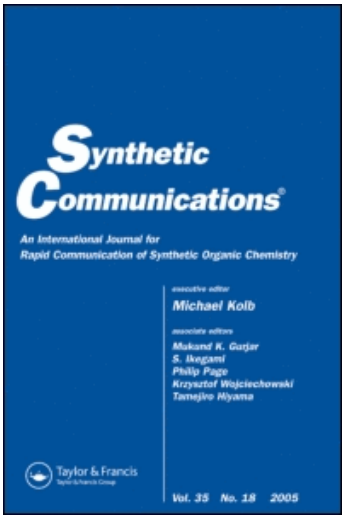

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AN IMPROVED METHOD FOR THE PREPARATION OF 4,5-DIAMINOCHRYSAZIN

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4,5-Diaminochrysazin was prepared from chrysazin by ethylation and nitration followed by reaction with hydroiodic acid (HI). Treatment of 1,8-diethoxy-4,5-dinitroanthraquinone with HI resulted not only in O-deethylation, but also in reduction of nitro groups with more than 95% yield. This is a unique finding and is reported for the first time with a definite improvement over literature methods and is suitable for scale-up.

Keywords: Anthraquinone; deethylation; ethylation; nitration; reduction

Amino and hydroxyanthraquinones have long been found use in anticancer therapy as exemplified by drugs Ametantrone and Mitoxantrone[1] and also in dyestuff industry.[2] In our on going programme[3] of making new anticancer molecules, an attempt to prepare new derivatives of mitoxantrone has been initiated. In this endeavor, we prepared 4,5-diaminochrysazin (1,8-dihydroxy-4,5-diaminoanthraquinone) as a key intermediate for making various aminoanthraquinone derivatives. In the literature, several methods have been tried to make various 4,5-daminocrysazin derivatives mainly as dye intermediates: (a) racting a mixture of 1,8-diamino-4-hydroxy-and 1,5-diamino-4-hydroxy anthraquinone with manganous oxide in sulfuric acid[4] to get a mixture of products (b) bromination of 1,8-diamino anthraquinone and hydrolysis in presence of boric acid[5] to get halogen substituted products (c) nitration of chrysazin followed by bromination and subsequent reduction with alkaline glucose,[6] or iron powder,[7] (d) reacting 1,8-dinitroanthraquinone with fuming sulfuric acid and reduction[8] to get a mixture of products (e) reducing a mixture of 1,5-dinitro-4,8-dihydroxy and 1,8-dinitro-4,5-dihydroxy anthraquinone with iron in sulfuric acid[9] and catalytic hydrogenation of 4,5-dinitro and 4,7-dinitro chrysazin in presence of sulfuric acid with catalyst Pd/C or Pt/C,[10] (f) direct nitration of chrysazin and insitu catalytic reduction of nitration liquors over Pt/C[11] to get a mixture of 1,8-dihydroxy-4,5-dinitro & 1,8-dihydroxy-2,5-dinitroanthraquinone, (g) reduction of 1,8-dihydroxy-4,5-dinitro anthraquinone and or 1,5-dihydroxy-4,8-dinitro

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anthraquinone with hydrazine hydrate[12] or with mixed reducing sugars.[13] (h) reduction of 1,8-dimethoxy-4,5-dinitroanthraquinone with Pd/C or Pt/C at 125 °C to give 4,5-diaminochrysazin.[14] Chang and Cheng[15] reported nitration of chrysazin to give a mixture of 4,5-dinitrochrysazin and 4,7-dinitrochrysazin in 85:15 ratio and subsequently reduced the mixture with iron powder. Shimazu et al.[16] prepared a mixture of 4,5-diaminochrysazin and 1,5-dihydroxy-4,8-diaminoanthraquinone from a mixture of dimethylcrysazin and 1,5-dimethoxy anthraquinone by the nitration of 1,5- and or 1,8-dimethoxy anthraquinone and then reduction with metal/acid followed by hydrolysis in sulfuric acid at 40–160 °C. All these methods were evaluated carefully as they lead either to a mixture of products with less purity and yields or economically not attractive. Because of demand for highly pure 4,5-diaminochrysazin in pharmaceutical synthesis, selective nitration and reduction methods were studied extensively in this laboratory. This article describes (1) ethylation of chrysazin to increase the solubility of chrysazin in subsequent nitration step, (2) an efficient and regioselective nitration of 1,8-diethoxychrysazin, (3) obtaining pure 1,8-diethoxy-4,5-dinitroantraquinone without purification and (4) reduction of nitrogroups and de-ethylation in a single step. This process thus illustrates the significant improvement over literature methods avoiding the usage of Pd/C or Pt/C and suitability for scale-up.

RESULTS AND DISCUSSION

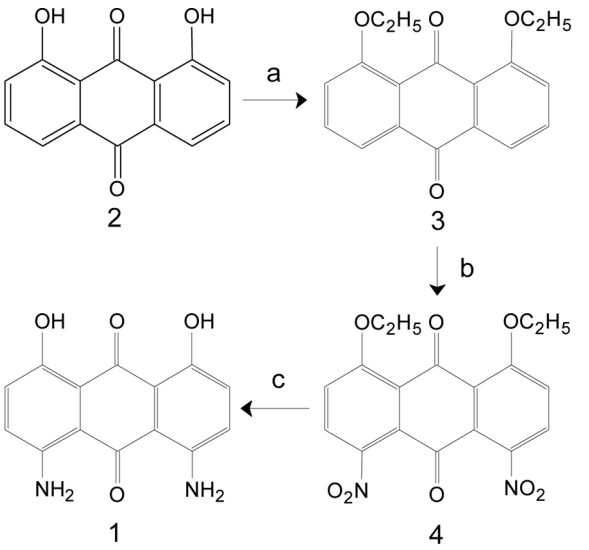
Direct nitration of chrysazin according to a classical procedure,[17,18] including addition of phosphoric acid,[19] resulted in so many regioisomers with unreacted chrysazin and that the desired 4,5-dinitrochrysazin could not be easily isolated. Of other nitrating systems,[20] such as nitronium tetrafluoroborate and trifluroacetyl nitrate, altering the molar ratio of nitrating reagent and the reaction solvent had no effect on the selective preparation of 4,5-dinitrochrysazin.[21] After numerous experiments, it was found that protection hydroxyl group of chrysazin (**2**) and nitration leads to an increase in the solubility of 1,8-diethoxyanthraquinone (**3**) in sulfuric acid and to give selectively the desired nitrated product 1,8-diethoxy-4,5-dinitroanthraquinone (**4**) in good yield and purity. This pure diethoxy dinitroanthraquinone on treatment with hydroiodic acid gave 4,5-diaminochrysazin (**1**) in high yield and purity (Scheme 1).

EXPERIMENTAL

Melting points were determined on an Acro melting-point apparatus and uncorrected. Infrared (IR) spectra were recorded on a Thermo Nicolet Fourier Transform (FT)-IR instrument in KBr discs. ^{1}H NMR spectra were recorded on a Bruker 200-MHz instrument. All chemical shift values are reported in δ units downfield from tetramethylsilane (TMS) as internal standarad. Mass spectra (MS) were recorded on a Micromass Q-TOF micro^{TM} (USA) instrument with AMPS Max 10/6A system.

Preparation of 1,8-Diethoxyanthraquinone (3)

To a stirred solution of compound **2** (50 g, 34.6 mmol) in N,N-Dimethyl formamide (500 ml) was added potassium carbonate (250 g, 1811 mmol) and diethyl



(a) K_2CO_3/DMF/Diethyl sulfate; (b) $H_2SO_4/HNO_3/H_3BO_3$; (**c**) HI

Scheme 1. Preparation of 4,5-diaminochrysazin.

sulfate (260 g, 1688 mmol) and heated to 100 °C slowly over a 2-hour period. The reaction mixture was then poured into water, filtered, washed with water and dried to get the product **3**. (60 g, 97%); mp > 170 °C (decomposition). IR (KBr) υ_{max} 2978, 2878, 1674, 1585, 1438, 1396, 1315, 1284, 1230, 1115, 1061, 1014, 895, 791, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.55 (6 H, t, $J = 7.0$ Hz), 4.25 (4 H, q, $J = 7.0$ and 13.9 Hz), 7.27 (2 H, d, $J = 7.6$ Hz), 7.59 (2 H, t, $J = 8.0$ Hz), 7.84 (2 H, d, $J = 7.6$ Hz); HRMS (ES+) m/z calcd. for $C_{18}H_{16}O_4$ $(M + H)^+$ 297.1127, Obs. 297.1115.

Preparation of 1,8-Diethoxy-4,5-dinitroanthraqunone (4)

To a stirred solution of sulfuric acid (339 ml) and boric acid (11 g, 177.9 mmol) which was maintained at a temperature of 0 to +2 °C, charged compound **3** (22 g, 74.3 mmol) and then added pre-cold nitrating mixture (Nitric acid, 11 ml, 172.3 mmol and sulfuric acid (13 ml) in 100 ml water) over a period of 2 hours. Reaction mixture was quenched with ice-cold water, filtered, and dried to get the product **4** (28 g, 97.6%); mp > 250 °C(decomposition); IR (KBr) υ_{max} 2978, 2878, 1693, 1593, 1527, 1416, 1358, 1300, 1230, 1107, 1022, 926, 822, 795, 733, 694 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6); δ 1.42 (6H, t, $J = 6.6$ Hz), 4.31 (4 H, q, $J = 6.0$ and 8.0 Hz), 7.63 (2 H, d, $J = 8.0$ Hz), 8.14 (2 H, d, $J = 8.0$ Hz); HRMS (ES+) m/z calcd. For. $C_{18}H_{14}N_2O_8$ (M + Na) 409.0648. Obs. 409.0651.

Preparation of 4,5-Diaminochrysazin (1)

Compound **4** (5 g, 12.9 mmol) in hydroiodic acid (40 ml, 292.41 mmol) was heated to 100 °C for 3 hours and quenched with ice-cold alkaline solution to get

the compound **1**, which was filtered and dried (3.4 g, 97.1%); mp > 300 °C (Decomposition); IR (KBr) υ_{max} 3400, 3305, 1570, 1516, 1207, 833, 551, 455, cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6); δ 7.14 (2H, d, J = 10 Hz), 7.28 (2H, d, J = 10 Hz), 7.94 (4 H, brs), 12.78 (2 H, s).

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REFERENCES

1. Zee-Cheng, R.; Cheng, C. C. Antineoplastic agents. Structure-activity relationship study of bis(substituted aminoalkylamino) anthraquinones. *J. Med. Chem.* **1978**, *21*, 291–294; (b) Xu, P.; Xiao, S.; Liao, Y. Synthesis of antineoplastic agent DHAQ. *Sichuan Yixueyuan Xuebao* **1985**, *16*(2), 105–108; *Chem. Abstr.* **1986**, *104*, 129592; (c) Chang, P. Synthesis and characterization of anticancer anthraquinones: Ametantrone and mitoxantrone. Part A. *Phys. Sci. Eng.* **1992**, *16*(4), 304–310; *Chem. Abstr.* **1993**, *119*, 116918.
2. (a) Stilmar, F. B.; Perkins, M. A. *The Chemistry of Synthetic Dyes and Pigments*; Reinhold: New York, 1955, p. 337; (b) Krenmueller, F.; Till, H.; Stoll, P. Aminoanthraquinones. DE 2340114, 1974; *Chem. Abstr.* **1974**, *80*, 133125t; (c) Greenhalgh, C. W.; Hughes, N. The reaction of leucoquinizarins with alkylenediamines. *J. Chem. Soc. C* **1968**, 1284–1288.
3. (a) Chandregowda, V.; Kush, A. K.; Reddy, G. C. Synthesis and in vitro antitumor activities of novel 4-anilinoquinazoline derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 3053–3062; (b) Chandregowda, V.; Kush, A. K.; Chandrasekara Reddy, G. Synthesis of benzamide derivatives of anacardic acid and their cytotoxic activity. *Eur. J. Med. Chem.* **2009**, *44*, 2711–2719.
4. Hederich, V.; Klemm, K.; Gehrke, G. Anthraquinone dyes for polyester fibers. DE 1180760, 1964; *Chem. Abstr.* **1965**, *62*, 6605.
5. Mitsubishi Chemical Industries Co., Ltd., Japan. Manufacture of anthraquinone dyes. JP 56163151, 1981; *Chem. Abstr.* **1982**, *96*, 124524.
6. Kurosawa, M.; Imai, H. Anthraquinone dyes for polyesters. JP 45032548, 1970; *Chem. Abstr.* **1971**, *74*, 88662.
7. Yamada, E.; Hamaguchi, K.; Akamatsu, T. 1,8-Dihydroxy-4,5-diaminoanthraquinone halides. JP 46010080, 1971; *Chem. Abstr.* **1971**, *75*, 110985.
8. Takeshita, A.; Sunami, M. Diaminodihydroxyanthraquinone. JP 52107027, 1977; *Chem. Abstr.* **1978**, *88*, 37506.
9. Kimura, Y.; Ban, K.; Kawashima, O. Diaminodihydroxyanthraquinone. JP 53056649, 1978; *Chem. Abstr.* **1978**, *89*, 129320.
10. Morley, J. O.; Hutcheson, R. Reduction of hydroxynitroanthraquinones or their alkylether or sulfonic acid derivatives to the corresponding amino compounds. DE 2810484, 1978; *Chem. Abstr.* **1979**, *90*, 22683.
11. Morley, J. O.; Hutcheson, R. Catalyzed hydrogenation of hydroxynitroanthquinones in strong acid. *J. Chem. Tech. Biotech.* **1980**, *30*(8), 409–414; *Chem. Abstr.* **1981**, *94*, 85651.
12. Jablonski, J.; Gogolewski, S.; Norek, A. Manufacture of 1,8-dihydroxy-4,5-diaminoanthraquinone and/or 1,5-dihydroxy-4,8-diaminoanthraquinone. PL 140698, 1987; *Chem. Abstr.* **1988**, *109*, 212379.
13. Dobrovolny, J.; Pokormy, M.; Tichy, J. Method of preparing diaminodihydroxyanthraquinone derivatives. CS 240795, 1987; *Chem. Abstr.* **1989**, *110*, 38767.

14. Hutcheson, R.; Morley, O. Studies on the catalytic hydrogenation of Some nitroanthraquinones in strong acid. *J. Chem. Res. (S)* **1979**, (9), 286; *Chem. Abstr.* **1980**, *92*, 110726.
15. Chang, P.; Cheng, C. C. An improved practical synthesis of leuco-1,4,5,8-tetrahydroxyanthraquinone. *Synth. Commun.* **1995**, *25*(13), 1893–1900; *Chem. Abstr.* **1995**, *123*, 111650.
16. Shimazu, Y.; Okino, E.; Hinakura, T.; Yamada, E. Anthraquinone dyes. JP 48100432, 1973; *Chem. Abstr.* **1974**, *80*, 109837.
17. Galinowski, S.; Swiatly, S.; Gogolewski, S.; Szafnicki, W.; Guzewska, T. 1,8-Dihydroxy-4,5- and 2,5-diaminoantraquinones. PL 126191, 1983; *Chem. Abstr.* **1986**, *105*, 24077.
18. (a) Powell, G.; Johnson, F. R. Nitromesitylene; In *Org. Syn. Collect. Vol. 2*; A. H. Blatt (Ed.); 1943; pp. 449–450; (b) Icke, R. N.; Redmann, C. E.; Wisegarver, B. B.; Alles, G. A. In *Org. Syn. Collect. Vol. 3*; E. C. Horning (Ed.); 1955; pp. 644–646.
19. Shargi, H.; Tamaddon, F. An efficient procedure for the preparation of 1-nitroanthraquinone. *Synth. Commun.* **1991**, *21*, 2349–2359.
20. (a) Kuhn, S. J.; Olah, G. A. Aromatic substitution.VII. Friedel-Crafts type nitration of aromatics. *J. Am. Chem. Soc.* **1961**, *83*, 4564–4571; (b) Cupas, C. A.; Pearson, R. L. Nitration via N-nitropyridinium salts. *J. Am. Chem. Soc.* **1968**, *90*, 4742–4743; (c) Olah, G. A.; Lin, H. C. Aromatic substitution XXXV. Boron trifluoride catalysed nitration of benzene, alkylbenzenes and halobenzenes with methyl nitrate in nitromethane solution. *J. Am. Chem. Soc.* **1974**, *96*, 2892–2898; (d) Crivello, J. V. Nitrations and oxidations with inorganic nitrate salts in trifluoro aceticanhydride. *J. Org. Chem.* **1981**, *46*, 3056–3060.
21. Chang, P. An improved procedure for the preparation of 4,5-dinitrochrysazin. *Synth. Commun.* **1994**, *24*(7), 931–937.