Synthesis of 3-ethylphthalides and their conversion to 3-methyl-3,4-dihydroisocoumarins: Synthesis of (+)-5-methylmellein.

B H Bhide*, A J Kalaria & S K Patel
Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120, India

Received 29 April 1998; accepted (revised) January 21 1999

Ortho-directed lithiation of N-methylbenzamides 1a-f with n-BuLi in ether/THF followed by alkylation with propanal gives 3-ethylphthalides 2a-f which on treatment with con. H2SO4 or AlCl3 afford 3-methyl-3,4-dihydroisocoumarins 3a-f.

In earlier communications1-5, we have reported the synthesis of several 3-methyl-3,4-dihydroisocoumarins including mellein derivatives using ortho metallation methodology6,7. Recently8, phthalides have been converted to 3-methyl-3,4-dihydroisocoumarins. This prompted us to publish herein our work on a two-step synthesis of (+)-3-methyl-3,4-dihydroisocoumarins. Ortho lithiation of N-methylbenzamides followed by reaction with propanal directly gave the new (+)-3-ethylphthalides 2a-f in 40-50% yields (Scheme I).

The phthalides 2a-f upon warming with H2SO4 gave (+)-3-methyl-3,4-dihydroisocoumarins 3a-f in 25-30% yields. This transformation was more facile with anhydrous AlCl3 (40-65%). The γ-lactone frequency in the IR of phthalides was observed around 1760 cm⁻¹, while in dihydroisocoumarins the δ-lactone frequency was around 1720 cm⁻¹. The above conversion was successfully extended to synthesise (+)-5-methylmellein 3g. A possible mechanism for the conversion of 3-ethylphthalide to 3-methyl-3,4-dihydroisocoumarin is presented in Scheme II.

Experimental Section

General. All the melting points are uncorrected. 1H NMR spectra were recorded on a Hitachi R-1500, 60 MHz instrument in CDCl₃ using TMS as internal standard (chemical shifts in δ, ppm). IR spectra were recorded in KBr on a Nicolet D-400 spectrophotometer (νmax in cm⁻¹).

General procedure for the synthesis of (+)-3-ethylphthalides 2a-f. n-Butyllithium [105 mmole] prepared from lithium (370 mmole) and n-butyl bromide (125 mmole) in diethyl ether (125 mL) was added with stirring to a solution of appropriate N-methylbenzamides (25.6 mmole) in 50 mL of dry THF (freshly distilled over LiAlH₄) at room

![Scheme I](image-url)
temperature under nitrogen atmosphere. The reaction mixture was heated under reflux for 30 minutes and then treated with n-propanal at 0 °C. It was stirred for 30 minutes at 0 °C and then for 10 hr at room temperature. The excess THF was distilled off. The residue obtained was decomposed with HCl (6M, 100 mL) and extracted with ether (2 x 50 mL). The organic layer was washed with cold water and NaHC03, dried over anhydrous Na2SO4, and the solvent evaporated to give the phthalide as an oily product. The phthalides 2a-f were purified by column chromatography over silica gel using 50 % pet. ether-benzene as eluent. The liquid products were further purified by distillation.

2a: bp 85 °C/2 mm Hg; yield 2.0 g (45 %). Anal. Calcd for C11H10O2: C, 75.1; H, 6.7 %. Found: C, 75.0; H, 6.8 %; IR : 1763 cm⁻¹ (γ-lactone); NMR : 0.98 (3H, t, J = 6.6 Hz, -CH2-CH3), 1.8 (2H, m, -O-CH-CH2-CH3), 2.5 (3H, s, Ar-CH3), 5.48 (1H, m, -O-CH2-CH2-CH3), 7.2-7.4 (2H, m, II-5 and II-6), 7.8 (1H, d, J = 8Hz, II-7).

2b: bp 135 °C/2 mm Hg; yield 1.9 g (43 %). Anal. Calcd for C11H10O2: C, 75.1 ; H, 6.7 %. Found: C, 75.2 ; H, 6.8 %; IR : 1769 cm⁻¹ (γ-lactone); NMR : 0.98 (3H, t, J = 6.5 Hz, -O-CH2-CH3), 1.9 (2H, m, -O-CH2-CH3), 2.4 (3H, s, Ar-CH3), 5.4 (1H, m, -O-CH-Ch2-Ch3), 7.2-7.4 (2H, m, II-5 and II-6), 7.6 (1H, q, J = 8Hz and Jm = 3Hz, II-7).

2c: bp 136 °C/2 mm Hg; yield 2.0 g (41 %). Anal. Calcd for C11H12O3: C, 68.75 ; H, 6.25 %. Found: C, 68.3; H, 6.2 %; IR : 1756 cm⁻¹ (γ-lactone); NMR : 0.98 (3H, t, J = 6.5 Hz, -CH2-CH3), 1.9 (2H, m, -O-CH2-CH2-CH3), 3.9 (3H, s, -OCH3), 5.4 (1H, m, -O-CH2-CH2-CH3), 6.8-7.1 (2H, m, II-4 and II-6), 7.8 (1H, d, J = 8Hz, II-7).

2d: mp 59 °C; yield 2.3 g (48 %). Anal. Calcd for C11H12O3: C, 68.75; H, 6.25 %. Found: C, 68.71; H, 6.3 %; IR : 1763 cm⁻¹ (γ-lactone); NMR : 0.9 (3H, t, J = 6.5 Hz, -CH2-CH3), 1.9 (2H, m, -O-CH2-CH2-CH3), 3.9 (3H, s, -OCH3), 5.58 (1H, m, -O-CH2-CH2-CH3), 7.0-7.2 (2H, m, II-5 and II-6), 7.5 (1H, q, J = 8Hz and Jm = 2Hz, II-7).

2e: mp 67 °C; yield 2.4 g (46 %). Anal. Calcd for C11H12O3: C, 64.07; H, 4.85 %. Found: C, 64.0; H, 4.7 %; IR : 1750 cm⁻¹ (γ-lactone); NMR : 1.0 (3H, t, J = 6.5 Hz, -CH2-CH3), 1.9 (2H, m, -O-CH2-CH2-CH3), 5.4 (1H, m, -O-CH2-CH2-CH3), 6.1 (2H, s, -O-CH2-CH2-CH3), 7.0 (1H, d, J = 8Hz, II-6), 7.5 (1H, d, J = 8Hz, II-7).
2f: mp 67 °C; yield 2.3g (44%). Anal. Caled for C_{12}H_{14}O_4: C, 69.9; H, 6.79 %. Found: C, 69.7; H, 6.7 %; IR : 1770 cm\(^{-1}\) (\(\gamma\)-lactone); NMR : 0.898 (3H, t, J = 6.5 Hz, -CH\(_2\)-CH\(_3\)); 1.8 (2H, m, -O-CH-CH\(_2\)-CH\(_3\)); 2.3 (3H, s, Ar-CH\(_3\)); 3.9 (3H, s, -OCH\(_3\)); 5.4 (1H, d, J = 8.5 Hz, -O-CH-CH\(_2\)-CH\(_3\)); 6.8 (1H, d, J = 10 Hz, H-5), 7.2 (1H, d, J = 8.5 Hz, H-6).

General procedure for the conversion of phthalides 2a-f to (+)-3-methyl-3,4-dihydroisocoumarins 3a-f and 3g:

Method A. Phthalides 2a-f (1.7 mmoles) were mixed with cold conc. H\(_2\)SO\(_4\) (2mL) and after shaking well the mixture was warmed on a boiling water-bath for 1 hr and kept at room temperature for 24 hr. The reaction mixture was decomposed by adding cold water and extracted with ether (2x25 mL). The organic layer was washed with NaHC\(_3\)O, dried over anhydrous Na\(_2\)SO\(_4\), and evaporated to give a solid product. The products were recrystallised from ether/n-hexane to give white crystalline 3a-f in 25-30% yields.

Method B. Phthalides 2a-f (1.7mmoles) were treated with anhydrous AlCl\(_3\) (300mg) in methylene chloride (25mL) at reflux temperature for 1-2 hr (monitored by TLC). Methylene chloride was evaporated and the residue decomposed with HCl (6N) and extracted with ether (2x25 mL). The organic layer was washed with NaHC\(_3\)O, dried over anhydrous Na\(_2\)SO\(_4\), and evaporated to give crude 3a-f. They were purified by column chromatography over silica gel using 50% pet. ether-benzene as eluent. Recrystallization from ether/n-hexane gave white crystalline 3a-f in 40-65% yield, identical with those obtained from method-A.

Treatment of 2f with anhydrous AlCl\(_3\) (300 mg) gave both 3f and 3g; however, when 2f was treated with excess anhydrous AlCl\(_3\) (500 mg) for a longer reaction period (3 hr), only (+)-5-methylmellein 3g was obtained.

3a : mp 66 °C(lit.\(^2\) 66 °C); yield 0.15g (51%). Anal. Caled for C\(_{11}\)H\(_{12}\)O\(_3\): C, 75.1; H, 6.7 %. Found: C, 75; H, 6.8 %; IR : 1721 cm\(^{-1}\) (\(\delta\)-lactone).

Acknowledgement

The authors are thankful to the Head, Department of Chemistry, Sardar Patel University, for providing facilities.

References