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Synthesis of the Antimycobacterial Naphthoquinone, 7-Methyljuglone and its Dimer, Neodiospyrin

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ABSTRACT

We report on the laboratory-scale synthesis of the antimycobacterial naphthoquinone, 7-methyljuglone (7-methyl-5-hydroxy-1,4-naphthoquinone) in a one step Friedel-Crafts acylation reaction. This compound was used to synthesize neodiospyrin, which possesses similar bioactivity.

KEYWORDS

7-Methyljuglone; Friedel-Crafts acylation; neodiospyrin; antimycobacterial.

The worldwide resurgence of *Mycobacterium tuberculosis* infections, especially in third world countries, increases the need to discover and synthesize new antituberculosis compounds. This resurgence is in part due to the increase in HIV-AIDS. In addition, the emergence of multidrug-resistant strains of *M. tuberculosis* increases the problem even further. There are various reports that certain naturally occurring naphthoquinones inhibits *M. tuberculosis* at low concentrations,[1–5] (7-methyljuglone MIC = 0.5 μg mL^{-1}; neodiospyrin MIC = 10 μg mL^{-1}) and shows good activity against multidrug-resistant strains. Currently only a few of these naphthoquinones are commercially available. We report here on a relatively quick and inexpensive laboratory-scale synthetic route to 7-methyljuglone and neodiospyrin.

7-Methyl-5-hydroxy-1,4-naphthoquinone (7-methyljuglone **1**) was previously synthesized in a two-step procedure.[6] During the first step maleic anhydride was used to react with 4-chloro-3-methylphenol in a Friedel-Crafts acylation reaction, with the yields ranging from 15–22%. During the second step of reductive dechlorination, yields ranged from 35–85% (overall average yield = 12%).[7] Due to the low yield and the difficulties experienced during the second step an alternative route to **1** was investigated. In this study maleic anhydride was used to react with *m*-cresol in a single step synthesis to yield **1** (yield: 16%).

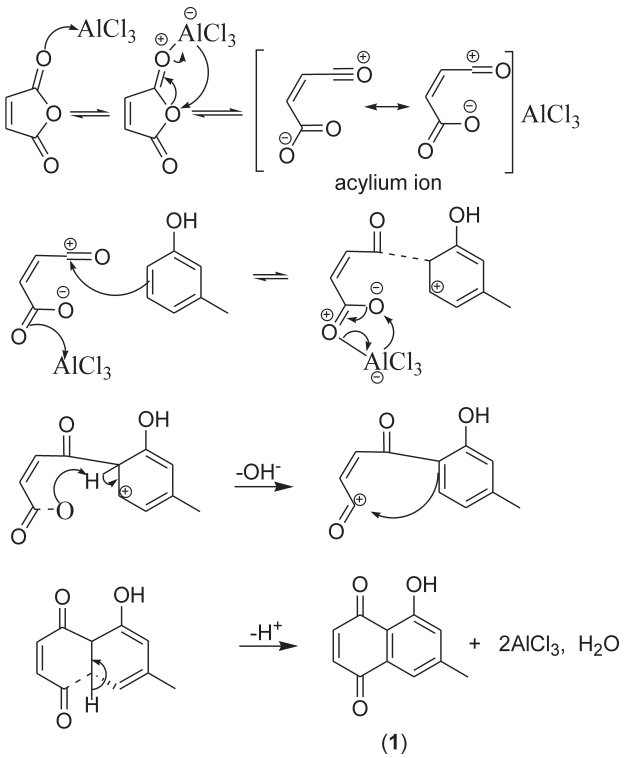
The Friedel-Crafts acylation reaction is a well-known method although the exact mechanism is not yet fully understood. The reaction generally gives good yields of the aromatic ketone when it is performed in an organic solvent. With the use of ionic melts the yields will be considerably lower. We propose that an electrophilic complex is formed (Scheme 1) between the catalyst and the ketone group of maleic anhydride.[8] This initiates ring opening to form the acylium ion. Nucleophilic attack occurs in the *ortho* position of *m*-cresol to the partially positively charged carbon of the acylium ion (lower temperatures favours attack in the *para* position).[9] A second molecule of $AlCl_3$ simultaneously forms a complex with the second ketone group as the process is repeated with nucleophilic attack in the *meta* position of *m*-cresol. The end result is that **1** is formed with the loss of one molecule of water.

In order to synthesize neodiospyrin (**2**) a quinol-naphthol coupling reaction was re-investigated.[10,11] The reduction of **1** was performed with $SnCl_2$ instead of hydrogen gas over a Adams catalyst as previously reported. Purified **1** was reduced to its corresponding hydroquinone with the use of $SnCl_2$ in THF and 4M HCl. The hydroquinone was purified with RP18 SPE chromatography after which it was dissolved in methanol and added to **1** in a phosphate buffer (pH 6.6), at room temperature. The resulting precipitate was filtered, washed with water and dried. LC-MS and ^{1}H-NMR analysis confirmed the formation of the dimer, **2** (Fig. 1).

Experimental

Synthesis of 1

Different ratios of the reagents (10.2 mmol maleic anhydride: 3.4; 6.8; 10.3; 20.5 mmol *m*-cresol) were added to $AlCl_3$



Scheme 1

Reaction mechanism of the Friedel-Crafts acylation reaction between maleic anhydride and *m*-cresol.

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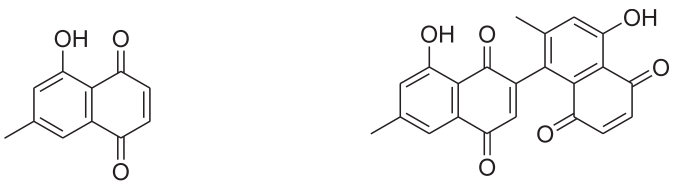

(**1**) (**2**)

Figure 1 Structures of 7-methyljuglone (**1**) and neodiospyrin (**2**).

(90.0 mmol) and NaCl (40 mmol) at 180°C. After 2 min of vigorously stirring the mixture, it was added to 30 mL of 12 N HCl and crushed ice.[7] After 20 min the resulting precipitate was filtered and washed with distilled water (5 times with 50 mL water). The precipitate was allowed to dry after which it was ground with mortar and pestle into a fine powder. The powder were repeatedly extracted with hexane and quantitatively tested on LC-MS for **1**. The optimum ratio of $AlCl_3$ was tested and the reaction repeated using 10.2 mmol of maleic anhydride with 10.3 mmol of m-cresol. It was found that 90.0 mmol of $AlCl_3$ and 40.0 mmol of NaCl gave the best results (less NaCl stopped the mixture from melting and too much NaCl made the mixture extremely viscous). A temperature of 180°C and reaction times of between 100 and 140 sec gave the highest yields.

The reaction was repeated using the best conditions (10.2 mmol maleic anhydride, 10.3 mmol m-cresol, 90.0 mmol $AlCl_3$, 40.0 mmol NaCl, reaction temp 180°C and reaction time 120 sec). The resulting precipitate was repeatedly extracted with hexane after which the hexane was dried and the compound purified with the use of a silica gel column chromatography. The mobile phase consisted of hexane:ethyl acetate (5:1).

Compound **1**: δ_H (200 MHz, $CDCl_3$) 2.37 (3H, s, 7-Me), 6.88 (2H, s, 2,3-H), 7.06 (1H, d, J 0.54 Hz, H-8), 7.42 (1H, d, J 0.54 Hz, H-6), 11.83 (1H, s, 5-OH); m/z $[M-H]^-$ 187 + H; m.p. 125–127°C (lit.[5] 126.5–127°C). The yield of **1** after purification was 305 mg (16%) as determined by LC-MS.

Synthesis of 2

For the synthesis of **2**, 0.13 mmol of **1** was dissolved in 2.5 mL tetrahydrofuran. This was added to a solution of tin(II)chloride (0.66 mmol) dissolved in 2.5 mL of THF and 10 mL of 4 M HCl at 60°C. The solution was stirred for 3 h after which the THF was evaporated. The reduced compound was recovered by passing the remaining aqueous solution through a RP18 SPE tube. After removing the HCl and tin(II)chloride by washing the tube with water, the compound was retrieved by washing with methanol (yield: 18 mg, 72%). A phosphate buffer was prepared by dissolving 5 mmol of KH_2PO_4 in 100 mL of water. The pH was adjusted to 6.6 with the dropwise addition of 10% KOH. 0.13 mmol of **1** was dissolved in 2 mL of methanol and 25 mL of the phosphate buffer. The solution was stirred vigorously while adding the hydroquinone (0.13 mmol) dissolved in 2 mL of methanol. The resulting precipitate was filtered off after 30 min, washed with 50 mL of water (5 times) and dried.[10] The compound was purified with silica gel chromatography with hexane:ethyl acetate (5:2) as the mobile phase.

Compound **2**: δ_H (200 MHz, $CDCl_3$) 2.28 (3H, s, 7-Me), 2.45 (3H, s, 7′-Me), 6.60 (1H, s, H-2′), 6.76 (1H, d, *J* 10.35 Hz, H-2), 6.92 (1H, d, *J* 10.35 Hz, H-3), 7.09 (1H, bd, *J*~1 Hz, H-6′), 7.25 (1H, s, H-6), 7.52 (1H, bd, *J*~1 Hz, H-8′), 11.75 (1H, s, 5′-OH) 12.27 (1H, s, 5-OH); m/z $[M-H]^-$ 373 + H; m.p. 216–219°C (lit.,[9] 220°C). The yield of **2** after purification 29.8 mg (60%) as determined by LC-MS.

Identification of Products

The products of the different reactions were analysed on a Shimadzu LC-MS 2010 EV using a Phenomenex RP18 column (150 × 2 mm, 4 μ) with 62.5% acetonitrile and 5% aqueous acetic acid as mobile phase. A flow rate of 0.2 mL min^{-1} was employed. The retention times of **1** and **2** was 4.15 min and 8.32 min respectively. The molecular mass of the products was determined with an APCI probe in negative ionization mode.

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References

1 N. Lall, *Isolation and Identification of Naphthoquinones from* Euclea natalensis *with Activity Against* Mycobacterium tuberculosis, *Other Pathogenic Bacteria and* Herpes simplex *virus,* Ph.D. thesis, University of Pretoria, Pretoria, South Africa, 2001.

2 O. Weigenand, A.A. Hussein, N. Lall and J.J.M. Meyer, *J. Nat. Prod.*, 2004, **67**, 1936–1938.

3 T.R. Garbe, *Can. J. Microb.*, 2004, **50**, 771–778.

4 N. Lall, M. Das Sarma, B. Hazra and J.J.M. Meyer, *J. Antimicrob. Chemoth.*, 2003, **51**, 435–438.

5 N. Lall, J.J.M. Meyer, Y. Wang, N.B. Bapela, C.E.J. van Rensburg, B. Fourie and S.G. Fransblau, *Pharm. Biol.*, 2005, **43**, 353–357.

6 R.G. Cooke and H. Dowd, *Australian J. Sci. Research,* 1953, **6**, 53–57.

7 O.C. Musgrave and D. Skoyles, *J. Chem. Soc. Perkin Trans.* **1**, 2001, 1318–1320.

8 A.J. Hanneford, P.W. Smith and A.R. Tatchell, eds, *Vogel's Textbook of Practical Organic Chemistry,* 5th edn., Longman Scientific & Technical, Essex, United Kingdom, 1989, pp. 1006–1007.

9 G.A. Benson, P.J. Maughan, D.P. Shelley and W.J. Spillane, *Tetrahedron Lett.,* 2001, **42**(49), 8729–8731.

10 L.K. Kumari, M.H. Babu and M. Pardhasaradhi, *Indian J. Chem.,* 1982, **21B**, 619–621.

11 A.V.B. Sankaram, A.S. Rao and G.S. Sidhu, *Tetrahedron Lett.*, 1975, **42**, 3627–3630.