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SYNTHESIS OF A 6H-BENZOFURO[3,2-c][1]BENZOPYRAN-6-ONE

A NEW APPLICATION OF THE HURTLEY REACTION

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Abstract: A copper(I)bromide promoted substitution of 2-bromobenzofuran-3- carboxylic acid (**2b**) with dimedone and subsequent lactonization offers a new route to a modified coumestane ring system.

The Hurtley reaction[1] is a versatile method for the synthesis of arylated β-dicarbonyl compounds which are difficult to access by other methods. The reaction proceeds smoothly with 2-bromobenzoic acids and related compounds[2], with various bromopyridine carboxylic acids[3] and in certain cases even with unactivated bromoaryl compounds[4]. Whereas bromothiophene carboxylic acids give fair yields of coupling products[5] seemingly no attempts have been made to extend this methodology to five membered heterocycles like furans and their benzoderivatives. In this paper we describe the preparation of 2-bromobenzofuran-3-carboxylic acid and its reaction with dimedone under modified Hurtley-conditions.

2-Trimethylsilylbenzo[b]furan-3-carboxylic acid (**2a**) was prepared from benzofuran-3- carboxylic acid[6]. The reaction of **2a** with bromine yields 2-bromobenzofuran-3- carboxylic acid (**2b**). On heating **2b** with dimedone in the presence of Cu(I)Br under conditions described by Setsune et al.[4] compound **3** could be obtained as colourless needles with mp 172-174°C . The lactonization was achieved with TFA giving **4** in 90% yield.

Compounds of type **4** exhibit considerable interest because of their biological activity[7].

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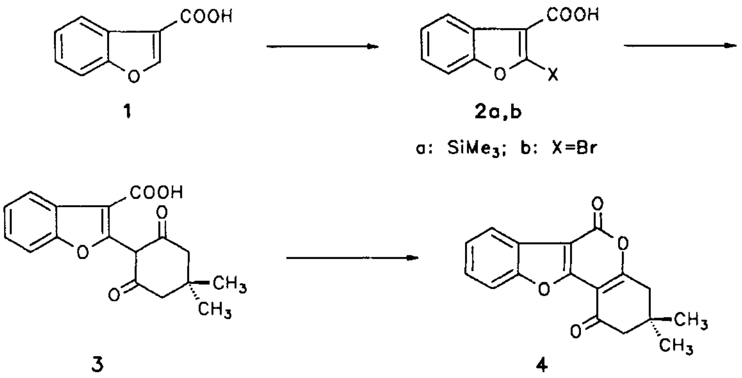
Experimental

2-Bromofuran-3-carboxylic acid (2b): A solution of 1.70 g (7.26 mmol) **2a** in 6 ml of dichloromethane was added at 0°C to a solution of 1.3 g (8.13 mmol) bromine in 5 ml of the same solvent and the mixture refluxed for 1 h. After evaporation of the solvent the residue was recrystallized from methanol/water to give 1.45 g (83%) of **2b** as colourless needles with mp 203°C. ^{1}H-NMR[$CDCl_3$/[D_6] DMSO]: δ=7.20-7.56 (m, 3 H, ar-H), 7.95-8.16 (m, 1 H, ar-H). ^{13}C-NMR[[D_6]DMSO]: δ=111.00 (d, C-7), 113.10 (s, C-3), 121.49 (d, C-5), 124.50 (d, C-6), 125.35 (d, C-4), 125.81 (s, C-9), 135.86 (s, C-2), 154.70 (s, C-8), 163.02 (s, COOH). IR[KBr]: 1680 cm^{-1}.



2-(5,5-Dimethylcyclohexane-1,3-dione-2-yl)-benzo[b]furan-3-carboxylic acid (3): A mixture of 150 mg (4.8 mmol) NaH and 350 mg (2.5 mmol) dimedone in 1,4-dioxane was heated under nitrogen to 70°C. A suspension of 500 mg (2.1 mmol) **2b** and 680 mg(2.5 mmol) Cu(I)Br in dioxane was added and the reaction mixture kept at 70°C for 5 h. After cooling to rt the suspension was treated with 20 ml water, filtered, the filtrate acidified with 5 ml conc. HCl and extracted several times with ether. The organic phase was dried with Na_2SO_4, the solvent removed in vacuo and the residue purified by radial chromatography (ethyl acetate/cyclohexane = 3/1). Compound **4** was obtained as colourless crystals (220 mg, 35%) with mp 172-174°C. ^{1}H-NMR[$CDCl_3$/[D_6]DMSO]: δ=1.19 (s, 6 H, 2 CH_3), 2.40 (s, 4 H, 2 CH_2), 7.17-7.65 (m, 3 H, ar-H), 7.95-8.12 (m, 1 H, ar-H). ^{13}C-NMR[[D_6]DMSO]: δ=27.82 (q, CH_3), 31.70 (s, C-3'), 46.54 (m, C-2', C-4', C-6'), 106.57 (s, C-3), 110.98 (d, C-7), 112.15 (s, C-2), 121.38 (d, C-5), 123.31 (d, C-6), 124.33 (d, C-4), 126.52 (s, C-9), 153.71 (s, C-8), 156.54 (s, C-1', C-3'), 164.25 (s, COOH). IR[KBr]: 1685 cm^{-1}, 1630-1580.

1H,6H-Benzofuro[3,2-c]-2,4-dihydro-3,3-dimethyl-1-oxo-benzopyran-6-one (4): A solution of 220 mg (0.73 mmol) **3** in 1 ml of TFA was stirred for 30 minutes, diluted with dichloromethane and treated with 5 ml 2N NaOH. The mixture was extracted with dichloromethane, the organic phase dried with Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from methanol/water giving 186 mg (90%) of colourless crystals with mp 206°C. ^{1}H-NMR[$CDCl_3$]: δ=1.20 (s, 6 H, 2 CH_3), 2.55 (s, 2 H, 2-H), 2.86 (s, 2 H, 4-H), 7.23-7.80 (m, 3 H, ar-H), 7.92-8.10 (m, 1 H, ar-H). ^{13}C-NMR[$CDCl_3$]: δ=28.22 (q, CH_3), 32.48 (s, C-3), 42.30 (t, C-2), 51.53 (t, C-4), 104.63 (s, C-6a), 107.76 (s, C-11b), 112.16 (d, C-10), 121.10 (d, C-8), 121.81 (s, C-6b), 125.17 (d, C-9), 126.73 (d, C-7), 155.52 (s, C-4a),156.59 (s, C-11a), 160.04 (s, C-10a), 172.99 (s, C-6). IR[KBr]: 1755 cm^{-1}, 1680.

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