Synthesis of naphtho-quinoxaline-7, 12-dione, anthra-ptereidine-7, 12-dione and anthra-pyridine derivatives

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ARTICLE INFO

Article type: Research article
Article history: Received August 2019
Accepted January 2020
October 2020 Issue
Keywords: Synthesis
Naphthotriazepine
Naphthothiazine
Quinoxaline
Anthra-ptereidine
Triazolopyridine derivatives

ABSTRACT

In present investigation, addition of nitroso group at position 1 of 2-aminoanthraquinone (1) yielded 2-amino-1-nitroanthraquinone (2) was carried out by the reaction of compound (1) with sodium nitrite in water. Compound (2) was used as an initial intermediate to produce 3-amino-2-cyano-naphtho[2,3-f]quinoxaline-7, 12-dione (4) by reaction of compound (2) with cyanoacetamide in dimethylformamide in presence of piperidine gave intermediate (3), then cyclization may be carried out by releasing of water molecule. Compound (4) consider good and available starting key to synthesis many new of quinoxaline-dione, naphthoquinoxaline-dione, anthrapetridine-dione, anthrapyridine-dione, triazolopetridine-dione derivatives. The structures of the resulting products were determined by elemental analysis, mass, IR and 1H NMR spectral data.

Capsule Summary: Naphtho-quinoxaline, anthra-ptereidine, anthra-pyridine, triazolopetridine, anthrapyridine, triazolopyridine derivatives were synthesized from 2-aminoanthraquinone and 3-amino-2-cyano-naphtho[2,3-f]quinoxaline-7,12-dione (4) and based on different reactive sites a series of new derivatives were prepared.

https://doi.org/10.5281/zenodo.3667527

INTRODUCTION

Anthraquinones are important members of the organic compound family. Their structure is observed in some synthetic dyes and in many naturally occurring substances, such as pigments, vitamins, and enzymes (Thomson, 1957; Fieser and Fieser, 1961; Fieser and Fiese, 1963). The quinone compounds occupy an important place among the different classes of anti-tumor agents (Valderrama et al., 2006). The hydroxylated 9,10-anthraquinones are widely found in nature and are known to display various pharmacological activities (Shi et al., 2001).

The synthesis of anthraquinone derivatives currently is of great interest. There are various methods that have been reported for the synthesis of anthraquinones. The most common ones including the intramolecular condensation of aryl and o-aroylbenzoic acid produce anthraquinone derivatives using benzoyl chloride and concentrated sulfuric acid (Clar, 1948; Clar, 1949), benzoyl chloride and zinc chloride (Clar, 1948), and POCl₃/P₂O₅Cl₄ (Sami and Saleh, 2001). It has been found that FriedelCrafts reactions between phthalic anhydride and substituted benzenes in the presence of a eutectic mixture of aluminum chloride and sodium chloride (2:1) melt have been used for the preparation of various anthraquinones (Hori et al., 1968).
Furan-2,3-diones have been shown to be very useful synthons for the preparation of various heterocycles. These compounds show typical carbonyl and lactone reactions, depending on the structures of the nucleophiles involved (Kollenz and Heilmaver, 1993; Ungören et al., 2005; Sener et al., 2004; Akbas and AslanÖlu, 2006). For example, furan-2,3-diones undergo cyclocondensations with 1,2-diamines to provide the corresponding quinoxalines and aromatic amines react with furan-2,3-diones to give the corresponding Schiff bases and pyrrole-2,3-dione derivatives, depending on the reaction times and temperature (Kollenz and Heilmaver, 1993; Amer et al., 1983).

Scheme 1: Synthesis scheme of the prepared compounds
Scheme 1: Continue...
Aminoanthraquinone, first produced commercially in the United States in 1921 (Eval Carcinog, 1982) is used as an intermediate in the synthesis of anthraquinone dyes, which are used in automotive paints, high-quality paints and enamels, plastics, rubber, printing inks, and in textile dyeing (Gosselin et al., 1983; Lewis, 2000). The 2-aminoanthraquinone used for the majority of the studies has a melting point range of 255 to 292 °C, with decomposition noted at 292 °C (Mustafa et al., 2010).

In present study, the reaction between phthalic anhydride and nitrobenzene in the presence of aluminum chloride and concentrated methanesulfonic acid gave 2-nitroanthraquinone directly. 1-Aminoanthraquinone was prepared by nitration of anthraquinone and reduction of nitroanthraquinones by NaHS followed by separation of 1-amino-anthraquinone from 2-aminoanthraquinone.

**MATERIAL AND METHODS**

**Instrumentation**

All the melting points of prepared compounds are measured using Electro thermal 15 V, 45W A9100 melting point apparatus, and are uncorrected. Elemental analysis were carried out at the Micro analytical Center of Cairo University by an automatic analyzer (Vario EL111 Germany). 1H NMR spectra accomplished using Varian Gemini-300 MHZ Spectrometer. Mass spectroscopy was recorded on GC-2010 Shimadzy spectrometer. Infra-red spectra were measured with a FT/IR(4100 jaso).

**Synthesis of 2-amino-1-nitroanthraquinone (2)**
Compound 1 (1.78 g, 8 mmol) was dissolved in 50 ml dimethylformamide, 5 ml from sodium nitrite solution (0.087 g in 5 ml water) was added dropwise during stirring on ice bath for 1/2 hour, the crude product was filtered off and washed by cold water, crystallized from DMF/H₂O.

**Synthesis of 3-amino-2-cyano-naphtho[2,3-f]quinoxaline-7,12-dione (4)**

A mixture of 2 (2 g, 8 mmol) and cyanoacetamide (0.69 g, 8 mmol) in 30 ml dimethylformamide containing 0.1 ml of piperidine was refluxed for 5 hours, the reaction mixture was concentrated under reduced pressure, the residue that separated out was treated with methanol collected by filtration and recrystallized from DMF/H₂O.

**Synthesis of 3,5-diamino-4-cyano-naphtho[2,3-f]pyrido[2,3-b]-quinoxaline-7,12-dione (7)**

A mixture of 4 (2.4 g, 8 mmol), malononitrile (0.56 ml, 8 mmol) in (50 ml) dimethylformamide and 0.1 ml of piperidine was warmed at reflux for 6 hours and concentrated under vacuum, the residue was poured on to 30 ml acidified cold water, then the product was filtered and crystallized from DMF/H₂O.

### Table 1: Characterization of the prepared compounds

<table>
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<tr>
<th>Comp No.</th>
<th>Nature of products</th>
<th>Molecular formula</th>
<th>Analysis%</th>
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<tr>
<td></td>
<td></td>
<td>(M.Wt)</td>
<td>Calculated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
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<td>C₁₈H₁₀N₂O₂</td>
<td>63.16</td>
</tr>
<tr>
<td>11</td>
<td>red</td>
<td>C₁₉H₁₀N₂O₂</td>
<td>64.77</td>
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<tr>
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<td>66.66</td>
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<td>64.04</td>
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<tr>
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<tr>
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<td>62.12</td>
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</tbody>
</table>

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editorci@bosaljournals.com
Synthesis of 2-cyano-3-ethoxymethyleneimine-
naphtho[2,3-f]-quinoxaline-7,12-dione (8)

A mixture of 4 (1.2 g, 4 mmol), triethylorthoformate (0.6 ml, 4 mmol) and acetic anhydride (60 ml) was refluxed for 4 hours. The solvent was removed under reduced pressure and the separated solid was collected by filtration and crystallized from dioxane/H₂O.

Synthesis of 4-amino-5-imino-anthra[1,2-b]pterdine-
7,12-dione (10)

Solution of 8 (2.8 g, 8 mmol) in (30 ml) dimethylformamide, hydrazine hydrate (0.4 ml, excess) was mixed, refluxed for 2 hours, the reaction solution was concentrated and the solid formed which separated out was filtrated off and crystallized from mixture of ethanol and water 2:8.

Synthesis of anthra[1,2-c]1,2,4-triazolo[3,2-c]pterdine-
7,12-dione (11)

A mixture of 10 (1.3 g, 4 mmol), excess of triethylorthoformate (3 ml) and acetic anhydride (30 ml) was
refluxed for 1 hour. The solvent was removed under reduced pressure and the separated solid was triturated with dimethylformamide and then poured on ice/water, collected by filtration and washed well with cold water.

**Synthesis of 3-acetamide-2-cyano-naphtho[2,3-f]quinoxaline-7,12-dione (12)**

A solution of 4 (1.2 g, 4 mmol) in acetic anhydride (30 ml) was refluxed for 3 hours, then cooled and poured into ice, the solid product that formed was collected by filtration and washed well with cold water, crystallized from DMF/H₂O.

**Synthesis of 1H-5-amino-2-methyl-naphtho[1,2-f]1,3,4-triazepino[3,4-b]quinoxaline-7,12-dione (14)**

A mixture of 12 (1.32 g, 4 mmol) and hydrazine hydrate (0.2 ml, 4 mmol) in (50 ml) dimethylformamide containing 0.1 ml of piperidine was refluxed with 3 hours and the solvent was evaporated under vacuum, the residue was triturated with ice/water, the formed product was filtered off and washed well with cold water, crystallized from DMF/H₂O.

**Synthesis of 2H-5-imino-3-thio-naphtho[2,3-f]1,5-thiazino[2,3-b]quinoxaline-7,12-dione (16)**

A mixture of 4 (0.6 g, 2 mmol) and carbon disulfide (4 ml) in (40 ml) pyridine was refluxed for 3 hours and the solvent was evaporated under vacuum, the product that separated out was filtered off and washed well with cold water, crystallized from DMF/H₂O.

**Synthesis of 1-(3H-3-imino-2-thio-7,12-dioxo-anthra[1,2-b]pyridine-2-yi) thiourea (20)**

To a solution of 4 (0.6 g, mmol) in (40 ml) acetic acid, ammonium thiocyanate (0.16 g, 2 mmol) was added and the reaction mixture was refluxed for 5-6 hours. The solid product which formed on cooling and under reduced pressure was filtered off and washed with methanol, crystallized from DMF/H₂O.

**Synthesis of 2H-5-imino-4-phenyl-3-thio-anthra[1,2-b]pyridine7,12-dione (22)**

A mixture of 4 (0.6 g, 2 mmol) and phenylisothiocyanate (0.32 ml, 2 mmol) in 40 ml pyridine was heated at reflux for 20 hours, the solvent was evaporated under vacuum and the residue was triturated with hot dimethylformamide and then poured on ice, collected by filtration and washed well with cold water.

**Synthesis of 5-chloro-naphtho[2,3-f]1,2,3-triazine[4,5-b]quinoxaline-7,12-dione (24)**

To an ice/cooled solution of 4 (0.6 g, 2 mmol) in 50 ml (HCl/AcOH; V/V), a solution of sodium nitrite (0.02 mol) in water (20 ml) was added drop wise, the solution was stirred at room temperature for an additional 2 hours, the crude product obtained was filtered off and crystallized from DMF/H₂O.

**Synthesis of 15-amino-anthra[1,2-b]1,2,3-triazolo[3,4-b]pyridine-8,13-dione (26)**

A mixture of 4 (0.6 g, 2 mmol), 5-amino triazole (0.14 g, 2 mmol) in (50 ml) dimethylformamide containing 0.1 ml piperidine was refluxed for 8 hours, the solvent was evaporated under vacuum and the residue was triturated with cold water, the solid product was filtered and crystallized from DMF/H₂O.

**RESULTS AND DISCUSSION**

The characterization data and synthesis pathways are shown in Table 1-2 and Scheme 1, respectively. Addition of nitroso group in position 1 of 2-aminoanthraquinone (1) to yield 2-amino-1-nitroanthraquinone (2) was carried out by the reaction of compound (1) with sodium nitrite in water. Compound (2) considers good and available starting material to produce many new anthraquinone derivatives, since it contains nitroso and amino active function groups, Reaction of compound (2) with cyanoacetamide gave intermediate (3), then cyclization may be carried out by releasing of water molecule or by addition of amino function onto cyano group to yield compound (4) or compound (5), respectively; the structure of the resulting product was established based on spectral and elemental analysis seemed that 3-amino-2-cyano-naphtho[2,3-f]quinoxaline-7,12-dione (4) was formed. The reactivity of o-aminonitrile of compound (4) was investigated towards many laboratory available reagents to synthesis of a new wide variety of fused heterocyclic compounds. Thus, compound (4) was condensed smoothly with malononitrile at refluxing in dimethylformamide/ piperidine solution yielding 6H-anthra[2,1-c] benzof][1,2,5-triazepine-9,14-dione (7). Compound (7) was assumed to be proceeded through intermediate (6), which underwent intramolecular cyclization of amino group onto cyano group. The condensation of o-aminonitrile of (4) with triethylorthoformate in refluxing acetic anhydride yielded the corresponding 2-cyano-3-ethoxymethylene-imine-naphtho [2,3-f]quinoxaline-7,12-dione (8), which underwent further cyclization up on treatment with hydrazine hydrate in dimethylformamide afforded 4-amino-5-imino-anthra[1,2-b]ptreidine-7,12-dione (10) via forming of intermediate (9). Further cyclization of compound (10) was achieved by its reaction with triethylorthoformate in acetic anhydride at reflux affording anthra[1,2-c][1,2,4-triazolo[3,2-c]pteridine-7,12-dione (11). Compound (4) reacted with acetic anhydride under reflux forming the 3-acetamide-2-cyano-naphtho[2,3-f]quinoxaline-7,12-dione (12). The compound (12) underwent further cyclization upon treatment with hydrazine hydrate in dimethylformamide containing a catalytic amount of piperidine at reflux temperature affording 1H-5-amino-2-
methyl-naphtho[1,2-\(f\)]1,3,4-triazepino[3,4-b]quinoxaline7,12-dione (14) via formation of intermediate (13). The reactivity of amino group of compound (4) was also explored through its reaction with carbon disulfide. Thus, refluxing of compound (4) with carbon disulfide afforded 2H-5-imino-3-thio-naphtho[2,3-\(f\)]1,5-thiazino[2,3-\(b\)]quinoxaline-7,12-dione (16). Compound (16) may be proceeded through the addition of the amino group to (CS\(_2\)) forming the intermediate (15) followed by a nucleophilic attack of the thiol group onto the cyano function. However, the reaction of compound (4) with ammonium thiocyanate in boiling acetic acid gave 1-(3H-3-imino-2-thio-7, 12-dioxo-anthra[1,2-\(b\)]pteridine-2-yl) thiourea (20) through intermediates (17-19). Similarly, compound (4) reacted with phenylisocyanate in pyridine at refluxed temperature affording 2H-5-imino-4-phenyl-3-thio-anthra[1,2-b]pteridine-7,12-dione (22) due to attack of imino group onto cyano function of intermediate (21). Diazotization and self-coupling of amino group of compound (4) with sodium nitrite and hydrochloric acid gave 5-chloro-naphtho[2,3-\(f\)]1,2,3-triazino[4,5-b]quinoxaline-7,12-dione (24). The formation of (24) was assumed to be proceeded via an initial diazotization of (4) and spontaneously undergoes intramolecular cyclization through nucleophilic addition of chloride ion on the positive carbon of cyano function. Finally, compound 15-amino-anthra[1,2-b]1,2,3-triazolo[3,4-b]pteridine-8,13-dione (26) may be obtained through the reaction of o-aminoanitride of (4) with 5-amino(1,2,4)triazole in dimethylformamide/pteridine solution at refluxing temperature. The formation of (26) may be proceeded via nucleophilic addition reaction of amino group onto cyano function yielded intermediate (25) which underwent cyclization via losing amino molecule. The prepared compounds might have the potential to be the leading compounds as bioactive agents (Baranov et al., 2019; Chen et al., 2019; Liu et al., 2019; Ratha et al., 2019; Saraswat and Yadav, 2020; Shchekotikhin et al., 2016; Srinivas et al., 2007; Starke et al., 2004; Tikhomirov et al., 2018; Yadav et al., 2018), which need to be studied in future studies as has been reported previously for related derivatives (Berhe et al., 2010; Chłoń-Rzepa et al., 2018; Elkmahwry et al., 2019; Gaggin et al., 2011; Hussain et al., 2019; Matviuk et al., 2013; Trotsko et al., 2020; Wang et al., 2018; Wröbel et al., 2019).

CONCLUSIONS

The 2-amino-1-nitroanthraquinone (2) was used to produce 3-amino-2-cyano-naphtho[2,3-\(f\)]quinoxaline-7,12-dione(4), which is considered as an intermediate for the synthesis series of new pyrido quinoxaline-7, 12-dione (7), naphthoquinoxaline (8), (12), antha-pterepidine-dione (10), triazolopertridine (11), naphthotriazinequinoline (14), naphthothiazinequinoline (16), anthrapyrid thiourea (20), anthrapyridine (22), triazine quinoxaline (24), triazolopyridine (26) derivatives, depending on presence of cyano and amino active groups of (4), through addition reaction or releasing water molecule or ethanol molecule or amonia molecule. Future studies can be focused on the activity evaluation of compounds prepared in this investigation.

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