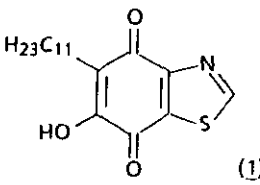
A NEW, EFFICIENT SYNTHESIS OF 5-UNDECYL-6-HYDROXY-4, 7-DIOXOBENZOTHIAZOLE (UHDBT), A POTENT ELECTRON TRANSPORT INHIBITOR

David L. Selwood* and Karamjit S. Jandu

Department of Medicinal Chemistry, The Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, England.

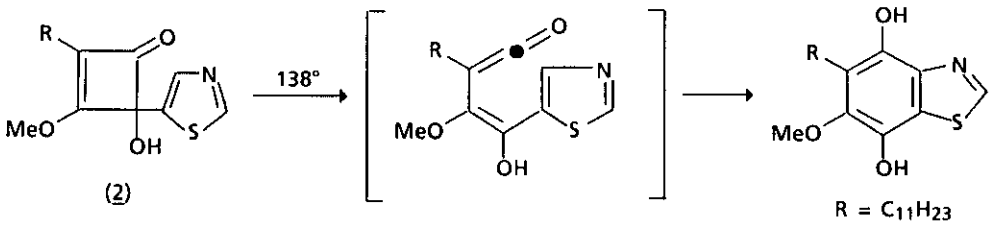
Abstract - An efficient preparation of 5-undecyl-6- hydroxy-4,7-dioxobenzothiazole (UHDBT) is described. The synthesis in 5 stages and 38% overall yield utilises thermal rearrangement of a 4-hydroxy-4-(5-thiazolyl)cyclobuten-3-one as its key step.

Since its original synthesis as a potential anti-malarial[1], 5-undecyl-6-hydroxy-4,7-dioxo-benzothiazole[2] (UHDBT) (1) has become a standard inhibitor used to characterise electron transport systems[3].



(1)

In connection with our work on developing new agents for the chemotherapy of onchocerciasis, we required a source of UHDBT. The published synthesis[1] of this compound requires 6 stages and gives an overall yield of 2.3%. However, the discovery by Liebeskind[4] and Moore[5] of a novel synthesis of quinones via thermolysis of 4-substituted-4-hydroxycyclobutenones, suggested a more efficient route could be developed. We now report the synthesis of UHDBT utilising thermal rearrangement of the cyclobutene-thiazole adduct (2) as the key step. The mechanism of the reaction[4,5] is presumed to be that of conrotatory ring opening of the cyclobutene such that the resulting ketene interacts directly with the thiazole moiety.



(2)

$R = C_{11}H_{23}$

The full synthesis is shown in Scheme 1. 1,2-Dimethoxy-3,4-cyclobutenedione (dimethylsquarate) (3) was converted to the undecylcyclobutenedione (4) by inverse addition of the undecyl Grignard reagent at 0°C and hydrolysis of the intermediate with 18% aqueous hydrochloric acid[6]. The undecylcyclobutenedione (4) was converted to the cyclobutene-thiazole adduct (5) by addition of 5-lithio-2-trimethylsilylthiazole[7] at -65°C in tetrahydrofuran. To our delight, the key thermal rearrangement proceeded smoothly at 138°C in refluxing xylene to give, after silver oxide oxidation, an 85% yield of the methoxy quinone (6). Finally, removal of the methoxy group was effected with lithium iodide/pyridine[8] to give UHDBT (1) in 95% yield. Attempts to use potassium hydroxide/methanol gave either an unacceptably slow reaction (50% yield, 2 days r.t.) or decomposition if more forcing conditions were employed.

To summarise, we have developed a short efficient synthesis of UHDBT in 5 stages and 38% overall yield from 1,2-dimethoxy-3,4-cyclobutenedione.

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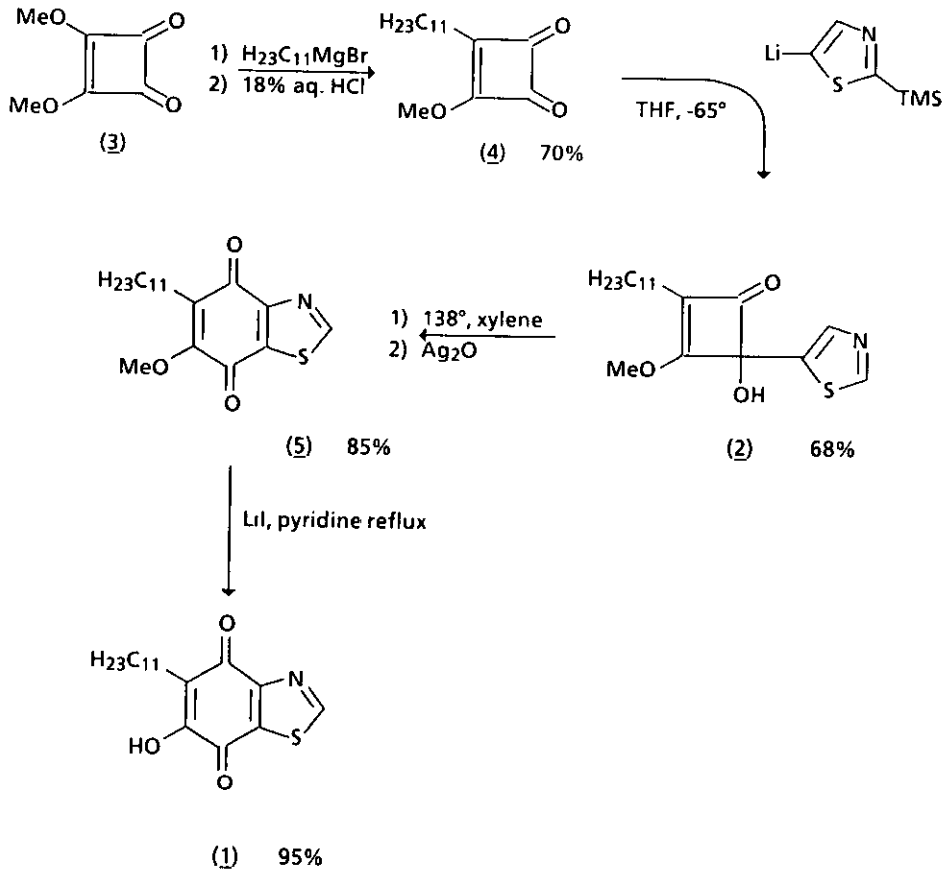
MeO
MeO
O
O
(3)
1) H23C11MgBr
2) 18% aq. HCl
H23C11
MeO
O
O
(4) 70%
THF, -65°
Li
N
S
TMS
H23C11
MeO
O
O
N
S
1) 138°, xylene
2) Ag2O
H23C11
MeO
O
OH
N
S
(5) 85%
(2) 68%
LiI, pyridine reflux
H23C11
HO
O
O
N
S
(1) 95%

SCHEME 1

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Nmr, Ir and Mass spectra were recorded using Bruker AM 200, Perkin Elmer 298 and Kratos ms 902 machines respectively.

Flash chromatography was performed according to the method of Still[9]. 1,2-Dimethoxycyclobutene-3,4-dione was synthesised from commercial squaric acid (Aldrich Chemical Company) by the silver salt method[10]. n-Butyllithium (1.6M in hexane) was obtained from Aldrich Chemical Company.

1-Methoxy-2-undecylcyclobutene-3,4-dione(4)

To 1,2-dimethoxycyclobutene-3,4-dione[10] (2.0g, 14 mmol) in tetrahydrofuran (50 ml) at 0°C was added undecylmagnesium bromide (18 mmol) [generated from magnesium (0.45g, 18 mmol) and 1-bromoundecane (4.3g, 18 mmol) in ether (50 ml)], maintaining the temperature at 0°C. After the addition was complete the reaction was allowed to warm to room temperature and stirred for 30 min then 18% aqueous hydrochloric acid (50 ml) added. The mixture was extracted with ether (2 x 50 ml), the ether washed with water (50 ml) and dried over magnesium sulphate. 'Flash' chromatography, eluting with 2:1 cyclohexane - ethyl acetate, gave (4) (2.6 g, 70%) as a colourless oil. ^{1}Hnmr [200 MHZ, $CDCl_3$]: δ 0.87 (t, J = 6.4 Hz, 3H), 1.27 (m, 16H), 1.66 (m, 2H), 2.57 (t, J = 7.6 Hz, 2H) 4.41 (s, 3H). ms [70eV] m/z 266 (M^+, 1.7%), 238, 223, 153, 140, 126 (100%). Hrms $C_{16}H_{26}O_3$ requires 266.18819, observed 266.18819.

4-Hydroxy-1-methoxy-4(5-thiazolyl)-2-undecylcyclobutene-3-one(2)

To 2-bromothiazole (0.97 ml, 1.76g, 9.02 mmol) in ether (75 ml) at -65°C, was added n-butyllithium (5.6 ml, 9.02 mmol), then chlorotrimethylsilane (1.1 ml, 0.94g, 9.02 mmol) and finally a futher equivalent of n-butyllithium (5.6 ml, 9.02 mmol), stirring the reaction for 30 min at -65°C after each addition. The 5-lithio-2-trimethylsilylthiazole thus generated was added via a double ended flexible needle to (4) (2.4g, 9.02 mmol) in tetrahydrofuran (50 ml) at -65°C. The reaction was stirred at -65°C for 45 min then 5% aq. ammonium chloride (20 ml) added at -65°C. After a further 30 min 5% aq. ammonium chloride (180 ml) was added slowly and the reaction allowed to warm to room temperature. The mixture was extracted with ethyl acetate (2 x 50 ml), the extract washed

with water (50 ml) and dried over magnesium sulphate. 'Flash' chromatography eluting with 3:1 cyclohexane-ethyl acetate gave (2) (2.15g, 68%) as a light brown oil. ^{1}Hnmr [200 MH_2, $CDCl_3$] ppm 0.87 (t, J = 6.4 Hz, 3H), 1.25 (m, 16H), 1.55 (m, 2H), 2.15 (t, J = 7 4 Hz, 2H), 4.05 (s, 3H) 7.80 (s, 1H), 8.80 (s, 1H). ms (70eV) m/z 351 (M^+, 25.4%), 278, 223 (100%), 205. Hrms $C_{19}H_{29}NO_3S$ requires 351.1878, observed 351.1878.

6-Methoxy-5-undecyl-4,7-benzothiazoledione (5)

A solution of (2) in p-xylene (75 ml) was heated to reflux (oil bath temperature 160°C) for 30 min. The solution was cooled and the xylene removed on a rotary evaporator The solid residue was dissolved in ether (100 ml) and silver (I) oxide (2.369, 11 mmol) and magnesium sulphate (10g) added and the reaction stirred for 6 h. The mixture was filtered through Celite and a short plug of silica; the silica was washed with ethyl acetate. The solvent was removed on a rotary evaporator and the residue recrystalised from ethanol/water to give (5) (1.7g, 85%) as a yellow solid. mp 49-51°C. ^{1}Hnmr (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6 7 Hz, 3H), 1.25 (m, 18H), 2.58 (t, J = 7.6 Hz, 2H), 4.09 (s, 3H), 9.05 (s, 1H). ms (70eV) m/z 351 (M^+ + 2), 349 (M^+, 45.6%), 334, 320, 294, 210 (100%), 194, 180. ir (KBr disc) cm^{-1} 2920, 2840, 1660, 1250. $C_{19}H_{27}NO_3S$ requires C65.33%, H7.7%, N4.01%, found C65.04%, H7.96%, N3.8%.

6-Hydroxy-5-undecyl-4,7-benzothiazoledione (1)

To (5) (1.2g, 3.5 mmol) in pyridine (75 ml) was added lithium iodide-trihydrate (0.74g, 3.9 mmol) and the mixture heated to reflux for 30 min. The pyridine was removed on a rotary evaporator, then the residue was dissolved in ethyl acetate (50 ml) and washed with water (25 ml). The solvent was again removed on a rotary evaporator and the resulting solid recrystalised from ethanol/water to give (1) (1.1g, 95%) as a light yellow solid mp 129-131°C (lit.[1] 129-130°C) ^{1}Hnmr (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.41, 3H), 1.2 - 1.7 (m, 18H), 2.59 (t, J = 7.48 Hz, 2H), 7.04 (s, 1H), 9.13 (s, 1H). ms (70eV) m/z 337 (M^+ + 2), 335 (M^+, 37.8%), 320, 318, 208, 196 (100%), 195. ir (KBr disc) cm^{-1} 2910, 2840, 1660, 1615, 1260, 1105. $C_{18}H_{25}NO_3S$ requires C64.47%, H7.46, N4.17%, found C64.30%, H7.46%, N4.02%.

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