International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol. 3, No.4, pp 1937-1940, Oct-Dec 2011

Synthesis of 2-bis-(1-methylimidazol-2-yl)methoxycarbonyl-9,10-anthraquinone

Ashnagar, A.[1]* and Bruce, J.M.[2]

[1]Pasteur Institute of Iran, Nanobiotechnology department, Pasteur Avenue, SQ.NO. 69, Post Code No. 1316943551, Tehran, Iran.

[2]University of Manchester, Dept. of Chemistry, UK.

Corres.author: alamdarashnagar@yahoo.com
Tel. No. 00982166953311, Fax No. 00982166465132

Abstract: Synthesis of 2-bis-(1-methylimidazol-2-yl)methoxycarbonyl-9,10-anthraquinone (I) from naphtha quinone (II) as the main starting material was achieved through several steps, i.e. Diels-Alder reaction between naphthoquinone (II) and isoprene (III) followed by aromatization of the mono-adduct (IV) by using freshly prepared manganese dioxide, then oxidation of the methyl group of 2-methyl-9,10-anthraquinone (V) by chromic oxide in acetic acid afforded 9,10-anthraquinone-2-carboxylic acid (VI). Conversion of the carboxylic group to acyl chloride by reaction of (VI) with oxylyl chloride followed by the nucleophilic addition of bis-(1-methylimidazol-2-yl) methanol (VII) to the acyl chloride afforded (I) in a relatively moderate yield.
Keywords: bis-(1-methylimidazol-2-yl)methanol, 2-methoxycarbonyl-9,10-anthraquinone.

Introduction

Imidazole (1,3-diazacyclopenta-2,4-diene) is a planar five-membered ring system with 3C and 2N atom in 1 and 3 positions. The systemic name for the compound is 1, 3 diazole, one of the annular N bear a H atom and can be regarded as a pyrole type N. Imidazole, due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring, is an aromatic heterocyclic organic compound which is a diazole and is classified as an alkaloid. Imidazole refers to the parent compound, whereas imidazoles are a class of heterocycles with similar ring structure, but varying substituents. Many drugs contain an imidazole ring, such as antifungal drugs and nitroimidazole. Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. Imidazole is amphoteric, i.e. it can function as both an acid and as a base. Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid "histidine", which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. Imidazole has become an important part of many pharmaceuticals. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system. Apart of its use for pharmaceutical purpose it also has varying applications in industries, the imidazole has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper

corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole (PBI) contains imidazole fused to a benzene ring and linked to benzene, and acts as a fire retardant. Imidazole can also be found in various compounds which are used for photography and electronics. Imidazole derivatives have a wide range of pharmacological activity, literature survey revealed that imidazole and its derivative are reported to have, analgesic and anti-inflammatory activity[1-4], cardiovascular activity[5,6], anti-neoplastic activity[7], anti- fungal activity[7,8],enzyme inhibition activity[9-11], antianthelmintic activity[12], anti-filarial agent, anti-viral activity and anti- ulcer activity. Other than their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents. 2-Nitroimidazole (azomycin) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) are anti bacterial agent with particular applications as trichomonacide. Along with metronidazole, other nitroimidazoles (misonidazole,metrazole and clotrimazole) are important anti cancer drugs. Two imidazolines, priscol and privine are valuable vasodialating and vasoconstricting drugs. 2-Aminoimidazolines are among a class which is known for fungicidal action. The modern scientific searches aim at discovering more effective and better-tolerated imidazole derivatives.

Experimental

Reagents and solvents (reagent grade) were purchased from BDH, Aldrich, Fluka and Merck. All solvents were distilled prior to use. Evaporation and concentration in vacuo were performed at water aspirator pressure. Column chromatography (CC) was carried out with SiO2 60 (particle size 0.040- 0.063 mm, 230-400 mesh; Merck) and commercially available solvents. Melting points (m.p.) were measured on a Buchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^{1}HNMR spectra were recorded in $CDCl_3$ and d_6-DMSO with 80 MHz and 300 MHz Brucker in struments at 20 °C. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Coupling constants (J) are given in Hz. Low resolution electron impact (E.I.) mass spectra were recorded on A.E.I. MS30 instrument.

Preparation of 9,10-anthraquinone-2-carboxylic acid (VI):

To a mixture of 2-methylanthraquinone (7 g, 31.53 mmol) in glacial acetic acid (280 mL), chromic oxide (excess, 21 g, 200 mmol) was added and the whole mixture was refluxed for 6 hours. A dark red solution was obtained which was diluted with water (600 mL). A grass green suspension was obtained which was filtered and the cake was washed with water (ca. 100 mL). The cake was dissolved in hot dilute ammonia (1:1 v/v) (400 mL), (temperature 60-80 °C), then cooled at room temperature and filtered. The filtrate (mother liquor) was acidified by adding dilute (1:1 v/v) HCl. A pale yellow suspension was obtained which upon filtration and washing the cake with water gave a pale yellow solid material (4.0 g, 15.87 mmol, 50.3%), m.p. 293-295 °C. Recrystallization from glacial acetic acid gave a pale yellow material (2.87 g, 11.39 mmol, 36%), m.p. 295-297 °C (sealed tube). It had ^{1}HNMR δ (3% d_6-DMSO, 80 MHz) 7.9 (dt,J_1=8 Hz, J_2=3 Hz), 8.05-8.43 (m, H-3 + H-4 + H-5 + H-8), 8.56 (d, J=2 Hz, H-1), 10.30 (bs, OH); MS (E.I.) m/z 252 ($M^{\cdot+}$, 100), 224 [$(M-CO)^{\cdot+}$, 31%], 207 [$(M-CO_2H)^{\cdot+}$, 32%], 196 [$(224-CO)^{\cdot+}$, 9%], 179[$(207-CO)^{\cdot+}$, 14%], 151[$(196-CO_2H)^{\cdot+}$, 35%], 75 [$(151-C_6H_4)^{\cdot+}$, 16%].

Preparation of 2-(chlorocarbonyl)-9,10-anthraquinone (VII):

To a solution of 9,10-anthraquinone-2-caroxylic acid (1.008 g, 4 mmol) in dry methylene chloride (20 mL), oxylyl chloride (0.7 mL, 2 equivalents) was added at room temperature. 3 Drops of dimethylformamide (DMF) was added as catalyst and the mixture was stirred at room temperature for 2 hours. Work up of the reaction mixture resulted in the formation of the desired product, 2-(chlorocarbonyl)-9,10-anthraquinone in almost quantitative yield. Its ^{1}HNMR δ (5% , $CDCl_3$, 300 MHz) and M.S.(E.I.) absolutely confirmed the structure of the product.

Preparation of 2-bis-(1-methylimidazol-2-yl)methoxycarbonyl-9,10-anthraquinone (I):

To the 2-(chlorocarbonyl)-9,10-anthraquinone compound prepared in situ in the previous experiment, dried methylene chloride (5 mL), pyridine (1 mL, 5 equivalents) and bis-(1-methylimidazol-2-yl)methanol (0.768 mg, 0.004 mmol, 1 equivalent) were added at room temperature and the mixture was stirred for 2 hours. After that the mixture was washed with water (3×50 mL). The organic layer was separated and dried over anhydrous sodium sulphate. Removal of the solvent afforded a yellow-brown solid material which

upon recrystallisation with chloroform:n-hexane (1:5 v/v) resulted the desired product (0.820 g, 1.925 mmol, 48% based on compound VI), m.p. 189-191°C. It had ^{1}HNMR δ (5%, $CDCl_3$, 300 MHz) 4.0 (s, 2× CH_3), 6.97 (d, 4× H, imidazole ring), 7.5 (s, OCH), 7.82 (d, H-6 + H-7), 8.3 (dd, H-5 + H-8), 8.39 (d, H-4), 8.47 (d, H-3), 8.98 (s, H-1).

Discussion

Compound (I) is a fascinating compound with several applications and properties including photosensitization one. We were approached by a colleague who requested us to synthesize (I), as we were heavily involved in the synthesis of various benzoquinones, napthoquinones and anthraquinones and their derivatives. Therefore, through a Diels-Alder reaction, naphthoquinone (II) was treated with isoprene (III), a simple straightforward reaction took place. Purification of the crude product, afforded compound (IV) which was refluxed in benzene in the presence of freshly prepared manganese dioxide. Dehydrogenation (aromatization) of the methyl substituted ring took place which after laboratory work up resulted in compound (V), i.e. 2-methyl-9,10-anthraquinone. The next step was the oxidation of methyl group to carboxylic acid group which was achieved by treatment of (V) with chromic oxide in acetic acid. Recrystallization of the crude product with acetic acid afforded 9,10-anthraquinone-2-carboxylic acid (VI) in 36% yield. Treatment of the latter compound (VI) with excess oxylyl chloride, which is a powerful chlorinating agent, gave the corresponding acid chloride (VII) in almost quantitative yield. Finally, to the acid chloride (VII), dried methylene chloride (5 mL), pyridine (1 mL, 5 equivalents) and bis-(1-methylimidazol-2-yl)methanol (0.768 mg, 0.004 mmol, 1 equivalent) were added at room temperature and the mixture was stirred for 2 hours. After laboratory work up and recrystallization of the crude product with chloroform:n-hexane (1:5 v/v), gave the desired product (I). It had a very clean ^{1}HNMR 300 MHz spectrum which confirmed its structure. Further works are needed to investigate the various applications of this compound. Schematic diagram of the synthesis of 2- bis-(1-methylimidazol-2-yl)methoxycarbonyl-9,10-anthraquinone (I) from 1,4-naphthoquinone is given in figure 1.

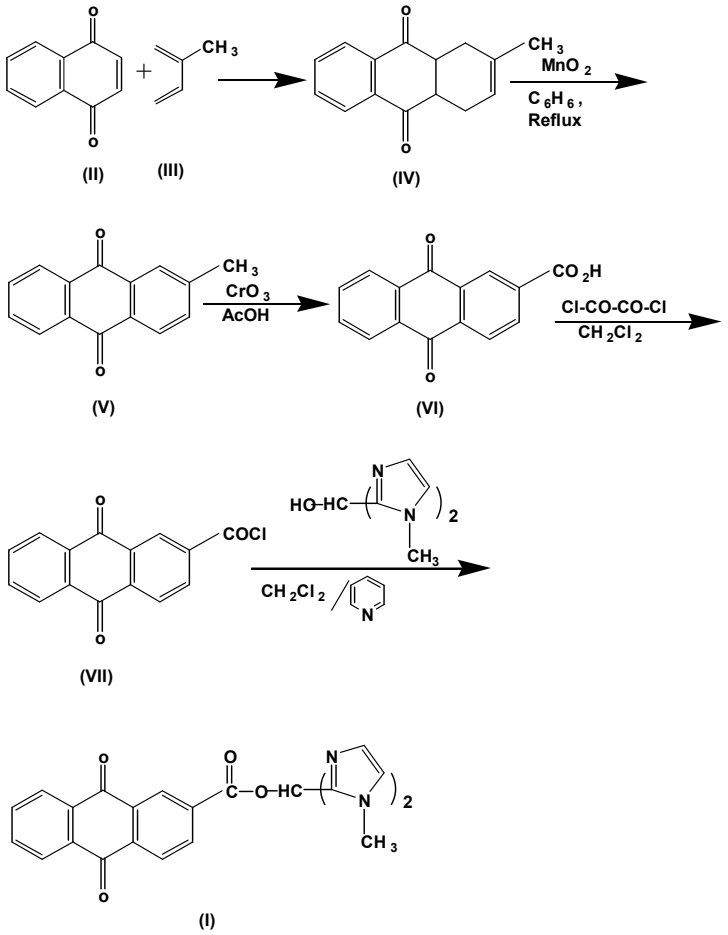

Fig. 1. Schematic diagram of the synthesis of 2- bis-(1-methylimidazol-2-yl) methoxycarbonyl-9,10-anthraquinone (I)

References

1. Suzuki M., Maeda S., Matsumoto K., Boll chem farm l, 1986, 34(8), 3111-3120.
2. Suzuki F., Kuroda T., Tamura T., J. Med. Chem. 1992, 35(15), 2863-2870.
3. El – Feky S.A., Abdel – Samii Z.K., Pharmazie. 1995, May 50 (5), 341-343.
4. Isikdag L., Meric A., Boll chem Farm. 1999 Jan, 138(1), 24-29.
5. Robertson D.W., Beedle E.E., Krushinski J.H., Pollock G.D., Willson H., Wyssvl J.S., Hayes, J. Med.Chem.,1985, Jun 28(6),717-27.
6. Erhardt P.W., Hagdon A.A., Davey D., Pease C.A., Venepalli, Griffin C.W., Gomez R.P., Wiggins J.R., Ingebretsen W.R., Pang D., J.Med. Chem., 1989, Jun 32 (6), 1173-6.
7. Johnson R.A., Huong S.M., Huang E.S., Anti viral research 1999, 41 (3), 101-111.
8. Brewer M.D., Dorgan R.J., Manger B.R., Mamalis P., Webster R.A., J. Med. Chem., 1987, Oct 30 (10),1848-53.
9. Nathanson J.A., Mol. Pharmacol., 1985, Sep 28 (3), 254-68.
10. Kruse L.I., Kaiser C., Frazee J.S., Garvey E., Hilbert E.L., Faulkner W.A., Flaim K.E., Sawyer J.L., Berkowitz B.W., J. Med. Chem. 1986, Dec 29(12) ,2465-72.
11. Liyk Hsu H.S., Kiyota H., Segawa M., J. Bio chem. 1998, 23(3), 416-422.
12. Lunt E., Newton C.G., Smith C., Stevens G.P., Stevens M.F., Straw C.G., Walsh R.J., Warren P.J., Fizames C., Lavelle F., J. Med. Chem., 1987, Feb 30(2),357- 66.

.

*****