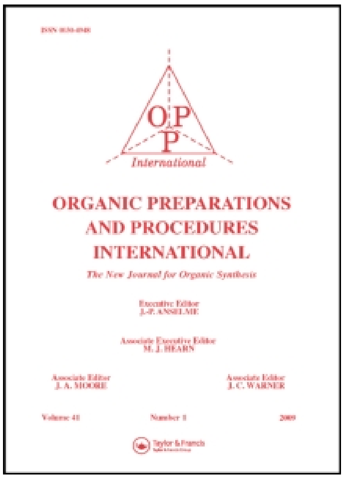

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Prabhu, V. S. and Keana, John F. W.(1984) 'IMPROVED PREPARATION OF 2-CHLORO-6-METHYLANTHRAQUINONE, A PRECURSOR FOR THE CORRESPONDING 6-CARBOXYLIC ACID ESTERS AND 2-CHLORO-6,9,10-TRIMETHYLANTHRACENE', Organic Preparations and Procedures International, 16: 5, 329 — 333

To link to this Article: DOI: 10.1080/00304948409457890

URL: http://dx.doi.org/10.1080/00304948409457890

ORGANIC PREPARATIONS AND PROCEDURES INT. 16(5), 329-333 (1984)

IMPROVED PREPARATION OF 2-CHLORO-6-METHYLANTHRAQUINONE, A PRECURSOR FOR THE CORRESPONDING 6-CARBOXYLIC ACID ESTERS AND 2-CHLORO-6,9,10-TRIMETHYLANTHRACENE

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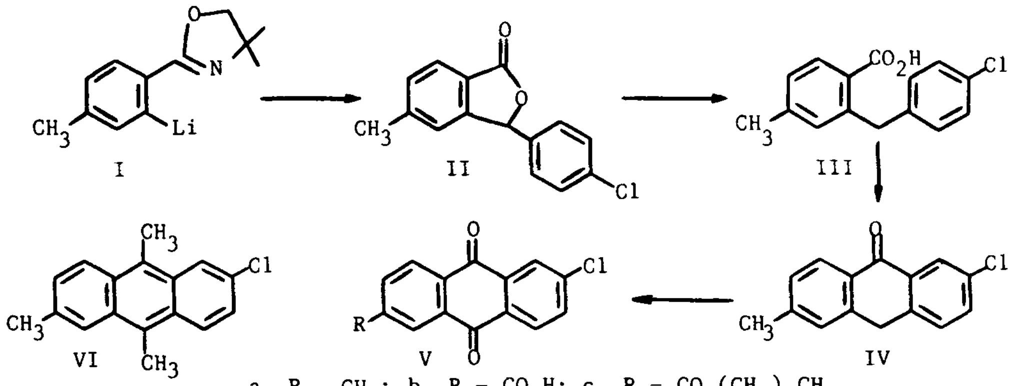
In connection with another project we required an efficient synthetic route to the title compounds. 2-Chloro-6-methylanthraquinone (Va) has been previously prepared in unspecified yield by a Sandmeyer reaction on the corresponding amine.[1] 2-Chloroanthraquinone-6-carboxylic acid (Vb) has been prepared in a multistep procedure involving cyclization of 2-(p-chlorobenzyl)terephthalic acid.[2] Apparently cyclization[3] of 2-(p-chlorobenzoyl)terephthalic acid leads to a mixture of Vb and the isomeric 2-chloroanthraquinone-7-carboxylic acid.[2]

Our synthetic route is shown below. Addition of p-chlorobenzaldehyde to aryllithium reagent I[4,5] gave, after acid-catalyzed hydrolysis and cyclization, lactone II. Reduction[5,6] of II to acid III was effected



a, R = CH_3; b, R = CO_2H; c, R = $CO_2(CH_2)_3CH_3$

by treatment under reflux with a solution of hydrogen iodide and hypophosphorous acid in glacial acetic acid. Cyclization of III with sulfuric acid gave anthrone IV which was immediately oxidized with potassium dichromate in acetic acid to give the desired anthraquinone Va. Thus, Va could be prepared in 58% overall yield from p-chlorobenzaldehyde.

Oxidation of Va with potassium dichromate in sulfuric acid[7] afforded acid Vb in 96% yield. Despite its limited solubility in a variety of solvents, this latter substance could be converted into the acid chloride and thence into butyl ester Vc in excellent yield. Alternatively, reaction of Va with methyllithium followed by reduction of the intermediate diol with stannous chloride[8] constituted a convenient synthesis of 2-chloro-6,9,10-trimethylanthracene (VI).

EXPERIMENTAL SECTION

Melting points (^{o}C) were recorded in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Varian XL-100 spectrometer. Chemical shifts are reported in δ units downfield from internal Me_4Si. Elemental analyses were performed by Mic Anal, Tucson, AZ. Reactions were run under a N_2 atmosphere.

3-(4-Chlorophenyl)-5-methylphthalide (II). - A solution of 4,4-dimethyl-2-(4-methylphenyl)oxazoline (7.56 g, 40 mMol), prepared from p-toluic acid by the method of Meyers,[9] in ether (150 mL) was treated at 0^{o} with n-butyllithium (20.5 mL of a 2.34 M ether solution, 48 mMol) and stirred for 4 hrs. To this solution of aryllithium reagent I thus generated,[4] was then added a solution of p-chlorobenzaldehyde (5.64 g, 40 mMol) in 1:4 THF-ether (50 mL). After 1 hr at 0^{o} followed by 16 hrs at 25^{o}, saturated aqueous NH_4Cl (10 mL) was added. Ether extraction (400 mL) afforded 14.1 g of crude alcohol as an oil which was dissolved in ethanol (150 mL) containing sulfuric acid (30 mL). This solution was refluxed for 24 hrs and then cooled. Dilution with water and ether extraction afforded crude

II (10.25 g). Crystallization from ethanol gave pure II as white needles (7.15 g, 69%), mp. 135-136°, NMR: δ 2.46 (s, 3), 6.32 (s, 1), 7.06-7.46 (m, 6), 7.84 (d, 1).

Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.53; H, 4.26; Cl, 13.73.
Found: C, 69.63; H, 4.26; Cl, 13.57.

2-[(4-Chlorophenyl)methyl]-4-methylbenzoic Acid (III). - To a stirred solution of 57% hydroiodic acid (50 mL) and 50% hypophosphorus acid (25 mL) was added with cooling acetic acid (140 mL), then acetic anhydride (140 mL) and then phthalide II (7.0 g). After 6 hrs at reflux the solution was cooled and diluted with water (600 mL). The precipitate was collected, dissolved in 5% aqueous potassium carbonate (100 mL) and filtered through Celite. Excess hydrochloric acid was added to afford acid III (6.9 g, 98%), mp. 154-156°. The analytical sample, mp. 156-156.5°, was obtained by crystallization from benzene-hexane. NMR: δ 2.38 (s, 3), 4.40 (s, 2), 7.0-7.3 (m, 6), 8.00 (d, 1), 11.6 (br, 1).

Anal. Calcd for $C_{15}H_{13}ClO_2$: C, 69.21; H, 5.04; Cl, 13.45.
Found: C, 69.09; H, 5.18; Cl, 13.18.

2-Chloro-6-methylanthraquinone (Va). - A solution of acid III (2.3 g) in concentrated sulfuric acid (20 mL) was stirred at 25° for 2 hrs and then poured into cold water (150 mL). The precipitate was collected and washed with 5% aqueous potassium carbonate (100 mL) followed by water, affording 2-chloro-6-methyl-9-anthrone (IV) (2.05 g, 96%), mp. 182-185° (a sample recrystallized from ethanol-CH_2Cl_2: mp. 188-189°), pure enough for the next reaction. NMR: δ 2.48 (s, 3), 4.26 (s, 2), 7.22-7.60 (m, 4), 8.20-8.32 (m, 2). A mixture of anthrone IV (3.4 g), glacial acetic acid (120 mL) and acetic anhydride (30 mL) was refluxed for 1 hr, cooled, and then treated portionwise with potassium dichromate (3.7 g). The mixture was warmed to 65° over 15 min and maintained there for 4 hrs. The mixture was cooled, diluted with water (500 mL) and filtered. The precipitate was washed with water and dried, affording Va (3.25 g, 90%), mp. 229-230°. A sample recrystallized from ethanol showed mp. 231-232°, lit.[1] mp. 228.5-229.5°.

2-Chloroanthraquinone-6-carboxylic Acid (Vb). - To a stirred, chilled solution of Va (2.0 g) in concentrated sulfuric acid (20 mL), water (20 mL) was added followed by portionwise addition of powdered potassium dichromate (6.0 g). After a heating period at 90-100° for 20 hrs, the mixture was cooled, diluted with water (200 mL) and filtered. The precipitate was washed with hot water and dried, affording crude acid Vb (2.15 g, 96%) as a brown solid, mp. 346-351°. Recrystallization from DMF gave pure Vb (1.89 g, 85%), mp. 352-354° (calibrated against uracil, mp. 338°), lit.[2] mp. 354-355.5°.

n-Butyl 2-Chloroanthraquinone-6-carboxylate (Vc). - A mixture of Vb (286 mg), thionyl chloride (710 mg) and benzene (5 mL) was refluxed for 4 hrs and then the volatiles were removed by vacuum evaporation. The residue was treated with refluxing n-butyl alcohol (10 mL) for 4 hrs, affording 340 mg (99%) of crude Vc, mp. 136-137°. A CH_2Cl_2 solution of Vc was filtered through silica gel. Addition of ethanol caused crystallization of Vc as greenish yellow plates (296 mg, 86%), mp. 137-138°. NMR: δ 1.03 (t, 3), 1.26-1.98 (m, 4), 4.42 (t, 2), 7.70-7.84 (m, 1), 8.18-8.50 (m, 4), 8.90 (s, 1).

Anal. Calcd for $C_{19}H_{15}ClO_4$: C, 66.65; H, 4.42; Cl, 10.22.
Found: C, 66.43; H, 4.36; Cl, 10.02.

2-Chloro-6,9,10-trimethylanthracene (VI). - To a stirred solution of Va (384 mg) in THF (20 mL) at -78° was added methyllithium (3.3 mL of a 1.1 M THF solution). After 2 hrs the reaction was worked up with saturated ammonium chloride and ether, affording 406 mg (94%) of crude diol, mp. 211-213° dec. (sample recrystallized from benzene, mp. 216-217° dec.), pure enough for the next reaction. NMR: δ 1.60 (s, 6), 2.10

(s, 2, OH), 2.42 (s, 3), 7.14-7.42 (m, 2), 7.58-7.86 (m, 4). A solution of this crude diol (290 mg) in ether (20 mL) was added dropwise to a stirred solution of stannous chloride (3.0 g), concentrated HCl (3 mL) and ether (15 mL). After 20 min the mixture was diluted with water and extracted with ether. The extract was washed with 10% NaOH, dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed over basic alumina. Elution with hexane-benzene (3:2) followed by crystallization from ethanol-CH_2Cl_2 gave pure VI (147 mg, 58%) as yellow needles, mp. 165-166°. NMR: δ 2.60 (s, 3), 3.02 (s, 6), 7.30-7.46 (m, 2), 8.00-8.28 (m, 4).

Anal. Calcd for $C_{17}H_{15}Cl$: C, 80.29; H, 5.95; Cl, 13.76.
Found: C, 80.34; H, 5.92; Cl, 13.54.

Acknowledgment.- This research was supported by Public Health Service Research Grant GM 27137 from the National Institute of General Medical Sciences.

REFERENCES

1. M. Hayashi and A. Nakayama, J. Soc. Chem. Ind. Japan, 37, Suppl. binding. 238B (1934).
2. A. W. Oxford and G. E. Gymer, U. S. Patent 3,873,538 (1975).
3. N. S. Dokunikhin, Z. Z. Moiseeva and S. N. Burenko, J. Gen. Chem. USSR, 31, 3716 (1961).
4. H. W. Gschwend and A. Hamdan, J. Org. Chem., 40, 2008 (1975).
5. M. S. Newman, V. S. Prabhu and S. Veeraraghavan, ibid., 48, 2926 (1983).
6. K. L. Platt and F. Oesch, ibid., 46, 2601 (1981).
7. M. A. Ilinskii and V. A. Kazakova, J. Gen. Chem. USSR, 11, 16 (1941).
8. M. S. Newman and K. Kanakarajan, J. Org. Chem., 45, 2301 (1980).
9. A. I. Meyers, D. L. Temple, D. Haidukewych and E. D. Mihelich, ibid., 39, 2787 (1974).

(Received April 3, 1984; in revised form July 23, 1984)