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Synthesis of 4,4′-Dibromobenzilic Acid

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Benzilic acid rearrangement of 4,4′-dibromobenzil under phase-transfer catalysis conditions proceeds rapidly with high yield.

Bromo derivatives of benzilic acid esters are useful as precursors of [^{3}H]-labelled derivatives. Dibromo-substituted benzilic acid has been prepared by Bickelhaupt [1] and by Biltz. [2] The drawbacks of their method are the relatively low yields and the lengthy reaction time. Our goal was to develop an improved synthesis of 4,4′-dibromobenzilic acid.

Since attempts to brominate benzil and α-chlorophenylacetic acid were unpromising, we prepared 4,4′-dibromobenzil using the method of Biltz. [3,4] The three by-products **3**, **4a** [3] and **4b** [3] were formed in less than 5% yield of the main product, isolated in 72% yield, Scheme 1. †

The conditions used by Biltz [2] to effect the conversion of **2** to **5** required 48 h and gave only a 58% yield of impure product. We explored a modification of their procedure and determined that the use of potassium hydroxide ‡ in benzene

† *Experimental.* Silufol-UV 254 nm plates were used for TLC analysis. Developers were 2,7-dichlorofluorescein and methylene Red. IR spectra were recorded as KBr pellets on a IKS-29 (LOMO, Russia) spectrometer. Liquid chromatography was performed on a high performance liquid chromatograph (HPLC) LC-512 with refractive index detector RIDK 101 on a column: Separon SGX C_{18}, 3.3 mm × 150 mm (Laboratorni Pristroje, Czechoslovakia), Zorbax ODS C_{18}, 4.0 mm × 250 mm (DuPont, USA), eluting with propan-2-ol–water (7:3) 0.4 ml min^{-1}. ^{13}C NMR spectra were recorded on a Bruker AC-200 P (Spektrospin AG, Switzerland) spectrometer, operating at 50.33 MHz with proton noise decoupling, using $CDCl_3$ as solvent and TMS as internal standard. Melting points were determined by capillary method and are uncorrected. All solvents were absolute grade (free from water) and dried according to the literature procedure. [7]

Synthesis. 4,5-Diphenyl-2-imidazolone **1**. [8] A solution of benzoin (265 g, 1.25 mol), urea (138 g, 2.30 mol) and acetic acid (1060 ml) was refluxed for 6 h and then kept for 14 h at room temperature. The precipitate formed was filtered off and washed with acetic acid, ether and hot water. The precipitate was dried at 120 °C to give 216 g (73%) of **1** as white crystals, m.p. 313–315 °C, TLC (ethanol) R_f = 0.77. IR (KBr) ν/cm^{-1}: 3420, 3150, 1680, 1640, 1600, 1505, 1070, 910, 765, 750, 685, 660, 520. ^{13}C NMR: C_1 175.20, C_2 118.89, C_3 129.70, C_4 126.97, C_5 128.97, C_6 128.01 ppm.

4,4′-Dibromobenzil **2**. A solution of **1** (60 g, 0.254 mol), Br_2 (240 g, 1.5 mol) and acetic acid (1500 ml) was refluxed for 1.5 h. Water (120 ml) was added and the solution was refluxed for an additional 10 min. The mixture was cooled in ice-cold water. The precipitate formed was filtered off, washed with acetic acid and recrystallised from benzene to afford 2 as yellow needles: yield 67 g (72%), m.p. 223–224 °C, TLC (chloroform) R_f = 0.80. IR (KBr) ν/cm^{-1}: 3090, 1675, 1590, 1486, 1070, 835, 680, 510. ^{13}C NMR: C_1 130.76, C_2 132.53, C_3 131.30, C_4 131.46, C_5 192.54 ppm.

4,4′-Dibromobenzilic acid **5**. (*a*) Compound **2** (5 g, 13.6 mmol) was dissolved in 15 ml benzene, then 10 ml water, 10 ml methanol, KOH (20 g, 0.365 mol) and Cetavlone (0.25 g, 0.686 mmol) were added and the mixture was stirred for 3 h at at room temperature. The water layer was separated, diluted with 300 ml of water and acidified with dilute HCl. The white precipitate was filtered off, washed with water and dried. The yield of **5** was 5.0 g (96%), m.p. 109–110 °C.

(*b*) Compound **2** (20 g, 0.543 mmol) was dissolved in 40 ml of benzene and 20 ml of water and NaOH (22 g, 0.550 mol) and Cetavlone (2.5 g, 6.86 mmol) were added. The mixture was stirred under reflux for 3 h at 80 °C. The water layer was separated and 300 ml of water was added. The solution was then acidified with dilute HCl, and the white precipitate was filtered off, washed with water and dried. The yield of **5** was 14.8 g (71%), m.p. 109–110 °C.

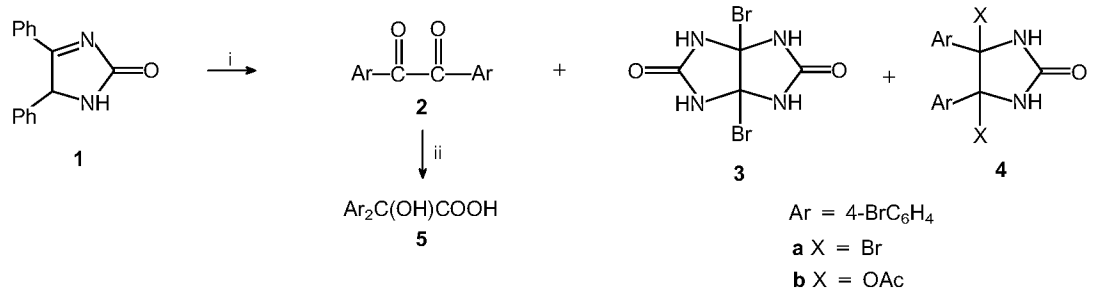
(*c*) The synthesis was realized as for (*b*), but 22 g (0.392 mol) KOH was used instead of NaOH. The yield of **5** was 86%, m.p. 109–110 °C.

(*d*) Similar synthesis to that of Poonia, ref. 6. Compound **2** (5 g, 13.6 mmol), NaOH (20 g, 0.500 mol) and 27 ml ethanol–water (7:3) were mixed with stirring and heated for 4 h under reflux. Water (60 ml) was then added and the mixture was stirred for a further 10 min. After the mixture had cooled the two resulting layers were separated and acidified. From the upper layer white crystals of **5** were precipitated. Yield 4.75 g (90%), m.p. 110–111 °C.

(*e*) Similar synthesis to Biltz, ref. 2. A sample of sodium ethoxide was prepared *in situ* (4.8 g, 0.209 mol; 120 ml ethanol). After the mixture had cooled compound 2 (8 g, 21.7 mmol) was added to the mixture. Within 1 h a yellow viscous solution was formed which was left untouched for 2 days. The mixture was poured into 1.5 l of water and acidified with HCl. A brown oil was precipitated which was dissolved in chloroform. Compound **5** precipitated on addition of pentane, yield 4.5 g (55%), m.p. 108–109 °C.

TLC (chloroform–ethanol; 95:5): R_f = 0.35. IR ν/cm^{-1}: 3400, 3060, 1720, 1580, 1485, 1065, 1050, 825, 675. ^{13}C NMR: C_1 122.98, C_2 131.55, C_3 129.00, C_4 139.80, C_5 80.30, C_6 177.38 ppm.

‡ NaOH was found to be less effective (71% yield).



Scheme 1 *Reagents and conditions*: i, Br_2, HOAc; ii, OH^-, PTC, room temperature.

and methanol[§] in the presence of hexadecyltrimethylammonium bromide (Cetavlone)[¶] as a phase-transfer catalyst (PTC) afforded a 96% yield of pure **5** after only 3 h at room temperature. Although Poonia's procedure[6] proceeds in 70% yield it requires 4 h at reflux. The mild conditions coupled with the short reaction time, yield and purity of the product recommends our procedure as the best method of obtaining **5**.

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[§] Ethanol, butan-1-ol and propan-2-ol were not as effective.
[¶] Tetrabutylammonium bromide was less successful.

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