ISSN: 0974 - 7516 Volume 8 Issue 8

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(8), 2012 [307-310]

Synthesis of polyfused heterocyclic compounds via reactivity 1, 4-naphthoquinone

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Received: 10th January, 2012 ; Accepted: 2nd February, 2012

ABSTRACT

In the present study, a series of poly fused heterocyclic compounds incorporating 1, 4-naphthoquinone have synthesized such as accridine, pyrazine, hydropyrazine, imidazole, phenazine, and bezophenazine derivatives respectively, via a nucleophilic substitution and cyclization reaction.

KEYWORDS

Accridine;
Benzophenazine;
Phenazine;
Imidazole.

INTRODUCTION

Quinones have recently attracted the interest of chemists due to the importance of their derivatives, which have widespread applications in different fields such as antitumers[1], drugs[2], photoconductor[3], substances, antivirus[4] and as vat dyes[5, 6]. A large Varity of compounds containing one or more heterocyclic ring fused to the quinine nucleus were prepared from 1, 4-naphthoquinone which has structure is common in various natural products[7], and is found to exhibit on interesting range of pharmacological properties including antibacterial[8, 9, 10], antiviral[11], trypanocidal[12], anticancer[13], antimaterial[14, 15, 16], and antifungal[17, 18, 19] activities. Other quinines such as 3,4,9-trioxo-1, 2,3,4,0-pentahydrobenz [g] indol[20], and derivatives of benz [G] 1,2,3,4-tetrahydroquinone-4, 5,10-trione[21] are also known for their biological activates against Gram-negative bacteria (serratia sp., Pseudomonas aeruginosa, ATCC-6NA-10245 Escherichia, Escherichia coli B-3704, Salmona sp, SW-476, Pseudomonas sp. SW-653, Gram positive bacteria such as Bacillus subtilis NRS-744, Micrococcus luteus SW-712, Bacillus niegaterium SW-354, Staphylococcus aureus B-767, Streptomyces sp. SW-123, Bacillus cereus ATCC-9634, and Fungi such as Candida albicans IMRU-3669, Aspergillus flavus S-C 43(313). The reaction of quinines with different reagents, which are mostly used in preparing heterocyclic compounds.

RESULTS AND DISCUSSION

1, 4-Naphthoquinone reacted with o, phenylenediamine to yield a large number of fused heterocyclic quinines can be conveniently prepared via a suitable nucleophlic substitution reaction of a bearing some relatively labile groups at position2 and 3. Those reactions involving a nucleophilic attack by one group of the difunctional nucleophiles on C-2, C-3 of quinines and subsequently by intermolecular attack of the other one C-1, C-4 followed by cyclization and removal of two H_2O molecules to form fused heterocycle compound 1(equation 1).

The reactions indicate that amino-1, 4-naphthoquinones (a) are intermediates but not 1, 4-naphthaquinoneimines (b) (equation 1)[11]. The forma-

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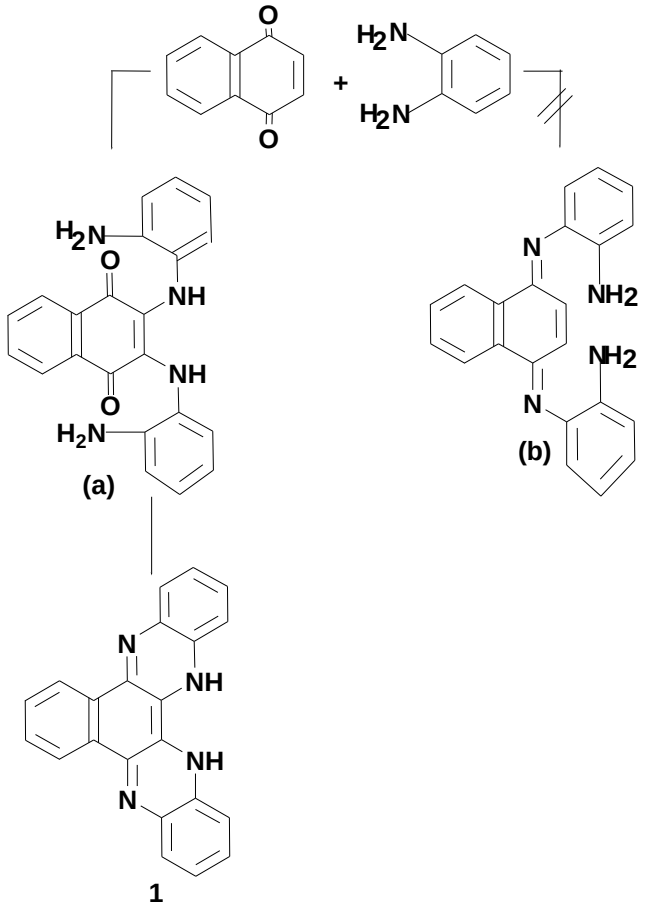
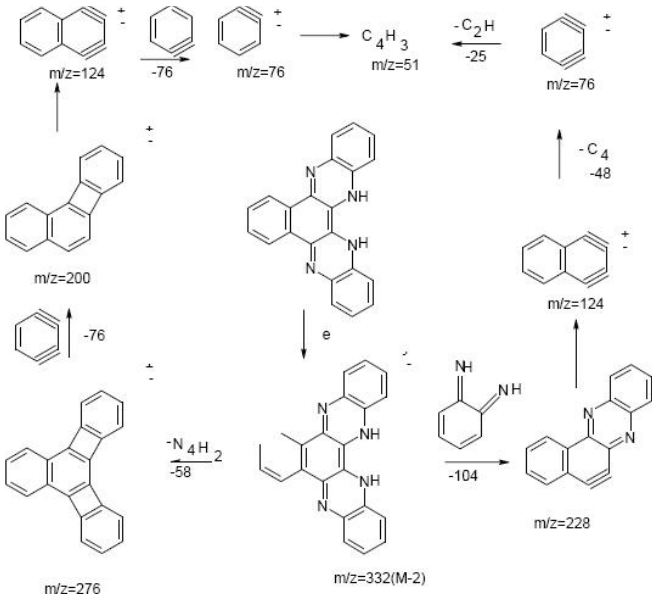
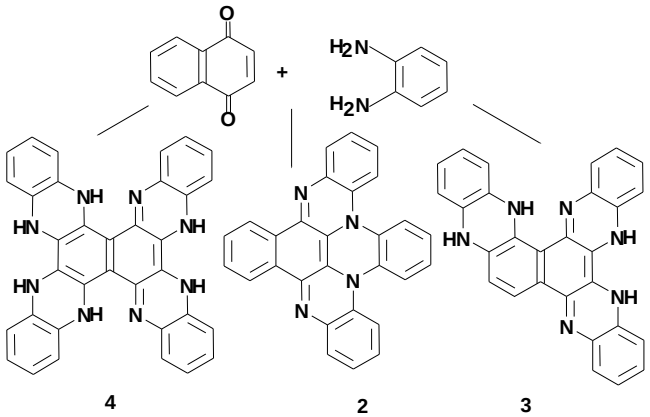


equation 1



equation 2

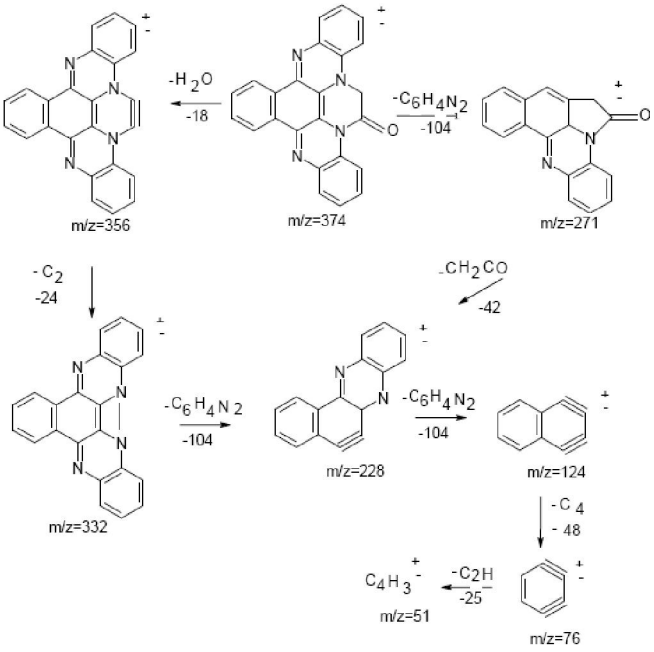
tion of 1 may be explained by a mechanism involving nucleophilic attack of the ethylenediamine molecule at position C-2, C-3 of the quinine with elimination of two H_2 molecules to give (a), followed by interamolecular cyclization through elimination of a molecule of water to give 1 (equation 1)[11]. The mass spectra of compound 1 reveals a molecular ion peak at m/z = 332 (M-2) and appearance of base peak at m/z = 75 (100%). The mechanistic fragmentation of mass spectra of compound 1 was suggested to proceed according to the following (equation 2).



scheme 1

A series of benzo [a] phenazine derivatives 2, 3, 4 were synthesized by reaction of 1, 4-naphthoquinone with o, phenylenediamine (Scheme 1).

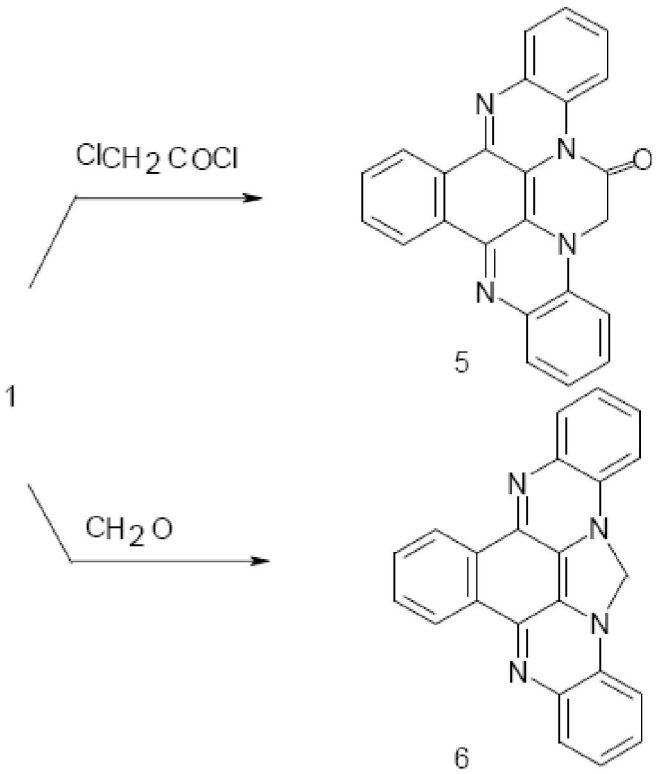
Also, compound 1 reacts with $ClCH_2COCl$ chloroacetylchloride in presence of triethylamine to eliminate two molecules hydrochloric acid was producing compound 5. The mass spectra of compound 5 reveals



equation 3

a molecular ion peak at m/z = 374 (M+) and appearance of base peak at m/z = 199 (100%). The mechanistic fragmentation of mass spectra of compound 5 was suggested to proceed according to the following (equation 3).

At the same manner compound 1 reacts with formaldehyde producing compound 6 (Scheme 2)



scheme 2

EXPERIMENTALS

All melting points were uncorrected. IR spectra were recorded on a pye unicam SP 1100 spectrophotometer using KBr disc. ^{1}H-NMR spectra were recorded on a varian EM-390 MHz Spectrophotometer using DMSO d6 as a solvent and TMS as an internal standard Chemical shifts are expressed as ppm, units. Mass spectra were recorded on an HP MS 6088 spectrometer. Analytical data were determined with a CE 440 Elemental Analyzer-Automatic Injector at Cairo University.

Reaction of o, phenylenediamine with 1, 4-naphthoquinone:

A solution of o, phenylene (1.08g, 0, 01 mole) and 1, 4-naphthoquinone (6.32g, 0.04 mole) in ethanol as solvent, the mixture was refluxed about 10 h. The reaction mixture was filtered on hot from unreacted materials, the filtrate was concentrated to one-third of its volume and triturated with water, whereby the products were separated, filtered, washed several times with water, and crystallized from aqueous ethanol to give compounds 1, 2, 3, 4.

Benzo [a] [1, 4] benzophenazine [3, 2-c] phenazine (1):

MP. 140-151 C, Yield 80%, ^{1}H-NMR (CDCl3, 300 MHz, δ): 6.97 (s, 2H, 2NH), 7.73-8.10(m, 12H, Ar-H$^+$). IR (νmax, KBr): 3400 Cm-1 (NH). Mass (m/z) 332. Elemental Analysis: found C, 79.00; H, 4.20; N, 16.80 require: C, 79.02; H, 4.22; N, 16.76.

Benzo [a] accridino bis [2, 3-c: 2, 3-c] phenazine (2):

MP. 199-201 C, Yield 25 %, ^{1}H-NMR (DMSO, 300 MHz, δ): 7.6-8.4(m, 16H, Ar-H$^+$). IR (νmax, KBr): 2990 Cm-1 (CH). Mass (m/z) 408. Elemental Analysis: found C, 82.00; H, 3.90; N, 13.70; requires: C, 82.34; H, 3.95; N, 13.72.

Benzo [a][1, 4] benzophenazino [3, 2-c: 3,2-c][1, 4] dihydrophenazino [3, 2-c] phenazine (3):

MP. 189-191 C; Yield 15 %, ^{1}H-NMR (DMSO, 300MHz, δ): 6.72(s, 4H, 4NH), 7.4-8.0(m, 14H, Ar-H$^+$). IR (νmax, KBr): 3350 Cm-1 (NH), 2980 CM-1 (CH). Mass (m/z) 438. Elemental Analysis: found C, 76.70; H, 4.12; N, 19.18; requires C, 76.71; H, 4.12; N, 19.18.

Benzo [a][1, 4] benzophenazino [3, 2-c: 3, 2-c] bis [1, 4:1,4] dihydrophenazine (4):

MP. >250 C, Yield 35 %, ^{1}H-NMR (DMSO), 300MHz, δ): 6.5(s, 6H, 6NH), 7.0-8.5(m, 16H, Ar-H$^+$). IR (νmax, KBr): 3300 Cm-1 (NH), 2950 Cm-1 (CH). Mass (m/z) 542. Elemental Analysis: found C, 75.30, H, 4.10; N, 20.70, requires C, 75.27; H, 4.0; N, 20.66.

Reaction of benzo [a] [1, 4] benzophenazine [3, 2-c] phenazine with chloroacetyl chloride:

Equimolar amounts of 1 (3.34g, 0.01 mole) and chloroacetyle chloride (1.12g, 0.01 mole) in ethanol as a solvent, few drops of triethylamine were added. The reaction mixture was refluxed for 10 h. The reaction

mixture was filtrated from unreacted materials, the filtrated was evaporated to one-third of its volume; ice-water was added, whereby the product was separated, washed several times with water, and crystallized from methanol to give compound 5.

MP 109-11 C, Yield 15 %, $^{+}$H-NMR (DMSO, 300 MHz, δ): 2.4(s, 2H, CH2), 7.53-8.27(m, 12H, Ar-H^{+}). IR (νmax, KBr): 1770 Cm-1 (C=O). Mass (m/z) 374. Elemental Analysis: found C, 77.10; H, 3.70; N, 15.00, requires C, 76.99; H, 3.77; N, 14.96.

Reaction of benzo [a] [1, 4] benzophenazine [3, 2-c] phenazine with formaldehyde:

Compound 1 (3.34g, 0.01mole) and formaldehyde (0.30g, 0.01mole) in equimolar ratios were dissolved in ethanol, and few drops of piperidine as catalyst were added, the reaction mixture was refluxed from unreacted materials, it was allowed to cool at room temperature then filtrated, washed several times with ethanol, dried and collected, and crystallized from aquious ethanol to give compound 6.

MP: 114-116 C, Yield 35 %, ^{1}H-NMR (DMSO, 300 MHz, δ): 3.4(s, 2H, CH2), 7.50-8.30(m, 12H, AR-H^{+}). IR (νmax, KBr): 2995 Cm-1 (CH). Mass (m/z): 346. Elemental Analysis: found C, 79.80; H, 4.00; N, 16.20, requires C, 79.75; H, 4.07; N, 16.17.

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