Novel Synthesis of Some Phthalazinone Derivatives

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Dimethyl homophthalate condensed with isatin to give the unexpected five membered lactone **3** rather than the half ester **1** and the δ-lactone **2**. Treatment of compound **3** with excess hydrazine hydrate afforded phthalazinone carbohydrazide **4** which represents a novel method for the synthesis of phthalazinone derivatives. The carbohydrazide **4** upon treatment with carbon disulphide afforded 1,3,4-oxadiazole derivative **5**, which reacted with ethylchloroacetate to give the *S*-alkylated product **6**. The structure of compound **3** compared with **2** was discussed using hyperchem professional (7) AM_1 calculations, X-ray single crystal structure and complete spectral data.

Keywords phthalazinone carbohydrazide, oxadiazole, triazolo oxadiazole, AM_1 calculation, condensation

Introduction

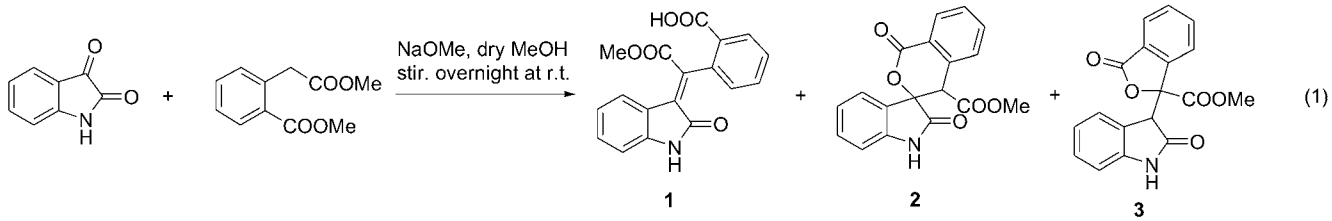
Heterocyclic compounds containing hydrazine have received considerable attention because of their pharmacological properties and clinical applications.[1-3] Phthalazine derivatives were reported to possess anticonvulsant,[4-6] cardiotonic,[7] antitumor,[8-11] antihypertensive,[12-14] antithrombotic,[15] antidiabetic,[16,17] antimicrobial,[18,19] anti-inflammatory,[20-25] cytotoxic,[26] vasorelexant[27] and vascular endothelial growth factor receptor II (VEGFR-2) inhibitory activities.[28] Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives.[29] Efficient method for the preparation of heterocyclic compounds containing phthalazine ring is therefore an interesting challenge.

Results and discussion

In our laboratories, it has been found that when a mixture of isatin and dimethyl homophthalate was treated in absolute methanol in the presence of sodium methoxide, the previously reported[30,31] half ester **1** or six-membered lactone (isocoumarin) **2** have not been isolated, but the lactone **3** was obtained as the sole product (Eq. 1).

The structure of **3** was illustrated from its analytical, as well as, spectral data. The infrared spectrum of this compound displayed three stretching absorption bands for the carbonyl group at 1775 cm^{-1} (ν_{CO} lactone), 1715 cm^{-1} (ν_{CO} ester) and 1619 cm^{-1} (ν_{CO} amide) besides the ν_{NH} at 3374 cm^{-1}. ^1H NMR of the product revealed a pattern completely different from that expected for **2** and can only be intelligibly interpreted in terms of the structure **3**. Thus, ^1H NMR spectrum of **3** (DMSO-d_6) shows from high to low field the following signals at δ 3.71 (s, 3H, COOMe), 5.48 (s, 1H, C^3-H indolinyl), 6.54—8.08 (m, 8H, ArH) and 10.59 (s, 1H, NH, exchangeable with D_2O). Furthermore, the mass spectrum of **3** shows the correct molecular ion peak at m/z=323 (6%) together with EI fragmentation pattern completely in accord with the proposed structure (*cf.* experimental part). The structure **3** was rigidly established from the X-ray single crystal structure (deposition no. CCDC 777721) (Figure 1).

Moreover, in agreement with the experimental result, Frontier coefficients of the reactive sites by applying the hyperchem professional (**7**) AM_1 calculations to the intermediates,[32] showed the higher stability of **3** than **2**. This is due to the lower value of HOMO at O^- and lower value of LUMO at the attacking carbocation center (C*) (Table 1).



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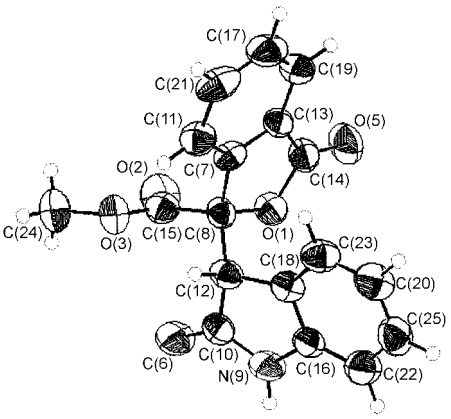
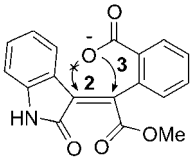


Figure 1 X-ray single crystal structure of the adduct **3**.

Table 1 Frontier coefficient of the reactive sites in **2** and **3**

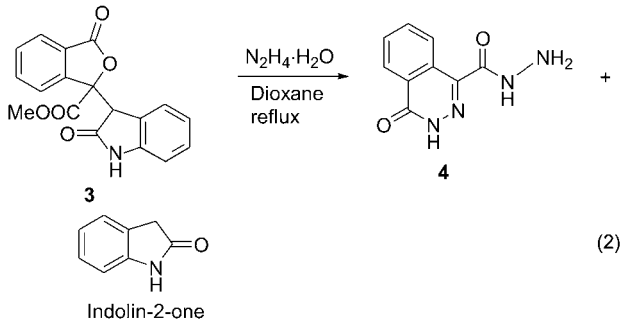


Compd.	HOMO (O^-)/eV	LUMO (C*)/eV
2	−11.031	−1.412
3	−11.544	−1.873

The formation of methyl-1-(2-oxo-3-indolinyl)-3-oxo-benzo[c]furan-1-carboxylate (**3**) could be visualized as Scheme 1.

Furthermore, upon treatment with excess hydrazine hydrate compound **3** afforded a product with molecular formula $C_9H_8N_4O_2$ [$M^+ = 204$ (100%)], which was analyzed and identified as 4-oxo-3,4-dihydrophthalazine-1-carbohydrazide **4** (Eq. 2). Evaporation of the excess solvent in the mother liquor left a solid product which was detected as indolin-2-one by m.p. mixed m.p. and TLC with an authentic sample.

This method represents a novel and convenient method for the synthesis of phthalazinone carbohydrazide **4**, which was expected to have interesting bio-



(2)

activities.

The structure of **4** was deduced from analytical and spectroscopic data. Thus, IR spectrum of compound **4** exhibits the stretching absorption bands at 3428, 3309, 3122 cm^{-1}, 1686 and 1614 cm^{-1} attributable for the group frequencies of NH_2, NH, CO hydrazide and C=N, respectively. ^1H NMR spectrum of **4** (DMSO-d_6) show the signals at δ 4.62 (s, 2H, NH_2, exchangeable with D_2O), 7.8—8.3 (m, 4H, ArH), 9.7 (s, 1H, NH exchangeable with D_2O) and 12.88 (s, 1H, $NH_{phth.}$, exchangeable with D_2O). Furthermore, the EI-MS fragmentation shows the molecular ion peak at m/z=204 (100%) which is the base peak (*cf.* experimental part).

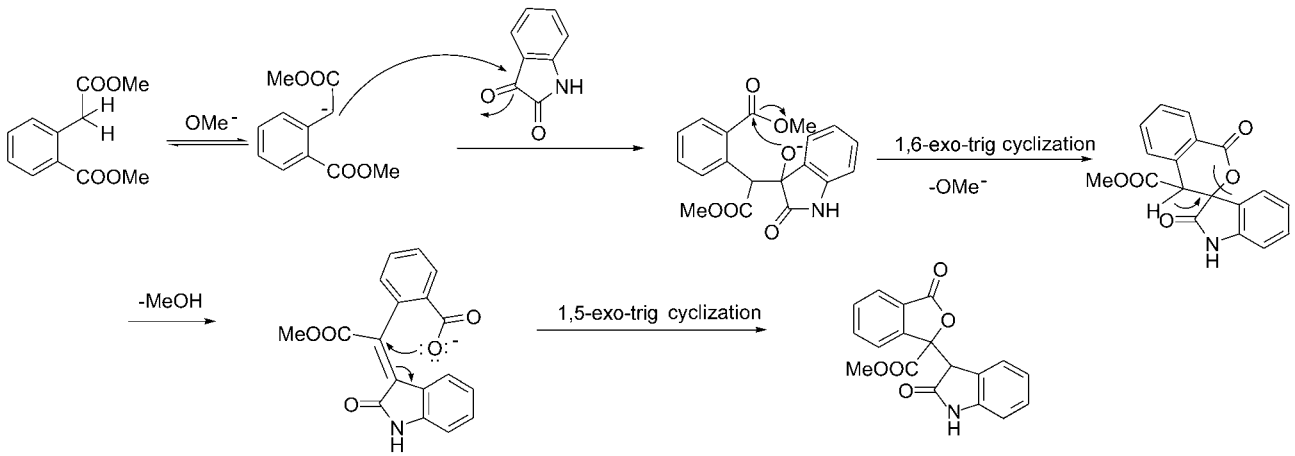
The conversion of **3** to **4** could be explained on the bases of the following pathway (Scheme 2).

The structure of **4** was rigidly confirmed chemically by the reaction with carbon disulphide in refluxing pyridine, which afforded 4-(5-mercapto-1,3,4-oxadiazol-2-yl)phthalazin-1(2*H*)-one (**5**) (Scheme 3).

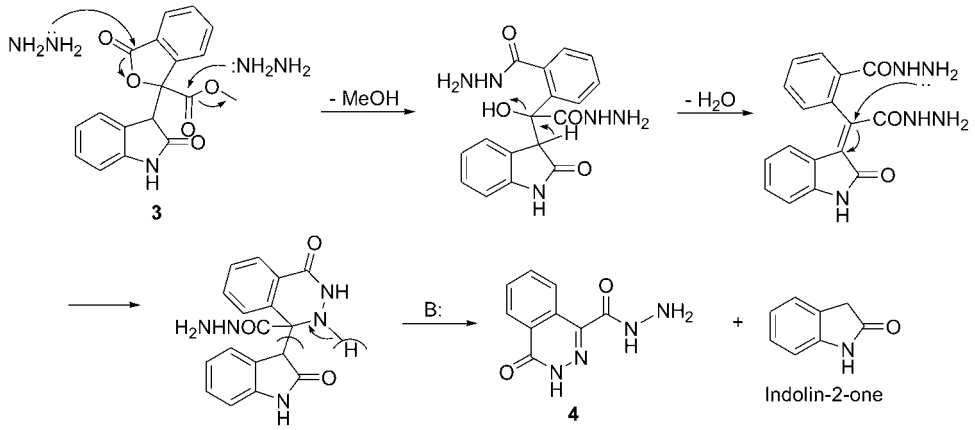
The elemental analyses and molecular weight determination indicate the incorporation of one sulfur atom to the molecular structure of the product whose molecular formula is $C_{10}H_6N_4O_2S$ [M^+=246 (89.71%)]. IR spectrum of **5** displayed ν_{NH} at 3169, 3110 cm^{-1}, ν_{CO} at 1681cm^{-1}, $\nu_{C=N}$ at 1642 cm^{-1} and $\nu_{C=S}$ at 1230 cm^{-1}. ^1H NMR spectrum of compound **5** [DMSO-d_6] was completely matched with the assigned structure (*cf.* experimental part).

The conversion of compound **4** to **5** could be explained according the following mechanism (Scheme 4).

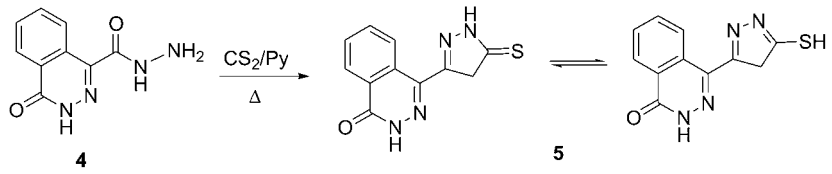
Scheme 1



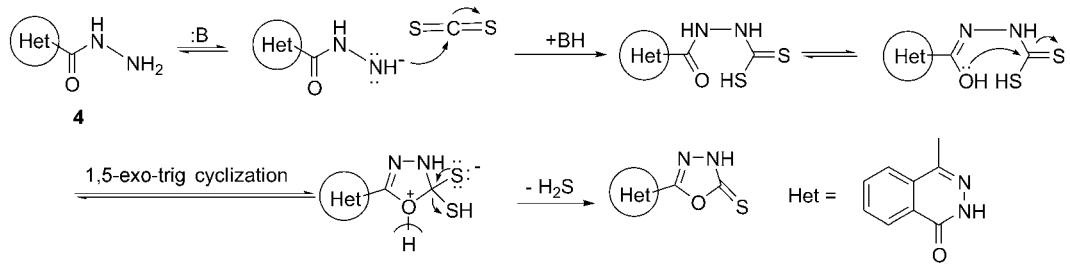
Scheme 2



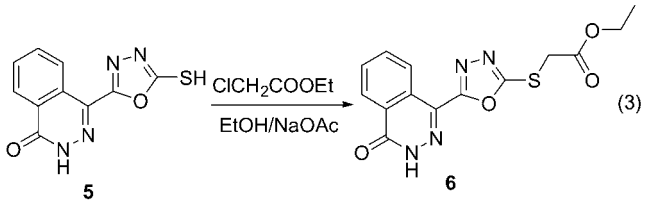
Scheme 3



Scheme 4



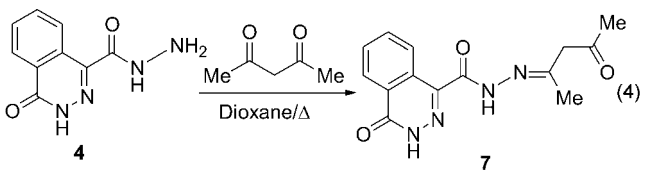
A strong clue for the structure **5** was forthcoming from the reaction of the oxadiazole derivative **5** with ethyl chloroacetate in refluxing ethanol in the presence of fused sodium acetate, which yielded ethyl-2-[5-(4-oxo-3,4-dihydraphthalazin-1-yl)-1,3,4-oxadiazol-2-yl-thio]acetate (**6**) as the *S*-alkylation product (Eq. 3).



The structure of **6** was deduced from the correct analytical and spectroscopic data. Thus, the IR spectrum of **6** displayed ν_{NH} at 3218, 3166 cm^{-1}, ν_{CO} (ester) at 1734 cm^{-1}, ν_{CO} (phthalazinone) at 1660 cm^{-1}. ^1H NMR spectrum of compound **6** [DMSO-d_6] was completely matched with the assigned structure. Furthermore the highest recorded peak at m/z=332 (44%) represents the molecular ion peak and the EI fragmentation pattern is completely in accord with the assigned structure (*cf.* experimental part).

The formation of *S*-alkylated product **6** could be explained on the basis of nucleophilic substitution reaction by the sulfur nucleophile on the electrophilic center of ethyl chloroacetate via S_N2 mechanism.

The hydrazide derivative was reported[33] to give pyrazolo derivative when treated with *β*-diketones. When compound **4** was subjected to react with acetyl acetone in refluxing dioxane, the normal condensation product **7** was afforded (Eq. 4).



The structure **7** was deduced from the analysis of the

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spectral data. Thus, the IR spectrum shows two carbonyl absorption bands at 1688, 1655 cm^{-1} and one sharp absorption band for NH group at 3236 cm^{-1}. Furthermore, ^1H NMR and mass spectra of **7** are completely consistent with the assigned structure.

Experimental

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were performed using a Heraeus CHN Rapid analyzer at the Microanalytical unit, Cairo University. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. ^1H NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP1000 EX instrument operating at 70 eV in EI mode.

General procedure for the condensation of isatin with dimethyl homophthalate

Formation of methyl-1-(2-oxoindolin-3-yl)-3-oxobenzo[*c*]furan-1-carboxylate (**3**): To a solution of isatin (1.47 g, 10 mmol) and dimethyl homophthalate (2.08 g, 10 mmol) in dry methanol (40 mL), sodium methoxide (1 g Na in 30 mL methanol) was added and the whole mixture was stirred overnight at r.t. The excess solvent was removed under reduced pressure and solid residue was treated with ice cold hydrochloride. The deposit was filtered off, dried and crystallized from methanol to give **3**. Yellowish white crystals (2 g, 62%). m.p. 220—222 ℃; ^1H NMR (DMSO-d_6) δ: 3.71 (s, 3H, OCH_3), 5.48 (s, 1H, CH), 6.54—8.08 (m, 8H, ArH), 10.59 (s, 1H, NH exchangeable with D_2O); IR (KBr) ν_{max}: 3374 (NH), 1775 (C=O lactone), 1715 (C=O ester), 1619 (C=O Isatin) cm^{-1}; MS *m/z* (%): 323 ($M^{\cdot+}$, 6), 264 (8), 191 (7), 163 (100), 132 (25), 104 (28), 77 (36), 76 (30). Anal. calcd for $C_{18}H_{13}NO_5$ (323): C 66.87, H 4.05, N 4.33; found C 66.52, H 4.12, N 4.41.

General procedure for the synthesis of 4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (4)

Lactonic ester **3** (1 g, 3 mmol) was dissolved in dioxane (20 mL) and excess hydrazine (4 mL) was then added. The reaction mixture was heated under reflux for 3 h. The excess solvent was removed under reduced pressure and the solid residue was crystallized from ethanol/dioxane to give **4**. White crystals (0.5 g, 79.3 %). m.p. 238—240 ℃; ^1H NMR (DMSO-d_6) δ: 4.62 (s, 2H, NH_2, exchangeable), 7.85—8.3 (m, 4H, ArH), 9.7 (s, 1H, NH, NH-CO, exchangeable), 12.88 (s, 1H, NH, NH-$CO_{phth.}$, exchangeable); IR (KBr) ν_{max}: 3428, 3309, 3122 (NH, NH_2), 1686 (C=O hydrazide), 1614 (C=N) cm^{-1}; MS *m/z* (%): 204 (M^+, 100), 173 (75), 145 (67), 117 (32), 102 (31), 90 (99), 76 (26), 63 (26). Anal. calcd for $C_9H_8N_4O_2$ (204): C 52.94, H 3.95, N 27.44; found C 52.71, H 4.17, N 27.63.

General procedure for the reaction of 4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (4) with CS_2

Formation of 4-(5-mercapto-1,3,4-oxadiazol-2-yl)-phthalazin-1(2*H*)-one (**5**): A mixture of acid hydrazide **4** (2.04 g, 10 mmol) and carbon disulphide (15 mL) in pyridine (30 mL) was refluxed in water bath for 6 h. The excess solvent was removed under reduced pressure, the obtained yellow crystals were collected by filtration and recrystallized from dioxane to give **5**. Pale yellow crystals (1.4 g, 57%), m.p.>300 ℃; ^1H NMR (DMSO-d_6) δ: 3.3 (br s, 1H, SH), 7.9—8.7 (m, 4H, ArH), 13.39 (s, 1H, NH, NH-$CO_{phth.}$); IR (KBr) ν_{max}: 3169, 3110 (NH), 1681 (C=O), 1642 (C=N), 1230 (C=S) cm^{-1}; MS *m/z* (%): 246 ($M^{\cdot+}$, 90), 186 (62), 145 (16), 103 (68), 102 (100), 90 (36), 76 (37), 75 (49). Anal. calcd for $C_{10}H_6N_4O_2S$ (246): C 48.78, H 2.46, N 22.75, S 13.02; found C 48.51, H 2.37, N 22.93, S 12.87.

General procedure for the reaction of the oxadiazole derivative 5 with ethyl chloroacetate

Formation of ethyl-2-[5-(4-oxo-3,4-dihydraphthalazin-1-yl)-1,3,4-oxadiazol-2-ylthio] acetate (**6**): A mixture of **5** (2.46 g, 10 mmol), ethyl chloroacetate (1.22 mL, 10 mmol) and fused sodium acetate (0.82 g, 10 mmol) in absolute ethanol (30 mL) was refluxed for 4 h. The reaction mixture allowed to cool was poured into water and then stirred for 15 min. The deposited solid was filtered off, dried and then recrystallized from ethanol/dioxane to give **6**. White crystals (1.33 g, 40%), m.p. 210—212 ℃; ^1H NMR (DMSO-d_6) δ: 1.20 (t, J= 7 Hz, 3H, CH_3), 4.18 (q, J=7 Hz, 2H, CH_2CH_3) 4.31 (s, 2H, CH_2S), 7.92—8.92 (m, 4H, ArH), 13.37 (s, 1H, NH, exchangeable with D_2O); IR (KBr) ν_{max}: 3218, 3166 (NH), 1734 (C=O ester), 1660 (C=O phthalazinone) cm^{-1}; MS *m/z* (%): 232 ($M^{\cdot+}$, 44), 213 (42), 189 (72), 173 (56), 145 (100). Anal. calcd for $C_{14}H_{12}N_4O_4S$ (332): C 50.60, H 3.64, N 16.86, S 9.65; found C 50.91, H 3.47, N 16.63, S 9.87.

General procedure for the reaction of the hydrazide derivative 4 with acetyl acetone

Formation of oxadiazole derivative (**7**): A mixture of hydrazide derivative **4** (2.44 g, 10 mmol) and acetyl acetone (1 mL, 10 mmol) in dioxane (20 mL) were refluxed for 4 h. The excess solvent was removed under reduced pressure, the obtained white crystals were collected by filtration and recrystallized from ethanol to give **7**. White crystals (0.73 g, 22%), m.p. 180—183 ℃; ^1H NMR (DMSO-d_6) δ: 1.79 (s, 3H, $COCH_3$), 2.11 (s, 3H, N=CCH_3), 2.9 (dd, J=19, 18.5 Hz, 2H, CH_2), 6.87 (s, 1H, NH, exchangeable with D_2O), 7.6 (d, J=9 Hz, $1H_{arom}$), 7.95—7.91 (m, $2H_{arom}$), 8.29 (d, J=9 Hz, $1H_{arom.}$), 12.7 (s, 1H, NH, exchangeable with D_2O); IR (KBr) ν_{max}: 3236 (NH), 1688, 1655 (C=O) cm^{-1}; MS *m/z* (%): 286 (M^+, 14.7), 268 (13.9), 239 (91.2), 173 (52.9), 145 (82.4), 117 (33.6), 90 (100). Anal. calcd for $C_{14}H_{14}N_4O_3$ (286): C 58.73, H 4.93, N 19.57; found C 55.14, H 4.60, N 20.75.

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