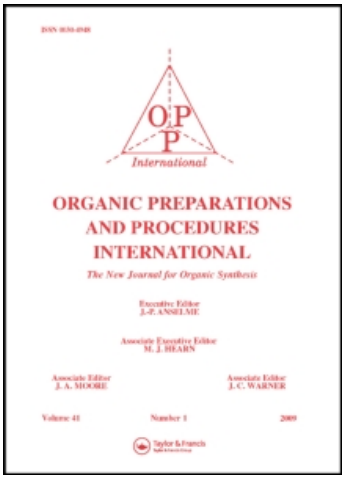

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AN IMPROVED SYNTHESIS OF 2-ANTHRALDEHYDE

Palanisamy Arjunan[a]; K. Darrell Berlin[a]
[a] Department of Chemistry, Oklahoma State University, Stillwater, OK

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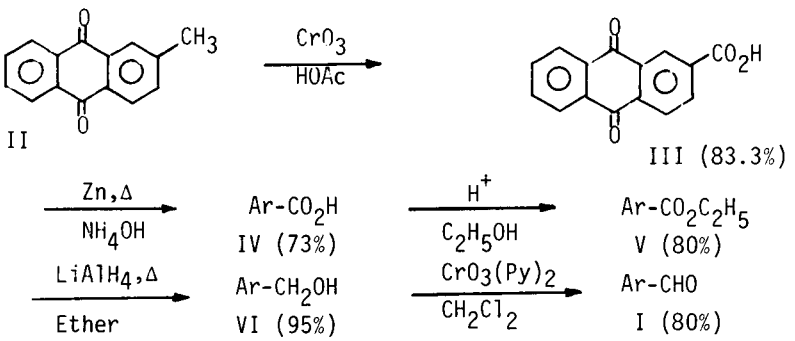
AN IMPROVED SYNTHESIS OF 2-ANTHRALDEHYDE

Submitted by (11/28/80) Palanisamy Arjunan and K. Darrell Berlin*

Department of Chemistry
Oklahoma State University
Stillwater, OK 74078

2-Anthraldehyde (I) was found to be a valuable synthon in the preparation of certain lipid mimics.[1] The synthesis as well as as spectroscopic properties of I have been reported.[2,3] Recorded methods for I have involved lengthy procedures, produced undesirable side-products and given poor yields.[2,3] An alternative route described in the Scheme was developed.



Ar = 2-Anthryl

The starting material 2-methylanthraquinone (II) is inexpensive and is readily available (Aldrich). Conversion of II to 2-hydroxymethylanthracene (VI) only partially paralleled literature procedures and required critical changes.[4-9] Oxidation[4] of II with CrO_3/HOAc gave anthraquinone-2-carboxylic acid (III) which was reduced by zinc-ammonia to anthroic acid (IV).[7] Esterification of IV gave ethyl 2-anthroate (IV)[8] which could be reduced with $LiAlH_4$ in dry ether to 2-hydroxymethylanthracene (VI).[9] Since VI was only sparingly soluble in ether, the yield of VI was maximized by Soxhlet extraction (ethanol) of the insoluble residues. Oxidation of VI to I was effected with Collins' reagent [$CrO_3 \cdot (Py)_2$].[10] Unlike the reported procedures,[2,3] the present method gave very pure I in an overall

yield of 37.4% (I was stored in a dark container since it is light sensitive).

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and were uncorrected. IR spectral data were collected on a Beckman IR-5A unit. NMR spectra signals were recorded in parts per million (ppm) downfield from TMS on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating a 100.1 MHz for ^1H NMR analysis. 2-Methylanthraquinone (Aldrich, mp 170-173°), CrO_3 (Baker analyzed reagent), zinc metal dust (90%, Baker and Adamson), $LiAlH_4$ (Ventron) were used as purchased without further purification. Anhydrous ether (Mallinckrodt) was dried over sodium before use. Anhydrous pyridine was obtained by distillation of reagent grade material (Baker) from BaO and was stored over Linde 4A molecular sieves. Methylene chloride (Eastman) was purified by shaking with conc. H_2SO_4, then by washing with aq. saturated $NaHCO_3$ and then water.[10] The purified solvent was stored in a brown bottle over Linde 4A molecular sieves and kept in the dark. Chromium trioxide (Mallinckrodt, analytical reagent) was stored in a vacuum desiccator over P_2O_5 prior to use. All organic extracts were dried over $MgSO_4$ and an evaporator was used to remove organic solvents in the usual workup.

Preparation of Anthraquinone-2-carboxylic Acid (III).-To 2-methylanthraquinone (20 g, 90 mmol) in a 3-L, three-necked flask fitted with a condsener, a thermometer and a mechanical stirrer was added glacial acetic acid (1000 mL), and the mixture was warmed gently with stirring to dissolve the 2-methylanthraquinone. Anhydrous CrO_3 (70 g, 700 mmol) was added slowly with vigorous stirring, and the reaction mixture was warmed to 70-80° (oil bath) and kept at that temperature (vigorous stirring) for 8 hs. The cooled reaction mixture was then diluted with 8 l. of water. The resulting precipitate was filtered and washed with water until the disappearance of the blue color of the chromium salts was observed in the washings. The remaining solid was then treated with dilute (1:1) ammonia solution at the boiling point until the filtrate ceased to form a precipitate by acidification. The filtrate was then cooled and acidified with conc. HCl. The deposited anthraquinone-2-carboxylic acid was filtered, washed with water, and dried (aspirator). Recrystallization (500 mL of HOAc) gave 18.9 g (83%) of III as a yellow powder, mp. 291-292° (dec), lit.[4] mp. 291-292°; IR (KBr) υ_{max}: 3000-3050 (O-H), 1700 (C=O, ketone), 1600 cm^{-1} (C=O, acid); ^1H NMR (DMSO-d_6: δ 7.84-8.52 (m, Ar-H).

Preparation of 2-Anthroic Acid (IV).-A suspension of III (10 g, 40 mmol), zinc dust (40 g, 600 mg atom) and $CuSO_4$ catalyst (ca. 0.5 g) in aq. ammonia (20%, 450 mL) was stirred (magnetic) under reflux until the temperature reached 70°. After 3 hs at 70°, the reaction mixture changed from dark red to amber, and the hot aqueous solution was filtered from insoluble

residues, cooled and acidified with dilute HCl (1:1, 400 mL). The precipitated yellow solid was filtered, dried (aspirator) and recrystallized (400 mL of HOAc) to give 6.4 g (73%) of IV as a yellow powder, mp. 283-285° (dec) lit.[7] mp. 274°; IR (KBr) υ_{max}: 3000 (O-H), 1670-1680 cm^{-1} (C=O); ^1H NMR (DMSO-d_6); δ 7.52-8.80 (m, Ar-H).

Preparation of Ethyl 2-Anthroate (V).-A mixture of the acid IV (4.9 g, 22 mmol), anhydrous C_2H_5OH (150 mL) and conc. H_2SO_4 (7 mL) was boiled (24 hs) and was cooled; the ethanol was evaporated. The resulting solid (in ether) was washed with water and then with saturated Na_2CO_3 solution. Recrstallization (95% C_2H_5OH) gave 4.4 g (80%) of V as white flakes, mp. 141-142°, lit.[8] mp. 137.5-139°; IR (KBr) υ_{max}: 1700 (C=O), 2950-2975, 1000-1300 cm^{-1} (C-O-C); ^1H NMR ($DCCl_3$): δ 1.38-1.54 (3 H, t, CH_3), 4.34-4.56 (2 H, q, CH_2), 7.42-8.56 (9 H, m, Ar-H).

Preparation of 2-Hydroxymethylanthracene (VI).-A suspension of $LiAlH_4$ (3 g, 79 mmol) in dry ether (600 mL) was placed in an apparatus with a Soxhlet extrator and a condenser (N_2 inlet). Ester V (12.1 g, 48 mmol) was placed in a sintered crucible inside the Soxhlet extrator. The solution was warmed with stirring (magnetic) until all of the ester had been transferred to the reaction flask. The resulting solution was cooled, and ethyl acetate was added dropwise to destroy the unreacted $LiAlH_4$. Water was added to obtain a clear mixture composed of two layers. The etheral layer was separated, was washed with water, dried and then evaporated to give a small amount of yellow solid A (recrystallized once from HOAc). The aqueous layer was concentrated in vacuo and a yellow solid was collected by suction. This latter solid was extracted via a Soxhlet extractor (95% C_2H_5OH) and gave a yellow solid B. Solids A and B were combined and recrystallized (C_6H_6) to give 9.6 g (95%) of VI, mp. 223-225° (dec), lit.[9] 223-224° (dec); IR (KBr) υ_{max}: 3300 (O-H), 1040-1050 cm^{-1} (C-O-); ^1H NMR ($DCCl_3$): δ 1.57 (1 H, s, O-H), 4.93 (2 H, s, CH_2), 7.40-8.46 (9 H, m, Ar-H).

Preparation of 2-Anthraldehyde (I).-A 250 mL three-necked flask equipped with a mechanical stirrer, a thermometer, and a drying tube was charged with pyridine (5 g, 60 mmol) and CH_2Cl_2 (75 mL). The solution was stirred at room temperature and anhydrous CrO_3 (3 g, 30 mmol) was added in one portion. After the deep burgundy-colored solution was stirred at room temperature for 15 min, a suspension of alcohol VI (1 g, 5 mmol) in 25 mL of CH_2Cl_2 was added. A tarry, black residue separated immediately. Stirring was continued for 15 min at room temperature, and the solution was decanted from the residue. The black residue was washed with 200 mL of

ether. The combined organic solutions were washed successively with 5% aq. NaOH solution (3 x 100 mL), 5% HCl (3 x 100 mL), 5% $NaHCO_3$ solution (3 x 100 mL) and finally with 100 mL of saturated aq. NaCl solution. The resulting solution was dried and evaporated to give a yellow solid which turned brick red in light. Consequently, the product was kept in the dark and recrystallized (C_6H_6) to give 0.8 g (81%) of a yellow powder, mp. 202-203° (dec), lit.[3] mp. 202-203° (dec); IR (KBr) υ_{max}: 1675 (C=O), 2800, 2950-3000 cm^{-1} [C(O)H]; ^1H NMR ($DCCl_3$): δ 7.46-8.58 (9 H, m, Ar-H), 10.16 [1 H, s, C(O)H].

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A TWO-STEP PREPARATION OF 1-BENZYLPYRAZOLE-2-^{15}N

Submitted by Murtedza bin Mohamed and John Parrick*
(8/19/80)
School of Chemistry
Brunel University
Uxbridge, Middlesex, UB83PH
ENGLAND

Recently an N-benzylpyrazole with a ^{15}N-label in a known position was needed. Although mono ^{15}N-labelled pyrazole is potentially readily prepared from commercially available hy-