THE SYNTHESIS OF 2,3-DIMETOXYPHTHALIDE (MECONINE, 1a) AND 2-BENZYLOXY PHTHALIDE (1b), AND THEIR REACTIONS WITH 2-LITHIUMFURAN

Cláudio C. Lopes[§§] and Paulo R.R. Costa[§*]

[§]Núcleo de Pesquisas de Produtos Naturais - Universidade Federal do Rio de Janeiro, C.C.S., Bloco H 21941 Rio de Janeiro, RJ, Brazil

[§§]Instituto de Química, Departamento de Química Analítica UFRJ, Brazil

The phtalides 1a and 1b were prepared from 2a (vanillin) and 2b in 72% and 68% overall yield respectivelly. Compound 1c is commercialy available. Their reactions with 2-lithiumfuran gaves the corresponding keto alcohols 4a-c in ~75% yield.

Phthalides (1) have been utilized as intermediates in the synthesis of different groups of natural products[1]. As part of a program of synthesis of biologically active quinones were designed synthetic approachs which uses the phthalides 1a,1b and 1c as precursors for ring A in the synthesis of natturaling occurring furanonaphthoquinones[2,3].

Meconine (1a), a constituent of opium straw[4], has been synthetized in good yield from as isovanillin derivative[1]. Since isovanillin 2c is considerable more expensive than vanillin (2a), we decided to develop a new synthesis of 1a starting from 2a. Vanillin (2a) was methylated under the usual conditions ($(CH_3)_2SO_4$, NaOH, H_2O) followed by readuction with $NaBH_4$ in methanol to the alcohol 3a. The product (3a) was treated with n-BuLi (2.0 equiv.) in a mixture of hexane and THF at room temperature followed by introduction of a stream of dry CO_2. The lithium carboxylate intermediate was extracted with water and lactonization to 1a was achieved by acidification of the aqueous solution to pH = 1 at 0°C[5].

To prepare the phthalide 1b, the aldehyde 2b was first benzylated ($C_6H_5CH_2Cl$, K_2CO_3, EtOH) followed by reduction with $NaBH_4$ in methanol giving the alcohol 3b. As above 3b was treated with n-BuLi (2.0 equiv.) in hexane and a stream of dry CO_2. The lithium carboxylate intermediate was extracted with water and lactonization to 1b achieved by acidification of the aqueous solution to pH = 1 at 0°C, as before.

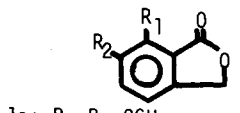
The reactions of 1a,1b and 1c with 2-lithium furan gaves regiospecifically the keto alcohols 4a-c (70-75%)[6]. With 2-lithium-di(2-furyl)cuprate in ether, tetrahydrofuran or pyridin were not observed products 4a-c. Although is reported in the literature the displacement of some allylic acetates with cuprates[7] the analysis of water basic fraction in our cases did not show the presence of the carboxylic acids 5a-c.

Work is in progress to synthetize furanonaphthoquinones from 4a-c.

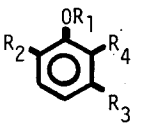
Acknowledgments: Financial support was provided by the Ministry of Planning (FINEP), the National Research Council of Brazil (CNPq) and the Research Council of this University (CEPG). One of us (C.C.L.) is greatful to Atlantic Foundation for a fellowship.

References and notes

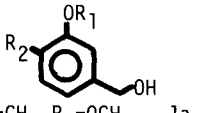
1. N.S. Narasimhan and R.S. Mali, Synthesis, 959 (1983).
2. For preceding papers in this area see P.R.R. Costa, C. C. Lopes and A.V. Pinto, Synth. Comm., 13, 691 (1983); C.C. Lopes, R.S.C. Lopes, A.V. Pinto and P.R.R. Costa, J. Heterocyclic Chem., 21, 621 (1984).
3. Some oxygenated furanonaphthoquinones were isolated from plants of the family Bignoniaceae. D.G.I. Kingston and M.M. Rao, Planta Med., 39, 230 (1980); A.B. de Oliveira, C.L. Zani and G.G. de Oliveira, XVI Congresso Latino-Americano de Química, Summary of papers, 446 (1984).
4. H. Ssmidt and P. Karrer, Helv. Chim. Acta, 28, 722 (1985).
5. For an analogous sequence of reaction with other substrates see B.M. Trost, G.T. Rivers and J.M. Gold, J. Org. Chem., 45, 1835 (1980).
6. For reaction of phthalides with Grignard reagents see: Robert C. Elder Field, Heterociclyc compounds, vol. 2, chap. 2, John Wiley & Sons, Inc, New York, 1951.
7. G. Fouquet and M. Schlosser, Angew. Chem., international ed., 13, 82 (1974); R. J. Anderson, C.A. Hennich and J.B. Siddall, J. An. Chem., 92, 737 (1970)



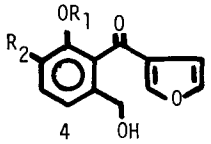
1a; $R_1=R_2=OCH_3$
1b; $R_1=OCH_2Ø, R_2=H$
1c; $R_1=R_2=H$



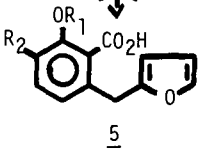
2a; $R_1=CH_3, R_2=OH, R_3=COH, R_4=H$
2b; $R_1=H, R_2=R_4=H, R_3=COH$
2c; $R_1=CH_3, R_2=OH, R_3=H, R_4=COH$



3a; $R_1=CH_3, R_2=OCH_3$ → 1a
3b; $R_1=CH_2Ø, R_2=H$ → 1b



4



5

a, n-BuLi,THF,hex,CO_2,HCl (3a → 1a,78%; 3b → 1b,75%)
b, 2-lithium furan,THF (1a → 4a(%); 1b → 4b (%); 1c → 4c (%).
2-Cooper lithium furan, Et_2O on pyridin or THF. Non identiffieded products.