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Synthesis of (*E*)- and (*Z*)-5-(Bromomethylene)furan-2(5*H*)-one by Bromodecarboxylation of (*E*)-2-(5-Oxofuran-2(5*H*)-ylidene)acetic Acid

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Abstract: (*E*)- and (*Z*)-5-(bromomethylene)furan-2(5*H*)-one have been prepared starting from the commercially available adduct between furan and maleic anhydride. A bromodecarboxylation reaction is a key step in the synthesis. The reaction gives the (*E*)- or (*Z*)-5-(bromomethylene)furan-2(5*H*)-one as the major product, dependent on the method used in the bromodecarboxylation.

Keywords: Alkenes, γ-alkylidene butenolides, bromodecarboxylation, carboxylic acids, halogenations

A number of 5-(bromomethylene)furan-2(5*H*)-ones have interesting biological activity.[1] It has been reported that (*Z*)-5-(bromomethylene)furan-2(5*H*)-one (**5**) (Scheme 1) is capable of interfering with *N*-acyl homoserine lactone-mediated quorum sensing in *Pseudomonas aeruginosa*.[2]

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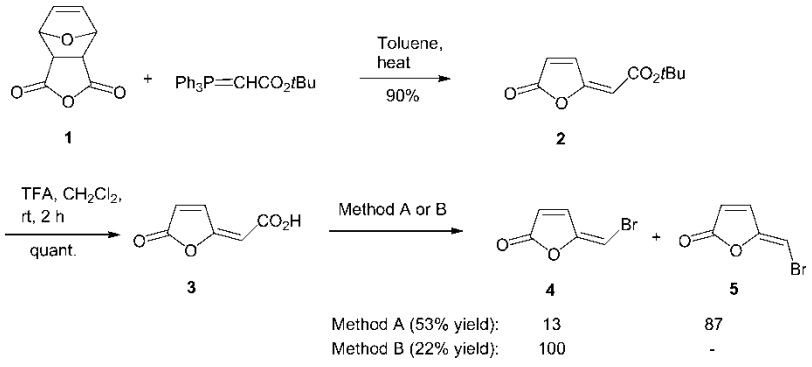

Scheme 1. Method A: 1, Br_2, TFA, CH_2Cl_2, rt, 3 d; 2, NEt_3, DMF, MW, 1 min. Method B: $Br^+(coll)_2PF_6^-$, CH_2Cl_2, rt, 2 h.

We needed both (*E*)- and (*Z*)-5-(bromomethylene)furan-2(5*H*)-one, (**4**) and (**5**) respectively, for biological testing.

(*Z*)-5-(Bromomethylene)furan-2(5*H*)-one (**5**) has previously been prepared from levulinic acid.[3] The preparation of the (*E*)-isomer **4** has, to our knowledge, not been reported.

The α,β-unsaturated ester **2** can be prepared in good yield from the commercially available anhydride **1** in a Wittig reaction,[4] and the ester **2** can be cleaved to the acid **3** in quantitative yield with trifluoroacetic acid in dichloromethane.

A number of methods have been used in the bromodecarboxylation of α,β-unsaturated acids having a β-aryl substituent.[5] Without such a substituent the methods are much more limited.[6] Bromination of the acid **3** with excess bromine in a mixture of trifluoroacetic acid and deuterated chloroform gave, according to ^{1}H NMR, the corresponding 2,3-dibromoalkanoic acid as the major product. When this crude product was heated in a microwave oven (200 W) for 1 min in dimethylformamide and in the presence of triethylamine,[6b] the (*Z*)-furanone **5** was isolated in 46% yield together with 7% of the (*E*)-isomer **4** (method A, Scheme 1). On the other hand, if the acid **3** was reacted with bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate[6a] in dichloromethane at room temperature (method B, Scheme 1), the (*E*)-furanone **4** was the only isomer observed (TLC and ^{1}H NMR). However, the yield in this reaction was low (22%).

Exposure of the (*E*)-isomer to UV light led to isomerization of the thermodynamically more stable (*Z*)-isomer. A thermal isomerization of (*E*)-5-(iodomethylene)furan-2(5*H*)-one to the (*Z*)-isomer has been observed.[7]

EXPERIMENTAL

^{1}H NMR and the ^{13}C NMR spectra were recorded on Bruker Avance DPX instruments. Mass spectra, under electron-impact conditions, were

recorded at 70 eV ionizing energy on a Fision ProSpec instrument. Microwave irradiation was carried out with a CEM MDS-81D microwave oven.

Preparation of (*E*)-5-(Bromomethylene)furan-2(5*H*)-one (4) and (*Z*)-5-(Bromomethylene)furan-2(5*H*)-one (5)[3]

Method A

(*E*)-*t*-Butyl 2-(5-oxofuran-2(5*H*)-ylidene) acetate (**2**[4]; 196 mg, 1.0 mmol) was dissolved in a mixture of CH_2Cl_2 (1 mL) and TFA (1 mL). The reaction mixture was stirred at room temperature for 2 h, evaporated, and redissolved in a mixture of $CDCl_3$ (2 mL) and TFA (0.1 mL). Bromine (2 mL, 2 M in CCl_4) was added, and the mixture was stirred at room temperature until ^{1}H NMR showed that all starting material had been consumed (3 d). The solvents were evaporated off, and the residue was dissolved in DMF (2 mL). Triethylamine (0.15 mL, 1.08 mmol) was added, and the mixture was heated in a microwave oven (200 W) for 1 min. Water was added and the product was extracted into Et_2O, washed with brine (3 × 10 mL), dried ($MgSO_4$), and evaporated. The products were separated by flash chromatography (silica, hexane–EtOAc 3 : 2). $R_f = 0.55$; (*E*)-5-(bromomethylene)furan-2(5*H*)-one (**4**). Yield: 12 mg (7%); mp = 33–35°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.42$ (dd, $J_{3,1'} = 1.8$ Hz, $J_{3,4} = 5.6$ Hz, 3-H), 6.55 (dd, $J_{1',4} = 0.7$ Hz, $J_{1',3} = 1.8$ Hz, 1′-H), 7.80 (dd, $J_{4,1'} = 0.7$ Hz, $J_{4,3}$ 5.6 Hz, 4-H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 94.66$, 122.81, 140.43, 152.12, 168.81. MS: m/z = 176 (M + 2, 100), 174 (M, 100), 148 (47), 146 (48), 122 (30) 120 (32), 95 (52). $R_f = 0.31$; (*Z*)-5-(bromomethylene)furan-2(5*H*)-one (**5**).[3] Yield 80 mg (46%); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.09$ (s, 1′-H), 6.30 (d, $J_{3,4} = 3.5$ Hz, 3-H), 7.37 (d, $J_{4,3} = 3.5$ Hz, 4-H). MS: m/z = 176 (M + 2, 100), 174 (M, 100), 148 (33), 146 (35), 122 (28) 120 (30), 95 (34).

Method B

Bis(2,4,6-trimethylpyridine)bromine(I) hexafluorophosphate[6a] (700 mg, 1.50 mmol) was added at 0°C to a solution of (*E*)-(5-oxofuran-2(5*H*)-ylidene)acetic acid (**3**[4]; 197 mg, 1.40 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0°C for 15 min and at room temperature for 2 h before Et_2O was added. The Et_2O was washed with 1 M HCl, saturated $NaHCO_3$, and brine before it was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (silica, hexane–EtOAc 4 : 1). $R_f = 0.33$; (*E*)-5-(bromomethylene)furan-2(5*H*)-one (**4**). Yield: 54 mg (22%).

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