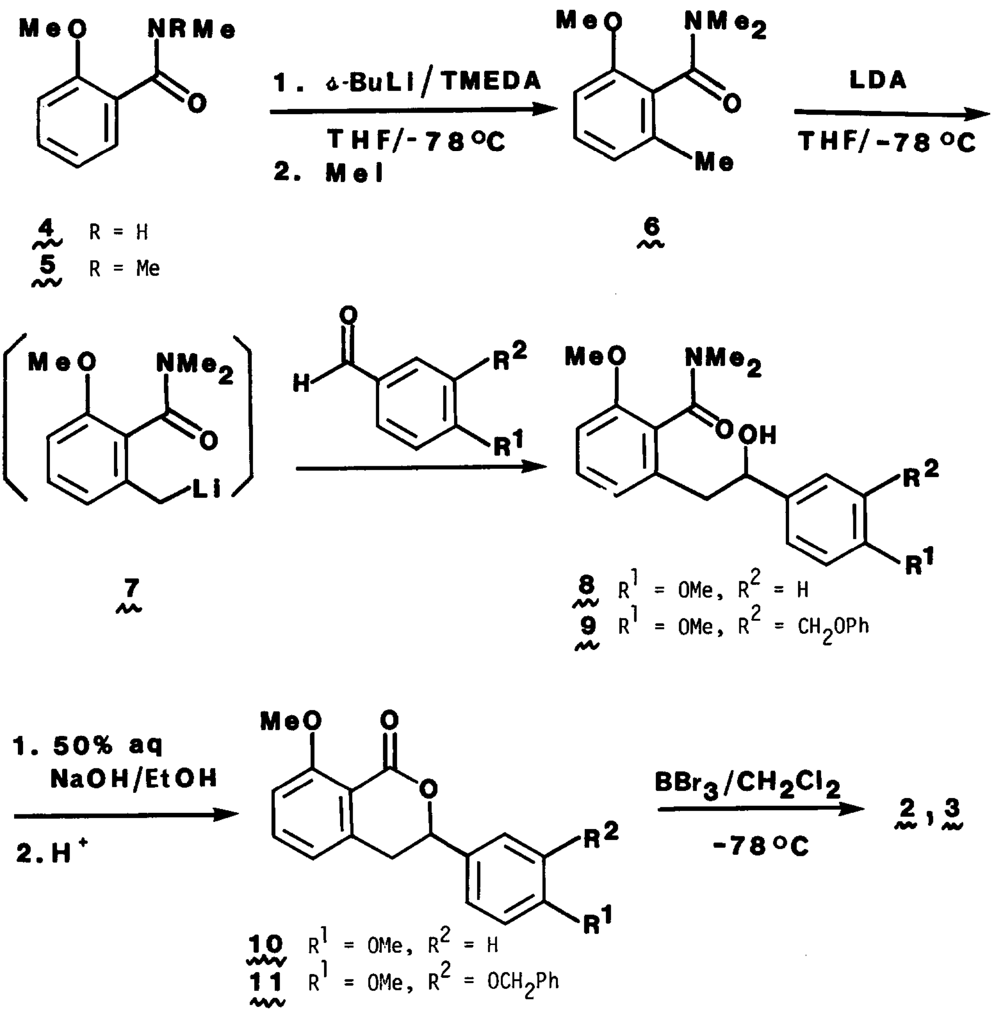
1



2 R^1 = OH, R^2 = H
(Hydrangenol)

3 R^1 = OMe, R^2 = OH
(Phyllodulcin)

Scheme 1



The syntheses of hydrangenol (2) and phyllodulcin (3) are outlined in Scheme 1. Ortho lithiation (2.4 equiv *s*-BuLi/2.4 equiv. TMEDA/THF/-78°C) of N-methyl-*o*-anisamide 4[6] followed by treatment with methyl iodide (2.0 equiv./-78°C) gave the *o*-toluamide 6 in 80% yield.[7] Metalation of 6 with LDA (1.6 equiv. n-BuLi/1.6 equiv. *i*-Pr_2NH/THF/-78°C) resulted in the formation of a burgundy-red solution of the metalated ortho-toluamide species 7[8] which, when quenched with *p*-anisaldehyde, provided the amide alcohol 8. Compound 8 was not isolated but directly converted into the isocoumarin 10[7] by base-catalyzed hydrolysis (50% aq. NaOH/EtOH/reflux 8 h) in 35% overall yield. The preparation of 10 was abbreviated by a one-pot sequence as follows.

Compound **5** was lithiated[9] (1.2 equiv. s-BuLi/1.2 equiv. TMEDA/THF/-90°C), methylated (excess MeI), and the resulting solution of **6** was warmed (60°C) under a stream of nitrogen to remove excess methyl iodide, cooled (-60°C), and sequentially treated with LDA (1.6 equiv. s-BuLi/ 1.6 equiv. i-Pr_2NH/TMEDA), and p-anisaldehyde (1.6 equiv). Alkaline hydrolysis of the unisolated hydroxyamide **8** under the same conditions as described above afforded compound **10** in 45% overall yield. Demethylation (8 equiv. $BBr_3/CH_2C\ell_2$/-78°C → RT) produced (±)-hydrangenol (**2**), mp 181-182°C (lit.[3] mp 181°C) in 94% yield.[11]

Application of the same sequence on **6** using o-benzylisovanillin[12] gave, via the intermediacy of **9**, the isocoumarin **11** (32% overall yield).[7] Isocoumarin **11** was also obtained in 21% overall yield starting with the dimethylamide **5** by the one-pot procedure described for hydrangenol. Selective demethylation and debenzylation of **11** was achieved with BBr_3 (2 equiv/ $CH_2C\ell_2$/-78°C, 1h → RT/12 h) to provide (±)-phyllodulcin (**3**), mp 128-130°C (lit.[4] 130-132°C) in 45% yield.[11]

These short routes to hydrangenol (**2**) and phyllodulcin (**3**) in 42% and 14% overall yields respectively constitute the most efficient syntheses of these natural products and augment further the utility of the directed metalation reaction in synthesis.[13]

References and Footnotes

1. Snieckus, V. Heterocycles, 1980, 14, 1649.

2. Dilithiated secondary amides corresponding to **1** are also useful synthons for isocoumarins (Narasimhan, N.S.; Mali, R.S. Chem. Ind. (London), 1975, 519); anthraquinones (Baldwin, J.E.; Bair, K.W. Tetrahedron Lett. 1978, 2559; Forbes, I.; Pratt, R.A.; Raphael, R.A. Tetrahedron Lett. 1978, 3965); PAH's (Jacobs, S.A.; Harvey, R.G. Tetrahedron Lett. 1981, 1093) and, most recently, anthracyclinones (Kende, A.S.; Rizzi, J.P. J. Am. Chem. Soc. 1981, 103, 4247.

3. a) Structure: Asahina, Y.; Asano, J. Chem. Ber. 1929, 62, 171, ibid. 1930, 63, 429; b) Absolute configuration: Arakawa, H. Bull. Chem. Soc. Jpn. 1960, 33, 200.

4. Synthesis: a) Naoi, Y.; Higuchi, S.; Nakano, T.; Sakai, K.; Nishi, A.; Sano. S. Syn. Commun. 1975, 5, 387 (<6% overall yield); b) Takeuchi, N.; Ochi, K.; Murase, M.;Tobinaga, S. J.C.S. Chem. Comm. 1980, 593 (14% overall yield); c) Takeuchi, N.; Murase, M.; Ochi, K.;Tobinaga, S. Chem. Pharm. Bull. Jpn. 1980, 28, 3013 (0.5% overall yield); d) Naoi, Y.; Higuchi, S.; Ito, H.; Nakano, T.; Sakai, K.; Matsui, T.; Wagatsuma, S,; Nishi, A.; Sano, S. Org. Prep. Proc. Int. 1975, 7, 129 (11% overall yield).

5. Japanese name: Amacha (sweet tea). This is served during the Hanamatsuri(Flower Festival). Phyllodulcin is 400 x as sweet as sucrose: Yamato, M.; Hashigaki, K.; Mito, K.; Koyama, T. Chem. Pharm. Bull. Jpn. 1978, 26, 2321.

6. Faust, J.A.; Jules, L.H.; Sahyun, M. J. Amer. Pharm. Assoc. 1956, 45, 514.

7. All new compounds show analytical and spectral data in accord with their structures. Only salient physical and spectral features follow: **6**: bp 95-97°C/0.1 mm; IR (neat) ν max 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.2, 2.43, 3.08, 3.73 (4 x s, 12 H); MS m/e 193 (M$^+$). **10**: mp 152°C (lit^{3a} 151°C); IR (KBr) ν max 1725 cm^{-1}; NMR ($CDCl_3$) δ 2.93 (q, 1 H, J = 6,15 Hz), 3.30 (q, 1 H, J = 10, 15 Hz), 5.33 (q, 1 H, J = 6,10 Hz); MS m/e 284 (M$^+$). **11**: mp 120-121°C; IR (KBr) ν max 1723 cm^{-1}; NMR ($CDCl_3$) δ 2.95 (q, 1 H, J = 5,16 Hz), 3.18 (q, 1 H, J = 12,16 Hz), 5.27 (q, 1 H, J = 5,12 Hz); MS m/e 390 (M$^+$).

8. Deprotonation of methyl groups ortho to other directed metalation functions is a protocol deserving greater exploitation: Gschwend, H.W.; Rodriguez, H.R. *Org. Reactions*, **1979**, *26*, 1 (see p. 17); Wakefield, B.J. "The Chemistry of Organolithium Compounds" Pergamon Press, New York, 1974, p. 30.

9. Since N,N-dimethylbenzamidessuffer displacement of Me_2NH by *s*-BuLi[10], N,N-diethylbenzamides have been always used to generate ortho metalated species. The successful ortho metalation of **5** (first achieved by M. Iwao, these laboratories) suggests a steric effect to nucleophilic attack from the OMe group.

10. Iwao, M.; Reed, J.N.; Snieckus, V., unpublished observations. See also Beak, P.; Brown, R.A. *J. Org. Chem.* **1977**, *42*, 1823.

11. Synthetic samples **2** and **3** were shown to be identical (IR, NMR, MS) with authentic (±)-hydrangenol and (±)-phyllodulcin kindly provided by Professor M. Yamato, Okayama University.

12. Robinson, R.; Sugasawa, S. *J. Chem. Soc.* **1931**, 3163.

13. We are grateful to NSERC of Canada for financial support (to R.B., V.S.) and to Professor M. Yamato for copies of spectra of (±)-hydrangenol and (±)-phyllodulcin.

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